Summary Basis of Approval
Cover Form

Appl #: 020491 Firm: ST.JOHN COMPANY

Reviewing Div: 110

Trade Name: CORVERT (IBUTILIDE FUMARATE) INJECTION

Generic Name:

IBUTILIDE FUMARATE

Approval Letter:	Y	Statistician Review:	Y
SBA Form:	N	Bio/Dissolution Review:	Y
Final Printed Labeling:	Y	Microbiologist Review:	Y
Medical Officer Review:	Y	NAS/NRC Review:	N
Chemist Review:	Y	Pharmacologist Review:	Y
Federal Register Notice:	N	Completion Date:	13-MAR-96

APPROVAL

LETTER

Willard

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-491

DEC 28 1995

The Upjohn Company
Attention: Hendrik J. de Koning Gans, M.D.
7000 Portage Road
Kalamazoo, MI 49001

Dear Dr. Gans:

Please refer to your October 27, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Corvert (ibutilide fumarate) 0.1/mg/mL in 10 mL Injection.

We acknowledge receipt of your amendments and correspondence dated October 31; November 11; and December 27 and 29 (two), 1994; January 5, 12, 19, 27, 30 and 31; February 2, 10, 15, 17 (two), 21 and 27 (two); March 1, 2, 3, 9, 10, 14, 16, 20, 27, 28, 29 and 31; April 6, 12, 14, 21 and 26; May 15, 17 and 30; June 30; August 3, 4, 7, 11 and 25; September 11 and 15; October 23 and 26; and November 10 and 14; and December 4 and 18, 1995. In addition, we acknowledge receipt of the facsimile copy of your December 27, 1995 amendment.

This new drug application provides for ibutilide injection to be used in the treatment of atrial fibrillation or flutter.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-491. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

LABELING

Mark-up

DRAFT PACKAGE INSERT

CORVERT™ Injection
(brand of ibutilide fumarate injection)
For intravenous infusion only

DESCRIPTION

CORVERT Injection (ibutilide fumarate injection) is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.087 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection.

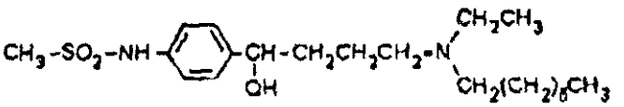
CORVERT Injection is an isotonic, clear, colorless, sterile aqueous solution.

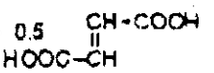
Ibutilide fumarate has one chiral center, and exists as a racemate of the (+) and (-) enantiomers.

The chemical name for ibutilide fumarate is Methanesulfonamide, N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl], (+) (-), (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is $C_{22}H_{36}N_2O_5S$ and its molecular weight is 442.62.

Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower.

The structural formula is represented below:





Ibutilide Fumarate

CLINICAL PHARMACOLOGY

Mechanism of Action: CORVERT Injection prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness in vivo, i.e., class III electrophysiologic effects. Voltage clamp studies indicate that CORVERT Injection, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which most other class III antiarrhythmics act. These effects lead to prolongation of atrial and ventricular action potential duration and refractoriness, the predominant electrophysiologic properties of CORVERT Injection in humans that are thought to be the basis for its antiarrhythmic effect.

Electrophysiologic Effects: CORVERT Injection produces mild slowing of the sinus rate and atrioventricular conduction. CORVERT Injection produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship between plasma concentration and antiarrhythmic effect, CORVERT Injection produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity. (See WARNINGS for relationship between QTc prolongation and torsades de pointes-type arrhythmias.) In a study in healthy volunteers, intravenous infusions of CORVERT Injection resulted in prolongation of the QT intervals that were directly correlated with ibutilide plasma concentrations during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was shown. The maximum effect was a function of both the dose of CORVERT Injection and the infusion rate.

Hemodynamic Effects: A study of hemodynamic function in patients with ejection fractions both above and below 35% showed no clinically significant effects on cardiac output, mean pulmonary arterial pressure, or capillary wedge pressure at doses of CORVERT up to 0.03 mg/kg.

Pharmacokinetics: After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a multi-exponential fashion. The pharmacokinetics of ibutilide are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg), a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers, and minimal (about 40%) protein binding. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation. The elimination half-life averages about 6 hours (typically ranges from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT Injection over the dose range of 0.01 mg/kg to 0.10 mg/kg. The enantiomers of ibutilide fumarate have pharmacokinetic properties similar to each other and to ibutilide fumarate.

The pharmacokinetics of CORVERT Injection in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, patient age, sex, or the concomitant use of digoxin, calcium channel blockers, or beta blockers.

Metabolism and Elimination: In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [^{14}C]ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (19%) was recovered in the feces.

Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω-oxidation followed by sequential β-oxidation of the heptyl side chain of ibutilide. Of the eight metabolites, only the ω-hydroxy metabolite possesses class III electrophysiologic properties similar to that of ibutilide in an in vitro isolated rabbit myocardium model; the plasma concentrations of this active metabolite, however, are less than 10% of that of ibutilide.

Clinical Studies: Treatment with intravenous ibutilide fumarate for acute termination of recent onset atrial flutter/fibrillation was evaluated in 466 patients participating in two randomized, double-blind, placebo-controlled clinical trials. Patients had had their arrhythmias for 3 hours to 90 days, were anticoagulated for at least two weeks if atrial fibrillation was present more than 3 days, had serum potassium of at least 4.0 mEq/L and QTc below 440 msec and were monitored by telemetry for at least 24 hours. Patients could not be on class I or other class III antiarrhythmics but could be on calcium channel blockers, beta blockers or digoxin. In one trial, single 10-minute infusions of 0.005–0.025 mg/kg were tested in parallel groups (0.3 to 1.5 mg in a 60 kg person). In the second trial, up to two infusions of ibutilide fumarate were evaluated, the first 1.0 mg, the second either 0.5 or 1.0 mg. In a third double blind study, 319 patients with atrial fibrillation or atrial flutter of 3 hours to 45 days duration were randomized to receive single, 1-minute intravenous infusions of either sotalol (1.5 mg/kg) or CORVERT (1 mg or 2 mg). In atrial flutter, 53% of patients receiving 1 mg ibutilide fumarate and 70% of patients receiving 2 mg ibutilide fumarate converted, as compared to 18% of those receiving sotalol. In atrial fibrillation, 22% of patients receiving 1 mg ibutilide fumarate and 43% of patients receiving 2 mg ibutilide fumarate converted as compared to 10% of patients receiving sotalol.

Patients in clinical trials were hemodynamically stable. Patients with specific cardiovascular conditions such as symptomatic heart failure, recent MI, and unstable angina were excluded. About two thirds had cardiovascular symptoms, and the majority of patients had left atrial enlargement, decreased left ventricular ejection fraction, a history of valvular disease, or previous history of atrial fibrillation or flutter. Electrical cardioversion was allowed 90 minutes after the infusion was complete. Patients could be given other antiarrhythmic drugs 4 hours post infusion.

Results of the first two studies are shown in the tables below. Conversion of atrial flutter/fibrillation usually (70%) occurred within 30 minutes of the start of infusion and was dose related. Most converted patients remained in normal sinus rhythm for 24 hours. Overall responses in these patients, defined as termination of arrhythmias for any length of time during or within 1 hour following completed infusion of randomized dose, were in the range of 45–50% at doses above 0.0125 mg/kg (vs 2% for placebo). Twenty-four hour responses were similar. For these atrial arrhythmias, ibutilide was more effective in patients with flutter than fibrillation (>50% vs <40%).

PERCENT OF PATIENTS WHO CONVERTED (first trial)						
			Ibutilide			
		placebo	0.005 mg/kg	0.01 mg/kg	0.015 mg/kg	0.025 mg/kg
	n	41	41	40	38	40
Atrial flutter	at any time*	0	14	30	58	55
	at 24 hours#	0	14	30	58	50
Atrial fibrillation	at any time*	5	10	35	32	40
	at 24 hours#	5	10	25	26	35
Both	at any time*	2	12	33	45	48
	at 24 hours#	2	12	28	42	43

* Percent of patients who converted within 70 minutes after the start of infusion.
\# Percent of patients who remained in sinus rhythm 24 hours after dosing.

PERCENT OF PATIENTS WHO CONVERTED (second trial)				
			Ibutilide	
		placebo	1.0 mg/0.5 min	1.0 mg/1.0 min
	n	86	86	94
Atrial flutter	at any time*	2	52	66
	at 24 hours#	2	45	59
Atrial fibrillation	at any time*	2	38	25
	at 24 hours#	2	21	17
Both	at any time*	2	45	45
	at 24 hours#	2	34	37

* Percent of patients who converted within 90 minutes after the start of infusion.
\# Percent of patients who remained in sinus rhythm 24 hours after dosing.

The numbers of patients who remained in the converted rhythm at the end of 24 hours were slightly less than those patients who converted ~~for any length of time~~, but the difference between conversion rates for ibutilide compared to placebo was still statistically significant. In long-term follow-up approximately 40% of all patients remained recurrence free 400 - 500 days after acute treatment, regardless of the method of conversion.

Patients with more recent onset of arrhythmia had higher rate of conversion. Response rates were 42% and 50% for patients with onset of atrial fibrillation/flutter for less than 30 days in the two efficacy studies compared to 16% and 31% in those with more chronic arrhythmias.

Ibutilide was equally effective in patients below and above 65 years of age and in ~~male and female but female patients were under-represented in the clinical studies (22%)~~ men and women.

INDICATIONS AND USAGE

CORVERT Injection is indicated for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm. Patients with atrial arrhythmias of longer duration are less likely to respond to CORVERT. The effectiveness of ibutilide has not been determined in patients with arrhythmias of more than 90 days in duration.

LIFE THREATENING ARRHYTHMIAS - APPROPRIATE TREATMENT ENVIRONMENT

CORVERT can cause potentially fatal arrhythmias, particularly sustained polymorphic ventricular tachycardia usually associated with QT prolongation (torsades de pointes), but sometimes without documented QT prolongation. In clinical studies, these arrhythmias which require cardioversion, occurred in 1.7% of treated patients during or within a number of hours of use of CORVERT. These arrhythmias can be reversed if treated promptly (see Warnings, Proarrhythmia). It is essential that CORVERT be administered in a setting of continuous ECG monitoring and by personnel trained in identification and treatment of acute ventricular arrhythmias, particularly polymorphic ventricular tachycardia. *Patients with atrial fibrillation of more than 2 - 3 days duration must be adequately anticoagulated generally for at least two weeks.*

CHOICE OF PATIENTS

Patients with chronic atrial fibrillation have a strong tendency to revert after conversion to sinus rhythm (see Clinical Studies) and treatments to maintain sinus rhythm carry risks. Patients to be treated with CORVERT, therefore, should be carefully selected such that the expected benefits of maintaining sinus rhythm outweigh the immediate risks of CORVERT and the risks of maintenance therapy and offer an ~~apparent~~ advantage compared to alternative management.

CONTRAINDICATIONS

CORVERT Injection is contraindicated in patients who have previously demonstrated hypersensitivity to ibutilide fumarate or any of the other product components.

WARNINGS

Proarrhythmia:

Like other antiarrhythmic agents, CORVERT Injection can induce or worsen ventricular arrhythmias in some patients. This may have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia that develops in the setting of a prolonged QT interval, may occur because of the effect CORVERT Injection has on cardiac repolarization, but CORVERT can also cause polymorphic VT in the absence of excessive prolongation of the QT interval. In general, with drugs that prolong the QT interval, the risk of torsades de pointes is thought to increase progressively as the QT interval is prolonged and may be worsened with bradycardia, a varying heart rate, and hypokalemia. In clinical trials conducted in patients with atrial fibrillation and atrial flutter, those with QTc intervals > 440 msec were not usually allowed to participate and serum K had to be above 4.0 mEq/L. Although change in QTc was dose-dependent for ibutilide, there was no clear relationship between risk of serious proarrhythmia and dose in clinical studies, possibly due to small number of events. In clinical trials of intravenous ibutilide, patients with history of heart failure or low left ventricular ejection fraction appeared to have a higher incidence of sustained polymorphic VTs than those without such underlying conditions; for sustained polymorphic VT the rate was 6.2% in patients with a history of CHF and 0.8% without it. There was also a suggestion that women had a higher risk of proarrhythmia, but the gender difference was not observed in all studies and was most prominent for nonsustained ventricular tachycardia. The incidence of sustained ventricular arrhythmias was similar in male (1.8%) and female (1.5%) patients, possibly due to the small number of events. CORVERT Injection is not recommended in patients who have previously demonstrated polymorphic ventricular tachycardia (eg, torsades de pointes).

During clinical trials, 1.7% of patients with atrial flutter or atrial fibrillation treated with CORVERT Injection developed sustained polymorphic ventricular tachycardia requiring cardioversion. In these clinical trials, many initial episodes of polymorphic ventricular tachycardia occurred after the CORVERT infusion was stopped but generally not more than 40 minutes after the start of the first infusion. There were, however, instances of recurrent polymorphic VT that occurred about 3 hours after the initial infusion. In two cases, the VT degenerated into VF, requiring immediate defibrillation. Other cases were managed with cardiac pacing and magnesium sulfate infusions. Nonsustained polymorphic ventricular tachycardia occurred in 2.7% of patients and nonsustained monomorphic ventricular tachycardias occurred in 4.9% of the patients (See Adverse Reactions).

Proarrhythmic events must be anticipated. Skilled personnel and proper equipment, including cardiac monitoring equipment, a defibrillator, and medication for treatment of sustained ventricular tachycardia including polymorphic ventricular tachycardia which does not respond to class I antiarrhythmics, must be available during administration of CORVERT. Before treatment with CORVERT, hypokalemia and hypomagnesemia should be corrected to reduce the potential for proarrhythmia. Patients should be observed with continuous ECG monitoring for at least 4 hours following infusion or until QTc has returned to baseline. Longer monitoring is required if any arrhythmic activity is noted.

Management of polymorphic ventricular tachycardia includes discontinuation of ibutilide, correction of electrolyte abnormalities, especially potassium and magnesium, overdrive cardiac pacing, electrical cardioversion, or defibrillation. Pharmacologic therapies include magnesium sulfate infusions. Treatment with anti-arrhythmics should generally be avoided.

PRECAUTIONS

General Precautions:

Antiarrhythmics: Class Ia antiarrhythmic drugs (Vaughan Williams Classification), such as disopyramide, quinidine, and procainamide, and other class III drugs, such as amiodarone and sotalol, should not be given concomitantly with CORVERT Injection or within 4 hours post infusion because of their potential to prolong refractoriness. In the clinical trials, class 1 or other class III antiarrhythmic agents were withheld for 4 hours after dosing, but thereafter were allowed at the physician's discretion.

Other drugs that prolong the QT interval: The potential for proarrhythmia may increase with the administration of CORVERT Injection to patients who are being treated with drugs that prolong the QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and certain antihistamine drugs (H1 receptor antagonists).

Heart Block: Of the 9 (1.5%) ibutilide-treated patients with reports of heart block, 5 had first degree, 3 had second degree, and 1 had complete heart block.

Laboratory Test Interactions: None known.

Drug Interactions:

Digoxin: Supraventricular arrhythmias may mask the cardiotoxicity associated with excessive digoxin levels. Therefore, it is advisable to be particularly cautious in patients whose plasma digoxin levels are above or suspected to be above the usual therapeutic range. Coadministration of digoxin did not have effects on either the safety or efficacy of ibutilide in the clinical trials.

Calcium channel blocking agents: Coadministration of calcium channel blockers did not have any effect on either the safety or efficacy of ibutilide in the clinical trials.

Beta Adrenergic Blocking Agents: Coadministration of beta adrenergic blocking agents did not have any effect on either the safety or efficacy of ibutilide in the clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No animal studies have been conducted to determine the carcinogenic potential of CORVERT Injection; however, it was not ~~mutagenic or~~ genotoxic in a battery of assays including the Ames assay, mammalian cell forward gene mutation assay, unscheduled DNA synthesis assay, and mouse micronucleus assay. Similarly, no drug-related effects on fertility or mating were noted in a reproductive study in rats.

Pregnancy: Pregnancy Category C

CORVERT Injection was teratogenic (adactyly, cleft palate, scoliosis) and embryocidal in reproduction studies in rats. On a mg/m² basis, the "no adverse effect dose" in these animal studies is approximately ~~the same as~~ the maximum recommended human dose; the teratogenic dose was ~~2-to-4~~ times the MRHD on a mg/m² basis. CORVERT should not be administered to a pregnant woman, unless the clinical benefit of the treatment outweighs the potential risk to the fetus.

Nursing Mothers:

The excretion of ibutilide into breast milk has not been studied; accordingly, breastfeeding should be discouraged during therapy with CORVERT.

Pediatric Use:

Clinical trials with CORVERT Injection in patients with atrial fibrillation and atrial flutter did not include anyone under the age of 18. Safety and effectiveness of ibutilide in pediatric patients has not been established

Geriatric Use:

. The mean age of patients in clinical trials was 65. No age-related differences were observed in pharmacokinetic, efficacy, or safety parameters for patients less than 65 compared to patients 65 years and older.

Use in Patients with Hepatic or Renal Dysfunction:

The safety, effectiveness, and pharmacokinetics of CORVERT Injection have not been established in patients with hepatic or renal dysfunction. However, it is unlikely that dosing adjustments would be necessary in patients with compromised renal or hepatic function based on the following considerations: 1) CORVERT Injection is indicated for rapid intravenous therapy (duration ≤ 30 minutes) and is dosed to a known, well-defined pharmacologic action (termination of arrhythmia) or to a maximum of two 10-minute infusions; 2) less than 10% of the dose of CORVERT Injection is excreted unchanged in the urine; ~~3) the hepatic metabolic clearance of ibutilide is perfusion rate limited;~~ and 3) drug distribution appears to be one of the primary mechanisms responsible for termination of the pharmacologic effect. Nonetheless, patients with abnormal liver function should be monitored for [illegible] have taken the 4 hour

by telemetry

In 285 patients with atrial fibrillation or atrial flutter who were treated with CORVERT Injection, the clearance of ibutilide was independent of renal function as measured by creatinine clearance (range 21 to 140 mL/min). assessed renal generally recommend

ADVERSE REACTIONS

CORVERT Injection was generally well tolerated in clinical trials. Of the 586 patients with atrial fibrillation or atrial flutter who received CORVERT Injection in phase II/III studies, 149 (25%) reported medical events related to the cardiovascular system, including sustained polymorphic ventricular tachycardia (1.7%) and nonsustained polymorphic ventricular tachycardia (2.7%).

Other clinically important adverse events with uncertain relationship to CORVERT Injection include the following (0.2% represents 1 patient): sustained monomorphic ventricular tachycardia (0.2%), nonsustained monomorphic ventricular tachycardia (4.9%), AV block (1.5%), bundle branch block (1.9%), ventricular extrasystoles (5.1%), supraventricular extrasystoles (0.9%), hypotension/postural hypotension (2.0%), bradycardia/sinus bradycardia (1.2%), nodal arrhythmia (0.7%), congestive heart failure (0.5%), tachycardia/sinus tachycardia/supraventricular tachycardia (2.7%), idioventricular rhythm (0.2%), syncope (0.3%), and renal failure (0.3%). ~~Although no cause effect~~

mw 97

relationship has been established, the incidence of these events, except for syncope, was greater in the CORVERT Injection group than in the placebo group.

Another adverse reaction that may be associated with the administration of CORVERT Injection was nausea, which occurred with a frequency greater than 1% more in ibutilide-treated patients than those treated with placebo.

The medical events reported for more than 1% of the placebo- and ibutilide-treated patients are shown in the following table.

Treatment-Emergent Medical Events with Frequency of More Than 1% and Higher Than That of Placebo

Event	Placebo N=127		All Ibutilide N=586	
	Patients		Patients	
	n	%	n	%
CARDIOVASCULAR				
Ventricular extrasystoles	1	0.8	30	5.1
Nonsustained monomorphic VT	1	0.8	29	4.9
Nonsustained polymorphic VT	--	--	16	2.7
Hypotension	2	1.6	12	2.0
Bundle branch block	--	--	11	1.9
Sustained polymorphic VT	--	--	10	1.7
AV block	1	0.8	9	1.5
Hypertension	--	--	7	1.2
QT segment prolonged	--	--	7	1.2
Bradycardia	1	0.8	7	1.2
Palpitation	1	0.8	6	1.0
Tachycardia	1	0.8	16	2.7
GASTROINTESTINAL				
Nausea	1	0.8	11	1.9
CENTRAL NERVOUS SYSTEM				
Headache	4	3.1	21	3.6

OVERDOSAGE

Acute Experience in Animals: Acute overdose in animals results in CNS toxicity; notably, CNS depression, rapid gasping breathing, and convulsions. The intravenous median lethal dose in the rat was more than 50 mg/kg which is, on a mg/m^2 basis, at least 250 times the maximum recommended human dose.

Human Experience: In the clinical trials with CORVERT Injection, four patients were unintentionally overdosed. The largest dose was 3.4 mg administered over 15 minutes. One patient (0.025 mg/kg) developed increased ventricular ectopy and monomorphic ventricular tachycardia, another patient (0.032 mg/kg) developed AV block—3rd degree and nonsustained polymorphic VT, and two patients (0.038 and 0.020 mg/kg) had no medical event reports. Based on known pharmacology, the clinical effects of an overdosage with ibutilide could exaggerate the expected prolongation of repolarization seen at usual clinical doses. Medical events (eg, proarrhythmia, AV block) that occur after the overdosage should be treated with measures appropriate for that condition.

DOSAGE AND ADMINISTRATION

The recommended dose based on controlled trials (see Clinical Studies) is outlined in the table below. Ibutilide infusion should be stopped as soon as the presenting arrhythmia is terminated or in the event of sustained or non-sustained ventricular tachycardia, or marked prolongation of QT or QTc.

Recommended Dose of CORVERT™ Injection

Patient Weight	*Initial Infusion (over 10 minutes)*	*Second Infusion*
60 kg (132 lb) or more	*one vial (1 mg ibutilide fumarate)*	*If the arrhythmia does not terminate within 10 minutes after the end of the initial infusion, a second 10-minute infusion of equal strength may be administered* [redacted] 10 minutes after completion of the first infusion.
less than 60 kg (132 lb)	*0.1 mL/kg (0.01 mg/kg ibutilide fumarate)*	

In a trial comparing ibutilide and sotalol (see Clinical Studies), 2 mg ibutilide fumarate administered as a single infusion to patients weighing more than 60 kg was also effective in terminating atrial fibrillation or atrial flutter.

Patients should be observed with continuous ECG monitoring for at least 4 hours following infusion or until QTc has returned to baseline. Longer monitoring is required if any arrhythmic activity is noted. Skilled personnel and proper equipment, such as a defibrillator, and medication for treatment of sustained ventricular tachycardia must be available during administration of CORVERT and subsequent monitoring of the patient.

Dilution: CORVERT Injection may be administered undiluted or diluted in 50 mL of diluent. CORVERT Injection may be added to 0.9% Sodium Chloride Injection or 5% Dextrose Injection before infusion. The contents of one 10-mL vial (0.1 mg/mL) may be added to a 50-mL infusion bag to form an admixture of approximately 0.017 mg/mL ibutilide fumarate. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Compatibility and Stability: The following diluents are compatible with CORVERT Injection (0.1 mg/mL):

5% Dextrose Injection
0.9% Sodium Chloride Injection

The following intravenous solution containers are compatible with admixtures of CORVERT Injection (0.1 mg/mL):

polyvinyl chloride plastic bags
polyolefin bags

Admixtures of the product, with approved diluents, are chemically and physically stable for 24 hours at room temperature (15° to 30°C or 59° to 86°F) and for 48 hours at refrigerated temperatures (2° to 8°C or 36° to 46°F). Strict adherence to the use of aseptic technique during the preparation of the admixture is recommended in order to maintain sterility.

HOW SUPPLIED

CORVERT Injection is supplied as an acetate-buffered isotonic solution at a concentration of 0.1 mg/mL that has been adjusted to approximately pH 4.6 in 10-mL clear glass flip-top vials.

Storage: Store the product at controlled room temperature (20° to 25°C or 68° to 77°F) [see USP]. Keep the product in its original carton until used.

10-mL vial containing 1 mg ibutilide fumarate in 10 mL (0.1 mg/mL) NDC 0009-8794-01

Caution: Federal law prohibits dispensing without prescription.

The Upjohn Company • Kalamazoo, Michigan 49001, USA Revised: December 1995

CSO

OVERVIEW

Willard

DEC 2 8 1995

CSO overview of NDA 20-491
Corvert (ibutilide fumarate) Injection
Updated December 21, 1995

Background

This NDA was submitted by The Upjohn Company on October 27, 1994 for ibutilide injection to be used in the treatment of atrial fibrillation and flutter. The related IND is

At the November 30, 1994 filing meeting, it was determined that the sponsor would need to submit follow-up data beyond the 1.0 hour post-infusion for Study P/7550/0014 and 1.5 hours post-infusion for Study P/7550/0015. At a meeting held with the sponsor December 9, 1994, Dr. Lipicky informed Upjohn that the Division did not believe enough information was present in the application to arrive at a favorable approval decision. In addition, the Division did not accept the limited scope used as the criterion for success. Upjohn was informed of the need to supplement the information in the application with more follow-up data gleaned from the patients charts as the review was underway. This follow-up information was submitted to the application on March 14, 1995.

Originally scheduled to go before the Advisory Committee in June, 1995, Upjohn asked for a delay in order to submit to the application a major amendment (that would move the User Fee Due Date forward 90 days) containing the results of a non-IND international study comparing the safety and efficacy of IV dl-sotalol and IV butilide in terminating atrial flutter and atrial fibrillation. The results of this trial were submitted to the application on August 3, 1995. On October 19, 1995, Corvert Injection was presented to the Cardio-Renal Advisory Committee. The Committee recommended by a unanimous vote that Corvert Injection be approved for marketing.

Group Leader Memorandum

In his December 4, 1995 memorandum, Dr. Chen concludes that ibutilide appears to be an effective and safe treatment for acute termination of atrial flutter/fibrillation. Approval is recommended.

Medical Reviews

Study P/7550/0014:

In his review of Study P/7550/0014 dated September 28, 1995, Dr. Raczkowski states that the generalizeability of this trial is limited to relatively healthy adult male patients with atrial fibrillation or atrial flutter due to the population enrolled. The treatment effect in this trial was probably overestimated somewhat because early relapse rates in ibutilide-treated patients were not systematically recorded. The treatment effect was also probably further overestimated somewhat due to spontaneous conversions that were not measured beyond 70 minutes.

Regarding safety, Dr. Raczkowski writes that treatment with ibutilide was associated with significant toxicity. For marketing approval a judgment must be made whether these safety risks generally exceed the benefits; at least in some patients, at some doses of ibutilide, or

under certain conditions.

Study P/7550/0015:

In her October 12, 1994 review of Study P/7550/0015, Dr. Gordon states that compared to male patients, female patients had a much greater propensity to experience proarrhythmic events. There is some indication that ibutilide causes more headaches and nausea compared to placebo. There is no evidence that ibutilide affects any laboratory value.

The adverse events caused by ibutilide in this study are limited primarily to sustained and nonsustained ventricular tachycardia and almost all of these events occurred while ibutilide was being infused (or shortly after) and while the patient was under close observation.

Dr. Gordon's review concludes that ibutilide is able to terminate atrial flutter and to a lesser extent atrial fibrillation when compared to placebo.

Supporting Studies:

In his reviews dated September 22, 1995, Dr. Chen reviews the supporting efficacy studies. He states that Study P/7550/0003 can be considered as a positive study supporting the short-term effectiveness of ibutilide in termination of atrial flutter. Study P/7550/0005 supports the short-term effectiveness of ibutilide in termination of atrial fibrillation. Study P/7550/004 enrolled only one patient. Little was gained from this study in understanding the pharmacology of ibutilide and no efficacy data were gained. Study P/7550/0018 was an open label pilot study that contributed very little to the development of ibutilide.

Study P/7550/0019 was a comparative study of the safety and efficacy of intravenous ibutilide with intravenous dl-sotalol to terminate the recent onset of atrial flutter or atrial fibrillation in patients who are hemodynamically stable. Dr. Chen writes that since comparative studies are not required for approval and it has not been demonstrated convincingly in this study that the benefit/risk ratio of ibutilide is more favorable than a therapy not yet firmly established, data from this study are probably not useful in the regulatory deliberation of this application.

There are several on-going studies that are included in Dr. Chen's reviews.

Statistical Review

In his review dated September 29, 1995, Dr. Hung states that the ibutilide 1 and 2 mg groups had a significantly greater rate of conversion of atrial arrhythmia than the sotalol group. Ibutilide 2 mg seemed to be more effective than sotalol in all subgroups. Numerically, the superiority of ibutilide 1 mg over sotalol did not seem as apparent in males, patients with AFL/AF, or patients using digitalis within 24 hours prior to infusion as in other subgroups.

All treatment groups showed a significant increase from baseline in QT and QTc intervals at Minute 30, Minute 60, and Hour 7. The ibutilide 1 mg and ibutilide 2 mg groups appeared to have a significantly greater increase in QTc than sotalol. The ibutilide 2 mg group appeared to have a significantly greater increase than the ibutilide 1 mg group.

Pharmacology Review

Dr. Gill-Kumar's October 19, 1995 review states that the non-clinical information submitted does not contraindicate approval of Corvert Injection.

The review does state that if this drug is approved, the sponsor should be required to determine the rate of production of
during storage. The possibility exists that this may also form during storage.

Biopharmaceutical Review

In his August 22, 1995 review, Dr. Marroum wrote that this NDA appears to be acceptable for meeting the biopharmaceutics requirements provided that the comments on pages 9 and 10 of his review are adequately addressed by the sponsor. A letter was drafted for Dr. Lipicky's signature with Dr. Marroum's comments to be sent to the firm. Dr. Lipicky did not sign the letter and stated that these are not issues the sponsor needs to formally address. The sponsor received the biopharmaceutics review in the Advisory Committee package. Dr. Marroum's comments were conveyed to the sponsor in this manner.

Chemistry Review

In her chemistry Review #5 dated September 27, 1995, Ms. Cunningham states that additional information is necessary for Methods Validation. In general, the methods are acceptable for regulatory purposes. The application is acceptable for approval from the chemistry perspective.

Microbiology Review

In his review dated November 21, 1995, Dr. Stinavage recommended approval based on the information supplied by the sponsor.

Environmental Assessment

A FONSI was signed by Dr. Berninger on November 21, 1995 and by Dr. Sager on November 22, 1995.

Summary

1) Labeling issues raised in the biopharmaceutics and pharmacology reviews (Attachments 1 and 2, respectively) have been addressed by Dr. Chen in his marked-up labeling (in the package under Proposed Labeling) and December 8, 1995 memorandum to Dr. Lipicky.

2) Dr. Gill-Kumar's concern raised in her pharmacology review (page 7 under Recommendations) that if the drug is approved the sponsor should be required to determine the rate of production of during storage was addressed in Chemistry Review #1. In her November 29, 1995 addendum to Chemistry Review #1, Ms. Cunningham states that the impurity was identified and the limit set for

decomposition product o be present in the ibutilide fumarate o
Corvert Injection. It is below the mit that could cause safety concerns.

3) For one of the clinical inspection sites only a draft letter to the investigator is available. COMIS has "PENDING" listed for this reason. The draft letter is included in the package under DSI audits.

4) For l clinical site, Dr. Pierce's November 16, 1995 E-mail (in the package under DSI audits) has raised two concerns. In his December 4, 1995 memorandum to Dr. Lipicky, Dr. Chen wrote that the problems at 's site were minor and inconsequential (last sentence on page 1 of the memorandum).

5) CDER Labeling and Nomenclature Committee had a concern that use of the syllables "Cor" and "vert" could constitute puffery in that the name would imply that the drug "converts the heart" to normal sinus rhythm when this may not always be the case. Also, if the product is later approved for another indication, the name could possibly be misleading at some future point in time. In a conversation with Ms. Willard on December 21, 1995, Dr. Wolters stated that the Division has no concerns with the name Corvert.

6) On page 13 of his Team Leader Memo under Conclusions, Dr. Chen wrote that "Further studies to better define the benefit/risk ratio in certain populations (e.g. CABG study) and to explore the higher doses should be a strong post-approval commitment." Dr. Lipicky does not want these studies to be placed in the AP letter as a Phase IV commitment (see page 4 of Dr. Lipicky's transmittal memo).

7) On page 4 of his transmittal memo to Dr. Temple, Dr. Lipicky wrote that he would like to suggest to the sponsor that "randomized, not placebo-controlled clinical trials where the infusion rate of ibutilide is low and the total dose is varied" be conducted. Dr. Lipicky would not like this in the AP letter (see page 4 of Dr. Lipicky's transmittal memo).

Diana M. Willard
Consumer Safety Officer

cc: original file
HFD-110
HFD-111/DWillard

DIVISION DIRECTOR MEMO

Willard

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : DEC 21 1995

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 Temby

SUBJECT: Approval of NDA 20-491, Intravenous Ibutilide, The Upjohn Company

TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

I can add little to the reviews and considerations that are in the attached loose-leaf volumes. Intravenous ibutilide should be approved, all reviewers, the Medical Team Leader, the Cardiovascular and Renal Drugs Advisory Committee, and I each came to that same conclusion. The Division's comments regarding labelling have been sent to Upjohn. Attached is the latest draft from Upjohn, the one identifiable with the label Latest Upjohn Draft (along with an IBM floppy and the label from WordPerfect 5.0). They have incorporated those suggestions made by the Division that they thought were appropriate, amended some of the changes suggested, and await your suggestions. I think that all aspects of labelling are reasonable and that your mark-up could be the basis for "Approved-on-draft."

A brief overview from me seems appropriate, else I am indeed reduced to merely signing leave slips.

The spectrum of atrial fibrillation/flutter varies from the variety that is clearly in the category of paroxysmal supraventricular tachycardia (i.e., relentlessly recurring, most often self limiting, young healthy patients with no organic heart disease) to chronic atrial fibrillation (i.e., patients with mitral stenosis and large left atria, who have had unremitting atrial/flutter fibrillation for many years). At the extremes there is little difficulty deciding what is what. In between, there are frequent ambiguities. Upjohn's clinical development program was intended to enroll patients with chronic atrial fibrillation. To be enrolled in their trials, patients had to have had sustained atrial fibrillation/flutter for at least 3 days and then had to be adequately anticoagulated for 2 weeks (or longer) and had to be in atrial fibrillation/flutter at the time of randomization. That this was chronic atrial fibrillation/flutter, I think, was confirmed by the only 2% spontaneous conversion rate of patients who received placebo.

About half of the patients enrolled had symptoms consistent with symptoms being produced by atrial fibrillation/flutter. It is unfortunate that symptoms post-randomization were not recorded, something the Division overlooked when the protocols were being reviewed. All patients randomized were patients that physicians would attempt to convert from atrial fibrillation/flutter to normal sinus (symptoms or not) is indeed a certainty. The Advisory Committee was specifically asked if the patients enrolled were patients that each of the members of the Advisory Committee would attempt to convert. The Advisory Committee said yes. The studies that support approval of ibutilide were conducted at over 70 tertiary care centers nation-wide. All patients that did not convert (not all, only 98%) during the randomized portion of the trials, were converted by one means or another (usually electroversion). So, the investigators certainly thought the patients randomized should be converted. So, symptomatic or not, the studied population should be considered a population that would ordinarily be considered for the therapy. It is true that high risk patients (except in study 19, ibutilide vs sotalol, where patients were at higher risk than elsewhere) were not enrolled and it is also true that patients with hepatic disease have not been studied at all.

There is no drug that has been approved in the last 50 years for the conversion of chronic atrial fibrillation/flutter on the basis of clinical trial data. Drugs to control ventricular rate in the face of continued atrial fibrillation/flutter have been approved, drugs that lengthen the time between recurrences of paroxysmal atrial fibrillation/flutter have been approved and a single drug that converts paroxysmal atrial tachycardia (PAT) has been approved for that purpose (but it was not successful in the case of atrial fibrillation/flutter; in fact it is a form of diagnostic tool to differentiate PAT from atrial flutter/fibrillation). So, Ibutilide is not another drug, it is the only drug that (if you agree) will be approved in the 20th century for conversion of chronic atrial fibrillation/flutter to normal sinus rhythm.

Clinical Trial Data-Base

Conversion to Normal Sinus Rhythm

From the data of the 5 controlled trials that were submitted (821 randomized patients), one can conclude that ibutilide was unquestionably, statistically significantly (almost all p values less than 0.0004), superior to placebo for converting chronic atrial fibrillation/flutter to normal sinus rhythm, as well as being superior to other drugs (in the sotalol comparison, p less than 0.0001) that are not approved but are used for this purpose (sotalol and procainamide). There is no question, ibutilide converts chronic atrial fibrillation/flutter to normal sinus rhythm and conversion rate is related to the dose of ibutilide infused. That ibutilide is superior to placebo is clear whether one sticks with the prospectively defined endpoint (normal sinus rhythm for any period of time, one hour after the termination of infusion of ibutilide) or any other arbitrary time period (i.e., for at least 24 hours, till the next intervention) that we retrospectively imposed for purposes of understanding the phenomenon.

We know that atrial fibrillation/flutter recurs. Ibutilide is not intended to alter that phenomenon. It is of some importance to note that conversion from atrial fibrillation/flutter from ibutilide does not alter the subsequent course of patients followed for 500 days (e.g., page 16, Dr. Gordon's review of study 015, page 7 of Dr. Chen's secondary review). Of course, this is not a negative statement. Ibutilide should not alter what happens after conversion, and it indeed does not (although it conceivably could have an adverse long-term consequence, or make patient's more difficult to manage; it does not). About 50% of patients converted from atrial fibrillation/flutter to normal sinus return to atrial fibrillation/flutter by 100 days, irrespective of the mode (ibutilide, spontaneous, electroversion) of conversion.

Proarrhythmic Effects

Ibutilide is also easily distinguishable from placebo on the basis of new ventricular arrhythmias, AV-block, and lengthening of QT interval (corrected, of course). Ventricular tachycardias, sustained and non-sustained were the principal arrhythmias noted and Torsades de Pointe, being the ventricular arrythmia that one would expect from a Class III agent was prominently noted. Both the degree of lengthening of the QT_c and the incidence of Torsades de Pointe were related to the dose of ibutilide infused, more lengthening and greater incidence, the higher the dose. All told there was a 2.4 % incidence of sustained polymorphic ventricular tachycardia (Torsades), but the total arrythmia incidence approached 23% (page 13 of Dr. Chen's secondary review).

Patients experienced ventricular arrhythmias (including Torsades) whether or not they converted from atrial fibrillation/flutter to normal sinus, or stayed in atrial fibrillation/flutter. All patients were able to managed satisfactorily, being in the hospital and in a setting where resuscitation equipment and trained personnel were available. There were no deaths observed during the controlled-trials in any group (placebo or ibutilide treated) while in hospital. The patient population was at some risk, during the 3 month follow-up from the time of conversion, there was about a 3.5% incidence of death. But, again, none during the trials nor during the hospitalization that was required to enter the trials.

Other Things to Consider

The table on page 10 of Dr. Chen's review is a reasonable summary of all the side effects that might be relevant. Ibutilide is relatively hemodynamically benign. Protocol 19 (the sotalol comparator), brought no new side effects to light and there were "sicker" patients enrolled in that trial.

Ibutilide is a teratogen, as well as being embryocidal. Appropriate labelling has been drafted by Drs. Gill-Kumar and Resnick, in this regard.

Miscellaneous Random Thoughts

The pharmacokinetics of ibutilide are well described (see page 25 of the Upjohn notebook distributed to the Advisory Committee for the Advisory Committee meeting). Ibutilide is optically active (existing as a + and - enantiomer, it is metabolized (by oxidation, enzyme not identified despite in-vitro liver microsome studies) and the metabolites are eliminated by the kidney. The enantiomers are both active and the metabolites by and large are not. Both enantiomers are handled about the same when introduced into the body, both enantiomers are controlled for during manufacture.

It is, I think important to note the three distinct phases (without biological attribution to the phases), with the terminal phase having a long (hours) half life. Also of note is that the volume of distribution is large (20 Liters), compared to plasma volume (about 4 liters). So ibutilide distributes to tissues, and dose so fast, half life in minutes.

A 10 minute infusion of ibutilide, considering its kinetic properties, is much like a bolus injection of ibutilide. The plasma concentration being nowhere close to steady state at the end of a 10 minute infusion. In this regard it is important, I think, to note that only about 50 % of patients who converted from atrial fibrillation/flutter to normal sinus, converted during the 10 minute ibutilide infusion. The remaining 50 % converting at some later time, up to 30 minutes after the termination of the ibutilide infusion.

Similarly, less than 20 % of patients who developed ventricular tachycardia, developed the ventricular tachycardia during the 10 minute ibutilide infusion. The remainder taking up to 40 to 50 minutes after the 10 minute ibutilide infusion was stopped.

For these phenomenological reasons, I think the extensive and elegant analysis performed by the sponsor attempting to relate the plasma concentrations of ibutilide to the effects observed were to no avail. It seems reasonably clear that the effects of ibutilide (either conversion, or ventricular tachycardia) can occur when the plasma concentration is falling. So, if the drug-receptor interaction is dependent on the concentration of ibutilide (and I think that is a reasonable expectation), the concentration that needs to be related is not the plasma concentration; rather some compartment (for lack of a better term) outside of the plasma (the myocardium would be a reasonable assumption).

So, a question then would be, is the concentration outside the myocardial cell or inside the myocardial cell the critical determinant. Unpublished observations from my laboratory, are that when ibutilide is applied to the inside of the squid giant axon (by internal perfusion) and the concentration of ibutilide in the bulk phase salt water outside the axon is zero (by superfusion), ibutilide blocks both the voltage-dependent sodium and voltage-dependent potassium current of the squid axon. So, that is evidence that the internal concentration of ibutilide can be a determinant (but, at present, I have no experiments that show that the internal concentration of ibutilide is the only determinant). Of incidental note is that both the enantiomers also block sodium and potassium currents in the perfused squid axon.

The available data then are consistent with (but do not prove) the following:

1) Ibutilide exerts its electrophysiological effects from the inside surface of the membrane.
2) The principal determinant of the electrophysiological effects is the concentration of ibutilide inside the myocardial cell.
3) Following a 10 minute intravenous infusion of ibutilide, as the plasma concentration of ibutilide is falling, the tissue concentration is still rising.
4) If one wanted to get a feeling for the relationship between concentration of ibutilide and its effects, one could use the plasma compartment as the measurement of concentration, provided that the infusion was to steady-state (an infusion much longer than 10 minutes).

The available data are also consistent with (but do not prove) that the proarrythmic effect of ibutilide has a dose-response that is to the left of the dose-response for conversion. However, either the ibutilide is less effective at producing proarrythmias than it is at converting or the dose-response for proarrythmia is shallower than that for conversion. Either way, one must experience some proarrythmic effect (from the point of view of the incidence in a population treated) if one is to obtain conversion.

I think this is testable, by conducting randomized, not placebo-controlled, clinical trials where the infusion rate of ibutilide is low (say over a 4 hour period) and the total dose (over that 4 hour period) is varied. This could, at the least, provide insight into whether it would advantageous to have a different dosing schedule than we are approving here. I would like to suggest this to the company.

cc
Orig.
HFD-110
HFD-110/Project Manager
HFD-110/RLipicky

↑
This should not be in a letter.

Dr. Chen's suggestions at the end of his review need not (should not) be in a letter.

Lipicky

MEDICAL

OFFICER'S

REVIEW

D. Willard

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 12/04/95

From: Shaw T. Chen, M.D., Ph.D., Medical Group Leader, HFD-110
Through: Director, Division of Cardiorenal Drug Products, HFD-110
To: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: NDA 20-491, COVERT Injection (Ibutilide fumarate injection) for Termination of Atrial Flutter/Fibrillation, Approvability

OVERVIEW

This memorandum and the attached material constitute the Division's recommendation that NDA 20-491, Covert Injection (ibutilide fumarate injection) be approved for acute termination of atrial flutter/fibrillation (AFL/AF).

Clinical Sections of the NDA were reviewed jointly by the following team:

Clinical Pharmacology:	Dr. Raczkowski
Efficacy:	Dr. Gordon (Study 15), Dr. Raczkowski (Study 14), Dr. Chen (Supporting Studies)
Safety:	Dr. Gordon
Statistics:	Dr. Hung

As of the date of this memo, the chemistry, biopharmaceutical, pharmacological, microbiology and statistical reviews have been completed. There are no major, unresolved preclinical issues which may affect the action recommended. Related labeling have been suitably edited.

Ibutilide fumarate is a racemic mixture containing equal amount of two enantiomers, which have slightly different pharmacology. Ibutilide, referring to the racemic in this memo, is a new antiarrhythmic agent with predominantly class III electrophysiologic properties. It was developed to minimize undesirable properties of current therapies, such as negative inotropic effect, class I activities, or interaction with autonomic nervous systems. However, although ibutilide may have distinctive in vitro electrophysiologic properties (see Clinical Pharmacology review), its safety profile is indistinguishable from those expected in similar antiarrhythmic drugs. While ibutilide is more effective than placebo in termination of atrial flutter/ fibrillation, whether there is a real patient benefit of such use may not be easy to determine from the data submitted. Nevertheless, the need of converting atrial arrhythmias in certain clinical settings probably justifies the risk, and the use of ibutilide in some, although not all, of these conditions has been studied in clinical trials. Approval can therefore be entertained, as also recommended by the Advisory Committee at the meeting of 10/19/95.

The adverse experiences in the NDA have been amended with the First Safety Updates of 02/27/95. Selected major trials have been inspected, and there was no major deficiency which may invalidate the results (see DSI report, problems at [redacted] were minor and inconsequential).

PRECLINICAL EVALUATIONS

Chemistry/Microbiology

While additional information on method validation was requested by the chemistry reviewer, manufacturing and control processes have passed the Agency's inspection successfully. The microbiologic reviewer's concerns regarding sterilization (Review of 4/13/95) have been satisfactorily addressed by the sponsor. There are no outstanding approvable issues which may affect the recommended regulatory action.

Preclinical Pharmacology

Ibutilide has been adequately characterized with respect to its preclinical pharmacokinetic and pharmacodynamic properties. There are no unresolved issues related to animal toxicity or carcinogenicity which may change approvability of the drug.

In her pharmacology review, Dr. Gill-Kumar was concerned that the degradation product on storage had a [redacted] than the parent drug, but if the extent of decomposition remains below [redacted] there will be no safety problem. The stability of the drug on storage was indeed acceptable according to the chemistry reviewer (Addendum to Chemistry Review). Thus additional data requested by Dr. Gill-Kumar are not needed.

Changes in proposed labeling, as recommended by the pharmacology reviewers, are summarized and commented below. They have been adopted with minor modification.

- Hemodynamic effects in animal (Page 2) were measured in a poorly designed study, thus have been deleted from the sponsor's draft labeling. Human data are sufficient.
- As a potential teratogen, the no-effect dose for ibutilide in rats, on a mg/M^2 basis, is close to that of maximum recommended human dose. This statement was added to the section on *Pregnancy, Labor and Delivery* (Page 5).
- Overdose experiences in animal (Page 9) was described for rats only, as the mouse study was small and did not use the same formulation. Doses should also be expressed in mg/M^2 for comparison between animal and human data.

CLINICAL PHARMACOLOGY

Pharmacokinetics/Pharmacodynamics

The **pharmacokinetics** of iv ibutilide has been well characterized in both normal subjects and patients with atrial fibrillation/flutter. Since neither dose nor plasma drug levels were clearly correlated with efficacy or safety (at least for the doses used in the clinical studies), detailed description of pharmacokinetic parameters has little bearing on the clinical use of ibutilide and dosage/administration of ibutilide are to be titrated for termination of arrhythmia. Furthermore, pharmacokinetic properties of ibutilide were not dependent on patient demographics, past medical histories, or concomitant medications.

Several studies described the **pharmacodynamics** of iv ibutilide. Results of electrophysiologic measurements were consistent with the sponsor's claim that ibutilide is an antiarrhythmic agent with Class III activities. In contrast to clinical endpoints, prolongation in QT intervals was more sensitive to dose, infusion rates, plasma concentrations, and patient age. However, it was not much useful as a titration endpoint for efficacy or safety purposes. Ibutilide has no appreciable inotropic effects

Biopharmaceutics

The application is approvable from the perspectives of biopharmaceutics. The development program of ibutilide suffered from the minor problems of the small sample size in radioisotope ADME study, inadequate sampling for population analysis, and high residual variability in the sponsor's two-compartment modeling.

There were no systematic studies in the renal or hepatic impaired patients. However, renal clearance was not a determining factor in the initial distribution phase and no significant difference was observed in the 24 patients with renal dysfunction (serum creatinine above 2.0) in clinical trials. Total lack of data in patients with hepatic impairment (one patient) may be more of a labeling concern, but the drug is intended to be used as an acute, iv treatment. Accumulation with one-time use is not a concern and the concentration of active metabolite constitutes only 10% of parent drug. Besides, there was no correlation between blood level and efficacy or safety and the infusion will be titrated for arrhythmia termination. Dosage adjustments for patients with hepatic/renal impairment are not necessary and further post-marketing studies are not required.

The changes in labeling as proposed by Dr. Marroum in his biopharmaceutical review (Pages 9 and 10) are all appropriate and have been incorporated in the marked-up draft.

CLINICAL: EFFICACY

Clinical Trials Supporting Approval

Ibutilide has been evaluated for acute conversion of atrial flutter/fibrillation in five completed studies[1]. Of the total 821 patients enrolled in these studies, 339 were treated with ibutilide and 127 with placebo in two double-blind, parallel placebo controlled studies (Studies 14 and 15), which constitute the major support for the claim. The sponsor also submitted in an amendment results of another completed trial (Study 19), a sotalol controlled, 319-patient study (ibutilide 211, sotalol 108). The remaining 36 patients received both ibutilide and placebo in two open label pilot dose-ranging studies (Studies 3 and 5).

Study	Doses[2]	Administration	Patients
0014	0.005, 0.010 0.015, 0.025 mg/kg[3]	10 min single dose infusion	100 AFL, 100 AF (approx 40/group)
0015	1.0 mg followed by 0.5 mg or 1.0 mg	up to two 10 min infusions	133 AFL, 133 AF (approx 89/group)
0019	1 mg or 2 mg	up to one 10 min infusion	59 AFL, 260 AF (approx 106/group)
0003	0.005+0.01+0.02 mg/kg	up to three 10 min infusions	17 AFL
0005	(same as Study 0003)	up to three 10 min infusions	19 AF

The atrial arrhythmias evaluated in these efficacy trials are of relatively recent onset (durations of 3 hours to 45 or 90 days). Patients were hemodynamically stable, adequately anti-coagulated, and may be asymptomatic (about half of all patients, 59% in Study 14 and 35% in Study 15). Specific cardiovascular conditions such as symptomatic heart failure, recent MI (in 1-3 months) and angina (Study 14 only) were excluded from the two large placebo-controlled trials, but majority of patients had left atrial enlargement, decreased left ventricular ejection fraction, or history of valvular diseases. Patients in the sotalol-controlled study (nearly half of patients in Study 19) were more symptomatic from hypertension, MI, coronary bypass surgery and heart failure. In all five studies, actual doses of ibutilide administered to each patient were variable, since infusion of ibutilide was discontinued whenever the atrial arrhythmia was terminated (but not necessarily converted to normal sinus rhythm). The primary efficacy endpoint in these studies was termination of AFL/AF, for any length of time, during or within 1 hour following completed infusion of randomized dose. After this evaluation period, cardiac rhythms were monitored by telemetry for up to 24 hours. As pointed out by Dr. Hung, there is no discrepancy between

[1] Four additional completed or terminated studies were also listed as supporting efficacy trials in NDA. Two (Studies 7,13) were pharmacodynamic studies in non-AF/AFL patients and had no efficacy data. The other two (Studies 4, 18) were open label and terminated after total enrollment of 3 patients. Three other large trials (Studies 17, 20, 21) are not yet completed (see Medical Review of Supporting Trials for protocols).

[2] For patients weighing less than 60 kg in Study 15, doses were based on body weight; 1.0 mg infusion was replaced with 0.01 mg/kg and 0.5 mg infusion with 0.005 mg/kg.

[3] Not all dose groups were studied concurrently, but not an issue for short-term treatments.

per-protocol (evaluable patients, primary analysis) and intent-to-treat (all randomized) analyses, and only results of the latter are summarized below. Results of the two smaller pilot studies (Studies 3 and 5) are in general consistent with that of the two major placebo-controlled trials and are referred to the primary review.

Overall Treatment Effects vs Placebo

The **primary efficacy** data in Table 1 below demonstrate that ibutilide, at 0.010-0.025 mg/kg[4], administered either as one single 10 min infusion or in two divided doses over 30 minutes, was consistently and significantly more effective than placebo in termination of AFL/AF (data from Statistical Review). At this dose range, the placebo-subtracted net response rates ranged from 31 to 46%, reaching a plateau around 0.015 mg/kg. Treatment effect was not significant for the 0.005 mg/kg dose by pair-wise comparison.

Table 1: All Patients;	Rate of conversion from AF/AFL; all randomized				
2	12	33	45	48	<0.0001
2			45	45	<0.0001

Ibutilide was significantly effective within both the AFL and AF strata, but not surprisingly, success rates were lower in the latter:

Table 2: AFL Patients;	Rate of conversion from AFL; all randomized				
0	14	30	58	55	<0.0001
2			52	65	<0.0001

Table 3: AF Patients;	Rate of conversion from AF; all randomized				
5	10	35	32	40	0.025
2			38	25	<0.0001

For arrhythmia termination, total dosage was probably more important than the number of infusions. Despit extensive discussion in the NDA, whether two infusions were more effective than one infusion in Study 15 could not be determined, since patients were observed for only ten minutes before the second infusion.

[4] Fixed doses of 1.0-2.0 mg in Study 15 are equivalent to 0.0125-0.025 mg/kg, based on mean body weight of 80 kg (Table 8.F.3 of NDA).

Dose Response

Due to safety concerns of QTc prolongation and proarrhythmia, doses higher than 0.025 mg/kg was not studied. Although responses to the effective doses of 0.010-0.025 mg/kg were indistinguishable in the two major trials (Studies 14 and 15), further increase in dose may still have additional improvement in response. Thus the high dose studied may not be the optimal effective dose and the dose-response relationship[5] has not been completely delineated. While available dose-response data are marginally adequate for prescription instruction, additional dose-range studies should be considered, as, despite the theoretical concern, proarrhythmias (VT's) have not been shown to be dose-related in the clinical trials (see also *Proarrhythmias* in *Safety*). In the two major placebo-controlled studies, treatment success was not related to plasma concentration of ibutilide.

Time-Effect Relationship

For patients responded to treatment as prospectively defined, termination of arrhythmia occurred with means of 18-20 minutes from the beginning of infusion in study 14, with 70% within 20 minutes and little variation for flutter or fibrillation. Onset of treatment effect was slightly later (23-30 minutes) in Study 15 (48% within 20 minutes), when dosing was prolonged in two infusions for some patients.

Concerned that conversion for 1-2 hrs, as originally defined endpoint, may be too short-lived and not clinically meaningful, the primary medical/statistical reviewers also examined the number of patients who remained in converted rhythm at the end of 24 hrs[6]. The success rates for this post hoc endpoint were slightly lower, but remained statistically significant (except for a marginal p value, 0.095, for the atrial fibrillation stratum in Study 14, see Statistical Review by Dr. Hung):

Table 4: % of all randomized remained out of AF/AFL at Hour 24

2	12	28	42	43	<0.0001
2			34	37	<0.0001

During the first 24 hrs, while a majority of patients who failed the study drugs had their arrhythmias terminated by other means (53-58% of treatment failures, see Management of Treatment Failures in Safety), a small number converted spontaneously (5% of failures). As noted by Dr. Raczkowski in his review, because of the additional interventions provided, true rate of spontaneous conversion could not be determined and the real treatment effect in the first 24 hours was probably different from that observed in the

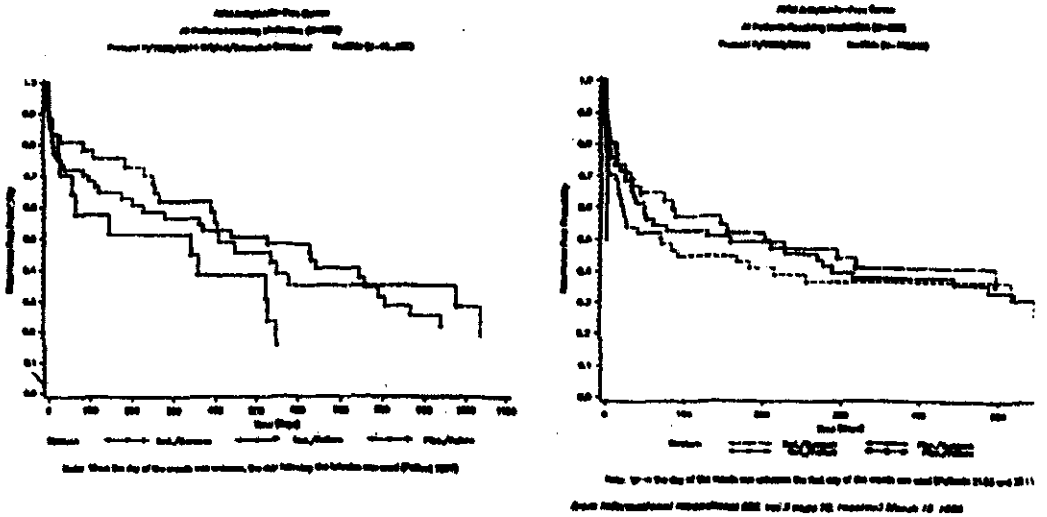
5 Range of actual doses delivered was probably narrower than the nominal randomized dose, since duration of infusion for the highest dose in Study 14 was significantly shorter than lower doses (see Primary Review).

6 Arrhythmia status at Hour 24 was prospectively specified in Study 15 and the results were consistent with the reviewers' analyses. The numbers were slightly different (by 1-2 patients) in the Statistical and the Medical Reviews, due to intent-to-treat and per-protocol analyses.

clinical trials. However, the spontaneous conversion rate could not be high, since 35-40% of failures remained in atrial fibrillation/flutter at Hour 24 despite other therapies), and adjustment due to this uncertainty was most likely insignificant.

Despite the problems in study design and data collection, the magnitude of the effect and the consistency between studies suggested that the ibutilide treatment effect lasted for at least 24 hrs.

For long-term effect beyond the 24 hr period, it is not clear how much longer the patients should remain free of arrhythmia after short-term, iv conversion for ibutilide to be considered clinically efficacious. Retrospectively collected information suggested that by 400-500 days, approximately 40-50 % of all patients remained recurrence free (see the Kaplan-Meier curves below, note that the two figures have different scale for the time, or horizontal axis). Differences between treatment groups were small and inconsistent, favoring ibutilide in Study 14 (left figure) but not in Study 15 (right figure). As pointed out in the Primary Medical Reviews, these post hoc data may not be reliable and should be viewed with reservation. Confounded by other interventions during long-term follow-up, whether patients remain arrhythmia-free months later could not be attributed to ibutilide therapy and was more of a safety than efficacy question (see below, Management of Treatment Failure in Safety).



For details of these figures, see primary medical reviews (page 23 for Study 14 and Page 16 for Study 15).

Responses in Subgroups

Ibutilide was equally effective in patients below and above 65 years of age and in male and female, but female patients were under-represented in the major studies (16%).

While there was no interaction between dose and **duration of pre-existing atrial arrhythmias**, success rates appeared to be higher in arrhythmia of shorter duration. This was suggested by the two pilot studies (Studies 3 and 5) and confirmed in the two major trials (although less evident in Study 15). Mean durations of arrhythmias were 18 days for success vs 27 days for failure in Study 14 (outliers truncated at 90 days, similar difference

between fibrillation and flutter), and 12 days (success) vs 15 days (failure) in Study 15 (with a reversed relationship for fibrillation). Using 30 days as an arbitrary cut-off, difference in success rates were 42% (acute) vs 16% (chronic) in Study 14 and 50% vs 31% in Study 15. Labeling should reflect this finding to discourage over-use in patients not likely to respond.

There was no evidence in the clinical trials suggesting that treatment success was related to left atrial size, left ventricular ejection fraction, or presence of valvular heart disease. Dr. Raczkowski was concerned (see his review) that severity of patients' cardiac diseases may be over-stated by these parameters and the need for terminating atrial fibrillation/flutter was not as apparent in Study 14. Specifically, patients with more severe heart failure or significant conduction abnormalities were not included in the major trials. Nevertheless, there were evidence that anti-arrhythmic therapies were considered clinically indicated by the investigators and not just because the patients were recruited for the ibutilide studies, as 90 % or more of patients who did not respond to the study drugs were treated subsequently with other modalities for their atrial arrhythmias (see Management of Treatment Failure in Safety). Although QTc prolongation increases with dose, it could not predict treatment effect and is therefore not a clinically useful endpoint for efficacy dose-titration (see below for safety).

Treatment effects of ibutilide in patients with **hepatic** or **renal** impairment have not been evaluated systematically in any of the clinical trials. While there was only one patient with hepatic failure in the clinical trials, experiences in 24 patients with serum creatinine above 2.0 did not suggest any distinguishable qualitative changes in pharmacodynamics by the disease state. As noted above in Biopharmaceutics, dosage adjustments due to kinetic variations in these subgroups are not required.

There were no **interactions** between ibutilide dose and concurrent use of digoxin, beta blockers or calcium antagonists, and response to ibutilide was probably not related to the use of these common cardiovascular medications. However, in Study 14, patients taking digoxin or betablockers seemed to have higher success rate of ibutilide treatment. As the effect was not seen in Study 15 and was just one of the multiple comparisons, the finding was inconclusive and labeling should remain silent in this respect.

Comparison with other Antiarrhythmics

Ibutilide (1 or 2 mg) appeared to be more effective in termination of atrial flutter/fibrillation than sotalol (1.5 mg/kg) in a large, direct comparison study (no placebo control, Study 19). This study was very similar in design to the two major efficacy trials (see comments above), except for a sicker patients group (more inclusive with heart failure, MI and coronary artery surgery patients) and collection of Holter recordings. Number and percentage of patients whose atrial arrhythmias were terminated for any length of time within one hour of starting infusion (treatment success) are shown below:

Arrhythmia	ibutilide 1 mg	ibutilide 2 mg	sotalol	chi-square p
All (n=319)	28 (27%)	52 (48%)	13 (12%)	<0.0001
atrial flutter (59)	9 (53%)	14 (70%)	4 (18%)	0.0027
atrial fib (260)	19 (22%)	38 (43%)	9 (10%)	<0.0001

However, aside from the problem of suboptimal dosage for sotalol, the relative benefit/risk ratio of ibutilide may not sound so favorable as the response rates suggest. Compared to that observed in the sotalol group, hypotension was not as common in the ibutilide-treated patients but proarrhythmia was a more serious and frequent safety concern (see primary medical review). It should be emphasized that, despite its common off-label use, sotalol has not been approved for acute termination of atrial flutter/fibrillation. Efficacy and safety of ibutilide relative to that of placebo cannot be inferred from this active-controlled study.

Ibutilide appeared to be more effective than procainamide, a commonly used agent in practice. In a small study (two groups of 30 patients each), success rates were 42-47% for ibutilide vs 0-9% for procainamide (ancillary of Study 14). Without submitting a full report to the Agency for review, the sponsor also presented the following preliminary report of Study 21, a 127 patient procainamide controlled study, at the Advisory Committee meeting of 10/19/95:

Arrhythmia	ibutilide N=62 1-2 mg	procainamide N=65 400-1200 mg	chi-square p
All (n=127)	53%	17%	
atrial flutter (41)	76% of n=17	13% of n=24	<0.003
atrial fib (86)	51% of n=45	20% of n=41	<0.003

Again, there are no adequate and well-controlled trials to support the use of procainamide for conversion of atrial flutter/fibrillation and this indication of procainamide has never been approved.

While comparison with agents of unproven efficacy was neither useful nor required for approval, the experience of ibutilide in the sotalol study may offer some support for the claim and may be included in the labeling (on clinical trials)[7]. As noted above, patients in the sotalol studies were more symptomatic and less exclusive than that of major placebo controlled trials. Treatment effects of ibutilide in such patients (approximately 40-50% response) were very similar to that observed in the placebo controlled trials, which should provide some assurance about the clinical benefit of ibutilide in patients whose need for termination of atrial arrhythmias was better justified.

CLINICAL: SAFETY

Database

The database appeared to be adequate for assessment of safety for short-term use[8] of ibutilide , which includes cumulative experiences of nearly 1,400 patients/subjects as of the Safety Addendum. Of the total, 88 were normal subjects in Phase I studies, 679 were treated with ibutilide and 247 were given control agents (139 placebo and 108 sotalol) for conversion of atrial flutter/fibrillation. Some of the remaining 382 patients in the three ongoing trials also received ibutilide for the atrial arrhythmias, but the exact number is unknown since the study drug assignments are still blinded.

[7] Results of the procainamide study (Study 21) should be reviewed before described in the labeling.

[8] As 10-20 minute iv infusion for acute treatment. Repeated use in the same patient was not evaluated.

The comparative safety analyses were based on the experiences of 502 patients (375 ibutilide, 127 placebo)[9]. A great majority were from two completed, double-blinded, placebo-controlled efficacy trials (Studies 14 and 15), but the ibutilide patients also include 36 from two open-label and baseline controlled studies (3 and 5). The demographics of these patients were essentially those of Studies 14 and 15, i.e., mostly white (78%) and male (84%). For ibutilide patients, more than half received total dose greater than 1.25 mg.

Data from the first 120-day Safety Update (2/28/95) and from the Safety Addendum of 8/4/95 have been incorporated into the following summary.

Comparative Experiences

As pointed out by Dr. Gordon in her Safety Review, while there was little difference between groups in adverse experiences of other organ systems, cardiovascular events were 3 times as frequent in ibutilide as in placebo-treated patients.

The percentage of patients who reported **any adverse event** was slightly higher in ibutilide than placebo group (38 vs 30%). Among the adverse experiences, the following were more common (by 1% or more) for ibutilide than placebo with incidence of ≥ 1% (rank by difference between groups):

ADE	Ibutilide(%) N=375	Placebo(%) N=127
VT, NS, poly[10]	4.0	0.0
VT, NS, mono[10]	4.0	0.8
extrasystole[11]	3.5	0.8
VT, sustained, poly[10]	2.4	0.0
nausea	2.7	0.8
AV block, all degrees	2.7	0.8
headache	4.8	3.1
hypotension[12]	2.9	1.6
hypertension	1.3	0.0

As expected, the most commonly reported adverse events were related to ibutilide's pharmacological effects and in general, these events were more common in patients who received 0.75mg or higher, but the frequency did not increase further with dose.

Experiences in about one-seventh of the patients who reported an adverse event were considered **serious** (5.3% ibutilide, 1.6% placebo, Safety Review Page 27). Except for

9 Data from Studies 7 and 13 were included in the Safety Update analyses (increased to 465 ibutilide and 139 placebo patients). However, subjects in these studies did not have atrial arrhythmias, the disease to be treated. Adding these patients but did not change overall profile (see below on Overall Exposure).

10 VT=ventricular tachycardia, NS=non-sustained, mono=monomorphic. poly=polymorphic.

11 Ventricular, including bigeminy.

12 Including postural.

proarrhythmia-related experiences, these predominantly cardiovascular events were reported in patients with complicated cardiac diseases and the causal relationships were difficult to determine (see case descriptions on Page 28-30, 33 of Safety Review). The imbalance in frequencies between groups was mostly due to proarrhythmia events and the absolute number of non-arrhythmic cases was too small to serve as a signal of any rare, serious safety concerns. The only case of death reported in the controlled studies was a placebo-treated patient.

Approximately 6% of all ibutilide treated patients in these controlled studies were **withdrawn** from the study drug (vs 0% in placebo) for adverse effects. The small numbers did not suggest any dose relationship (Safety Review, Page 34) and all discontinuations were due to cardiovascular events (mostly proarrhythmias, see below and Safety Review, Pages 35). As pointed out by Dr. Gordon, the above rate of withdrawal due to adverse events may be under-estimated. Since ibutilide dosing was of short duration, there was probably not enough time for registering some withdrawal-leading complaints before many patients completed the infusions.

Of 375 patients who had routine clinical **laboratory** evaluations, abnormal findings were scattered, non-serious, and without a clear trend or causality (see Safety Review). Other than two ibutilide patients who had substantial treatment-emergent increases in serum creatinine (from 1.4 and 1.8 to 2.3 and 3.1 mg/dl, respectively), laboratory data for individual patients were largely unremarkable.

Relative to **other antiarrhythmic agents** commonly used (off-label) in termination of atrial arrhythmias, ibutilide was more tolerable with respect to hemodynamics (hypotension due to sotalol or procainamide) and other known non-cardiovascular adverse experiences (of procainamide)[13]. However, proarrhythmia or other rhythm disturbances were more frequent in ibutilide than sotalol (twice as common, see below and primary medical review of Study 19) or procainamide[13] treated patients. Although neither sotalol nor procainamide has been approved for the same indication (termination of atrial flutter/fibrillation), because of their wide use, safety of ibutilide relative to these two agents may be described in the labeling (clinical trials)[13].

Overall Exposures

Due to completion of various studies at different times and sequential submission of safety updates and study reports, adverse experiences in the following databases have been examined by Dr. Gordon in her review:

Total Ibutilide-treated patients	Additional Studies*,[14] included	Adverse Experience Tables in Safety Reviews (Page No.)
465	7, 13	20 (all events), 32 (serious), 36 (withdrawal)
586 (All Patients)	19	(Addendum) 15 &16
679 (All Subjects)	4, 7, 13, 18, 19	(Addendum) 17 (events), 19 (serious)

* In addition to 4 controlled studies (14, 15, 3, 5). Footnote 14 on next page

[13] From sponsor's presentation of Study 21 (procainamide study) at the Advisory Committee meeting. No study report has been submitted and reviewed yet.

Of these, the "All Patients" database of 586 patients was the most representative of the total ibutilide exposure in *patients with atrial flutter/fibrillation.* In general, compared with the experience in controlled trials, there were no significant, qualitative differences in the total exposures in terms of the frequency or its variation with dose. There was no rare, unexpected, or unusually severe adverse experience that was reported only in the larger databases. Some minor adjustments of the incidences in the overall populations are summarized as follows:

ADE	Controlled(%) N=375	All Patients(%) N=586	All Subjects(%) N=679
VT, NS, poly[10]	4.0	2.7	2.7
VT, NS, mono[10]	4.0	4.9	4.6
extrasystole[11]	3.5	5.3	4.6
VT, sustained, poly[10]	2.4	1.7	1.8
nausea	2.7	1.9	1.9
AV block, all degrees	2.7	1.9	1.8
headache	4.8	3.6	4.0
hypotension[12]	2.9	2.0	2.4
hypertension	1.3	1.2	1.0

Other complaints notable only in all patients/subjects were infrequent and not clinically serious, which included:

ADE	All Patients(%) N=586	All Subjects(%) N=679
tachycardia	2.7	2.1
bundle branch block	1.9	1.9
QT prolongation	1.2	1.2
bradycardia	1.2	1.0
chest pain	--	2.1
local pain	--	1.3
palpitation	--	1.0

Pattern and frequency of serious experiences in the "All Subjects" database (Addendum to Safety Review, Page 19) were similar to that of the controlled trials (Safety Review Page 27). Of 679 patients/subjects who received ibutilide, one death occurred 20 days after treatment with ibutilide and was attributed to sepsis and pneumonia. Ibutilide had no significant effect on blood pressures.

14 Studies 7 and 13 were not on patients with atrial arrhythmias. Study 19 was sotalol controlled, no placebo. Studies 4 and 18 were terminated with total of 3 patients enrolled. Description of adverse events in unblinded, on-going studies (17, 20,21) is referred to Dr. Gordon's review. These additional studies were not placebo-controlled, thus no accumulated comparison with placebo was provided in the previous section on Comparative Experiences.

Overall safety experiences were not significantly influenced by patient age and sex. There were small differences in some of the studies which may suggest a higher risk of proarrhythmias for female than male patients (see below on proarrhythmias), but the finding was inconsistent and appeared to be limited to non-sustained VTs. Patients with disease states which may affect the pharmacokinetics of ibutilide infusion have not been studied systematically in the development program, thus safety of ibutilide in these special patients must rely on inference from the drug clearance data (see Clinical Pharmacology Review). Recent use of some cardiovascular drugs probably did not change the risk of proarrhythmia (see below), but other adverse effects due to drug interaction have not been fully investigated.

Proarrhythmias

Not a surprising finding, treatment-associated arrhythmias were more common in the ibutilide than the placebo group. In controlled studies, the incidence of **all arrhythmias** was **22.9%** in 375 **ibutilide** patients vs **4.7%** of 127 **placebo** patients, with little dependence on the dose (Table on Page 20 of Safety Review). Although **ventricular tachycardia** (VT) was less frequent, it remained as the most serious safety concern of i.v. ibutilide in these patients:

	0.0	2.4	1.7	1.8
	0.0	4.0	2.7	2.7
	0.0	0.3	0.2	0.7
	0.8	4.0	4.9	4.6

sust=sustained, non-sus=non-sustained, poly=polymorphic, mono=monomorphic.

In the "all-patients" database (N=586), the 95% confidence intervals were 0.7-2.7% for sustained polymorphic, 1.3-3.9% for nonsustained polymorphic and 3.2-6.6% for non-sustained monomorphic VTs. Again, in this database, incidences of VTs were not dose-related (most likely due to small number of events and lack of power), except for non-sustained, monomorphic VT (from Table on Page 16 of Review on Safety Addendum).

	1.3	2.0	1.6
	3.9	3.0	2.3
	0.0	0.5	0.0
	1.3	4.9	5.9

In the only study that using Holter monitoring (Study 19, sotalol controlled), additional episodes of VTs were identified on the recordings (see MOR page 7) but not reported as medical events. However, blinded readings of the same tapes by a panel of cardiologists were variable and there were no baseline data. Thus it is not clear how many of these extra

cases were treatment emergent and the clinical meaning of these asymptomatic, otherwise non-detectable arrhythmias remained to be determined.

Most of the proarrhythmias occurred within one hour[15] of treatment, consistent with the sponsor's speculation that these events were related to spikes in ibutilide concentration near the end of infusion. Thus it is somewhat reassuring that the ventricular arrhythmias should be manageable while the patients are still under close monitoring. In clinical trials, while all patients with sustained polymorphic VT received DC shock, there was no evidence that they were difficult to treat. Three of the 9 VTs (in the controlled trials) degenerated into fibrillation, but no deaths have been reported in the ibutilide group ("all patients", N=586).

In an attempt to identify (pre-treatment) risk factors for proarrhythmias, the sponsor has screened demographic and clinical variables (see sponsor's presentation at Advisory Committee meeting) with univariate correlation analyses and performed stepwise logistic regression analyses on those of $p \leq 0.2$. Of the 19 variables, only pre-dose slow pulse (<60 bpm, p=0.0078), low body weight (p=0.0112), and history of heart failure (p=0.0298) appeared to be potentially significant predictors for polymorphic VTs. However, the numbers of patients in subgroups were small and the variabilities in heart rates and body weights were too large to make any sense out of these associations (no difference in per kg dose). The increase in polymorphic VT in patients with heart failure and/or low ejection fraction, on the other hand, should be addressed in the labeling:

	6.2	0.8	3.4	0.6
	4.1	2.2	4.1	3.9
	5.2	4.9	2.7	3.9
	("All Patients", N=586)		(Controlled Trials, N=302)	

While proarrhythmias have been reported more commonly in female than male patients (reference 30, NDA Item 8), this relationship was not consistent in all trials and appeared to be limited to non-sustained VTs in ibutilide studies. Sustained VTs were probably too rare to show the difference and the Advisory Committee concluded that there was no overall correlation with gender.

	1.8	1.5
	2.2	3.8
	1.3	5.9

(from Sponsor's presentation at Advisory Committee Meeting)

Among the other factors examined, incidence of proarrhythmias did not appear to be related to presenting arrhythmia (flutter or fibrillation), the dose of ibutilide received, pre-dose and

15 Mostly within 20 minutes after infusion. Two patients had polymorphic VT 3 hrs after dosing. In contrast, monomorphic VTs may occur up to 11 hrs later. One patient had monomorphic VT 2 days after ibutilide therapy while being started on quinidine.

changes in QTc intervals, or prior use of certain cardiovascular medications. Lack of correlation in some of these factors, however, may be solely due to inadequate power. As useless for predicting treatment success, QTc intervals at baseline or increase after dose could not be relied upon as a warning sign for polymorphic VT.

Management of Recurrence or Treatment Failures

If one assumes that termination of atrial fibrillation and flutter is desirable clinically, whether intravenous treatment with ibutilide will complicate further management of the arrhythmia for patients who failed to respond initially or relapsed after successful therapy is a legitimate safety concern. Unfortunately, some of the following information was not prospectively defined endpoints, but instead collected at the request of the Agency during regulatory review of completed studies. Since the randomization codes remained unbroken until all patients completed the studies, further management of arrhythmias was supposed to be blinded even the data collection was not.

As described above in Time-Effect Relationship of the Efficacy section, nearly half of the patients whose atrial arrhythmias were **successfully terminated by ibutilide** during the study remained recurrence-free at 400-500 day follow-up and the percentage was indistinguishable from those of other treatment groups. While the retrospectively collected data may not be as reliable, there is no evidence that patients responded to ibutilide therapy had higher risk of relapse than those treated with placebo. However, there is no information on whether recurrent arrhythmias in these patients were more difficult to manage than in those never received ibutilide.

For **ibutilide treatment failures**, subsequent management of the index arrhythmias was not more difficult than in those received placebo in the controlled trials. The success rates of conversion by other means were not lower in patients received ibutilide:

	Rx failure	Emergency	1.5<<24 hrs/ (% of Rx failure)	Not @ 24 hrs
	40	0	23 (58%)	17
	105	3	61(58%)	41
	84	0	52 (62%)	32
	102	2	66 (65%)	34

Approximately 60% of all treatment failures were converted successfully within the first 24 hrs, with little difference between groups. Thus the initial success with ibutilide was not offset by later difficulty of treating failures with other means. Total rates of conversion by ibutilide and other interventions at 24 hrs are:

	placebo	ibutilide
Study 14	58%	72%
Study 15	63%	87%

For patients not responded to ibutilide, conversion of atrial arrhythmias did not require more aggressive methods than those used in the placebo patients, as the following tables shows.

	Electro	Pacing	Meds	Spontaneous
	70%	13%	13%	4%
	59%	26%	5%	10%
	85%	8%	2%	6%
	74%	6%	9%	11%

As the majority of non-responsive patients were electro-cardioverted, the numbers of attempts and energy required suggest that ibutilide therapy, even not effective, may make cardioversion easier (no formal statistical test):

	1.0/1.8	1.0/1.6	168/433	108/350
	1.4/1.8	1.2/1.6	240/454	178/321

(Amendment 022, pp 2/39-2/40, MOR of Study 15, p.22)

For patients who failed the ibutilide treatment and remained in atrial flutter/fibrillation, management was not significantly different between groups:

	Electro	Pacing	Meds	None
	18%	6%	59%	35%
	20%	10%	44%	34%
	31%	0%	53%	16%
	15%	0%	41%	41%

(emergency conversion not included)

Less ibutilide-treated patients in Study 15 did not response to electroversion than did the placebo patients, a finding consistent with the differences in the numbers of attempts and energy requirement for those successfully cardioverted. (Note that in the above table, the percentages of patients who remained in arrhythmia and not treated with other methods were *relative to the treatment failure in each group*, which were about 10% of *total patients randomized* with little variation between groups, see below on Benefit/Risk.)

For those patients who received pharmaceutical intervention for persistent or recurrent

arrhythmias, there was no substantial difference between treatment groups in patterns of anti-arrhythmic agent use after study drug therapy (sponsor's presentation at Advisory Committee meeting). Most commonly used agents were procainamide, quinidine and amiodarone.

Long-Term Follow-up

In addition to further antiarrhythmic management of treatment failure or recurrence, long-term adverse experiences beyond 24-72 hrs post study were also considered essential in risk/benefit assessment. As noted in the MO Safety Review, follow-up information up to 3 months post treatment was collected retrospectively after submission of NDA. To monitor the process, the primary medical reviewers for the two major efficacy trials, Drs. Raczkowski and Gordon, also inspected directly the patient records at the participating clinical centers.

As a result of this post hoc search, follow-up data for total of 431 patients, or 92% of randomized patients in the two major efficacy trials (Studies 14 and 15), were available. Of these, 118 were on placebo and 431 received ibutilide. The percentages of patients who died or had serious adverse experiences were similar in placebo and ibutilide groups (see Table below). Likewise, incidences of cardiovascular (CVs) events or ventricular arrhythmias (VTs) were not significantly different.

	3.4	47.5	32.2	1.7
	3.5	44.1	34.8	2.6

There was no substantial variation between the individual studies[16] (see MO Safety Review) in the above safety parameters and causes of deaths were mostly due to underlying disease and not remarkable. Heart failure was more common in follow-up of Study 15 (7.2% in ibutilide vs 1.2% in placebo), but the finding was not observed in Study 14 and remained inconclusive.

BENEFIT/RISK ASSESSMENT

There is little doubt that ibutilide is more effective than placebo in termination of atrial flutter and fibrillation of recent onset, with a better response rate in the former variant of these arrhythmias. The studies were of appropriate design and execution was without serious problem that statistical interpretation of the drug effect was relatively easy.

The basic regulatory issues for approval of this application are, therefore, clinical ones: *is the disease worth the treatment* and *does the benefit, if any, justify the risk.*

Ample experiences have suggested that control of ventricular rates with adequate anti-coagulation can prevent major morbidity associated with chronic atrial flutter/fibrillation, thus the

16 In Study 15, collective respiratory events were reported more frequently in the ibutilide patients (8.3% vs 3.7%, see MO Safety Review), but individual adverse experiences in the collection were rare (1-3 reports), non-specific (cough) and unrelated to each other (pneumonia and lung carcinoma).

arrhythmias were considered relatively benign and non-life threatening, especially in asymptomatic patients without serious underlying heart diseases. For these chronic cases, temporary conversion without long-term maintenance of normal sinus rhythm is most likely of little benefit. On the other hand, rapid conversion of these atrial arrhythmias to sinus rhythm in certain more acute clinical settings is less questionable. Patients who are post cardiac surgery or symptomatic with serious underlying structural or functional cardiac diseases, are clearly appropriate candidate for acute conversion of their atrial arrhythmias. Unfortunately, the NDA was submitted before the CABG study is completed and there was no systematic evaluation of patients at higher risk of decompensation in the development program.

In the absence of such studies, however, there is evidence in the completed clinical trials that termination of atrial flutter/fibrillation was clinically desirable for patients in the studies. In both efficacy trials, a great majority of non-responders to study drug were treated with other methods during or shortly after study, with approximately 90% of all randomized patients received either pharmaceutical agents or electrical conversion/pacing (see above in Management of Recurrence or Treatment Failures). Therefore few unresponsive patients were left untreated with other means and patients were recruited into the ibutilide studies for clinically indicated treatment, not just for participating in drug development.

While entry criteria in the two large placebo-controlled efficacy trials excluded patients with more serious cardiovascular diseases (symptomatic heart failure, recent MI and angina), they were not totally asymptomatic and in fact, majority of patients had left atrial enlargement, history or echographic evidence of valvular diseases, or decreased left ventricular ejection fraction. Experiences in the sotalol controlled studies, although did not offer additional support for the claim *vs placebo*, also provided some reassurance that ibutilide was effective (same response rates as in placebo controlled trials) in a patient population with more symptoms of hypertension, myocardial infarction, heart failure and history of coronary artery bypass surgery (see primary MO review). Thus it is reasonable to extrapolate the results of the clinical studies in this application to a specific patient group with more stringently defined indication for termination of atrial flutter/fibrillation.

Whether an individual patient with atrial flutter/fibrillation should be converted and by which method is a clinical judgement which can only be made at bedside. If one leaves that out of the regulatory thinking, then acute conversion with iv ibutilide can be considered as one of the *tools* for physicians to use. The effectiveness and risk of iv ibutilide should be evaluated against that of other methods available, not many of which, with the exception of electric shock, have been shown to be effective for the indication being sought. While there was no direct comparison with non-pharmaceutical interventions, ibutilide is probably less effective, but conceivably causes significantly less discomfort and without excessive risk of proarrhythmias (e.g. serious bradycardia from electroversion). As a tool, the clinical benefit derived from its use is usually too remote from the immediate consequence of treatment. Patient outcomes depend on subsequent management of underlying diseases and are affected by many confounding factors over the time course which are beyond practical control in a short-term study. If, especially as in the case of atrial fibrillation/flutter, there is no effective maintenance therapy to sustain the short-term effect, the long-term clinical benefit of the tool would be even more difficult to demonstrate. But lack of maintenance treatment should not inhibit development of short-term therapy for some patients who may benefit from it. Intravenous ibutilide may be such an effective tool for the physician, its use will result in the implicit, but difficult to prove, benefit.

As noted in the Safety section, major risk of ibutilide treatment for termination of atrial

fibrillation/flutter is cardiovascular, especially the proarrhythmic effect. Overall incidence of all VTs in all treated patients (N=586) was approximately 10%, half of which were the relatively less serious form of non-sustained monomorphic VT. Sustained, polymorphic VT was reported in 1.7% of patients, none of which resulted in death or was particularly difficult to treat. As it was shown in the clinical trials, proarrhythmia was less of a safety concern in the controlled, closely monitored setting, ibutilide should be administered in practice with the same degree of vigilance. There is no evidence that iv ibutilide treatment will complicate further management of atrial fibrillation/flutter in treatment failure or recurrence, or associated with long-term adverse experiences up to three months after ibutilide therapy. Thus the risk is small, rarely serious and manageable, whether it is justified by the potential benefits depends on the severity of symptoms, underlying disease and hemodynamic decompensation.

The benefit/risk ratio of iv ibutilide therapy for acute termination of atrial fibrillation/flutter is, therefore, acceptable in symptomatic patients with serious underlying heart diseases. Such patients were reasonably well-represented in the clinical trials.

PEDIATRIC/GERIATRIC/FEMALE USE

There are no clinical trials assessing the efficacy or safety of ibutilide in pediatric patients, either completed or in progress. The sponsor claimed that the drug has little potential for use in children and thus did not commit to any study in children.

Efficacy and safety of ibutilide as treatment for atrial flutter/fibrillation in the elderly (65 year and older) are not significantly different from that of general patient population.

Female patients should be treated with ibutilide in the same manner as male patients. In ibutilide studies, higher risk of proarrhythmia in female patients was limited to non-sustained VTs and appropriate warning was included in the labeling.

DRAFT LABELING

The draft labeling submitted by the sponsor has been edited.

CONCLUSIONS

Ibutilide appeared to be an effective and safe treatment for acute termination of atrial flutter/fibrillation. Approval for such indication with the edited draft labeling is recommended.

Further studies to better define the benefit/risk ratio in certain populations (e.g. CABG study) and to explore the higher doses should be a strong post-approval commitment.

cc:
ORIG: NDA- 20-491
HFD-110
HFD-110/CSO
HFD-110/MGordon, VRaczkowski
HFD-110/SChen/12/04/95

Shaw T. Chen, M.D.,Ph.D.

1.1A

(2)

MEDICAL OFFICER'S REVIEW

SEP 28 1995

Date: 22 September 1995
To: Raymond J. Lipicky M.D.; Director
Division of Cardio-Renal Drug Products; HFD-110
From: Victor F.C. Raczkowski, M.D., M.S.; Medical Officer
Division of Cardio-Renal Drug Products, HFD-110
Through: Shaw Chen, M.D., Ph.D.; Supervisory Medical Officer
Division of Cardio-Renal Drug Products, HFD-110
Subject: NDA 20-491 Corvert™ Injection (ibutilide fumarate injection)--"Protocol #14"

Vict F.C. R 8/2 L

This document contains my review for **A Placebo-Controlled Dose-Response Study to Assess the Effects of Intravenous Ibutilide in Patients with Atrial flutter or Atrial Fibrillation** (Protocol Number: P/7550/0014; Technical Report Number: 7216-94-007). I have reviewed this study in considerable detail because this is one of the principle studies submitted by the sponsor in support of efficacy of this drug. A table of contents follows the abstract. My assessment of the study may be found on pages 41-46.

1. ABSTRACT

This was a randomized, double-blind, placebo-controlled study of a parallel design that was performed at multiple clinical centers in patients with sustained atrial flutter or sustained atrial fibrillation. The study was designed to evaluate the safety and effectiveness of single doses of ibutilide fumarate (0.005, 0.010, 0.015, or 0.025mg/kg) administered as ten-minute infusions. A response was defined as "the termination of atrial flutter or atrial fibrillation.

Two-hundred patients with sustained atrial flutter or atrial fibrillation were treated in the study by nine investigators. The study was designed in two tiers to allow for an interim safety evaluation. In the first tier, fifty patients (evenly stratified between atrial fibrillation and atrial flutter) were randomized to a ten-minute infusion of placebo, 0.005 mg/kg ibutilide fumarate, or 0.010 mg/kg ibutilide fumarate. When safety was ascertained, Tier II was initiated with fifty new patients. These patients were randomized to a ten-minute infusion of placebo, 0.015 mg/kg ibutilide fumarate, or 0.025 mg/kg ibutilide fumarate. After these first 100 patients were enrolled, the protocol was amended to include an additional 100 patients randomized to placebo, 0.005, 0.010, 0.015, or 0.025 mg/kg ibutilide fumarate. The number of patients enrolled in each treatment group (placebo, 0.005, 0.010, 0.015, 0.025 mg/kg) were 41, 41, 40, 38, and 40, respectively Overall, the arrhythmia terminated in 34% (54 of 159) of the patients treated with ibutilide fumarate, but in 2.4% (1 of 41) of the patients treated with placebo. By treatment group, the conversion rates in the groups treated with ibutilide fumarate (0.005, 0.010, 0.015, and 0.025 mg/kg) were 12.2, 32.5, 44.7, and 47.5%, respectively. For patients successfully converted in this study with ibutilide fumarate, doses of 0.005, 0.010, 0.015, and 0.025 mg/kg corresponded to average absolute doses of 0.44, 0.79, 1.24, and 1.86 mg, respectively. Termination of arrhythmia was not directly related to plasma concentration.

The likelihood of successful termination of the arrhythmia was inversely correlated with the duration of the arrhythmia. Other factors, such as concomitant treatment with beta-adrenergic blocking agents, or *not* being treated with concomitant digoxin also were correlated with successful termination of the arrhythmia in some strata.

Pharmacokinetic data were analyzed from only 93 of the 159 patients who received ibutilide. Because of the variability of the plasma concentration data, the estimates of the pharmacokinetic parameters were also highly variable. But overall, ibutilide had a large volume of distribution (mean=6.6 L/kg) and had a high systemic clearance (mean=37 ml min^{-1}/kg). This estimate of the volume of distribution may be artificially low because blood samples for plasma concentration analysis were not gathered beyond three hours.

Atrial cycle length, the QT interval, and the QTc interval were all prolonged by ibutilide infusion. Ibutilide did not appear to alter QRS duration significantly. Data were insufficient to draw conclusions about the effects of ibutilide on the PR interval.

Ibutilide had significant, persistent, and possibly dose-related effects on pulse. This effect can probably be attributed to termination of the atrial arrhythmia. Ibutilide did not appear to have any consistent, significant, dose-related, and persistent effects on systolic or diastolic blood pressure.

Fifty-four of the 200 patients enrolled in the trial experienced at least one adverse event, half of whom experienced an adverse event of the cardiovascular system. Eight patients treated with ibutilide experienced serious adverse events, all of which were related to the cardiovascular system. These included six cases of polymorphic ventricular tachycardia. Overall, eleven patients experienced proarrhythmia and six patients were classified as having hypotension as an adverse event. Two patients treated with ibutilide fumarate required emergency defibrillation. Several medical events in the study (sinus arrest, severe AV block, severe bradycardia) confirm that potentially adverse electrophysiological properties of ibutilide are not limited to the induction of ventricular tachycardia. The safety of electrical cardioversion after administration of ibutilide is difficult to assess from this study because the data were not gathered prospectively.

Medical Review

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2. DESCRIPTION OF THE STUDY

2.1 Title

A Placebo-Controlled Dose-Response Study to Assess the Effects of Intravenous Ibutilide in Patients with Atrial flutter or Atrial Fibrillation (Protocol Number: P/7550/0014; Technical Report Number: 7216-94-007).

2.2 Objectives

2.2.1 Primary Objectives

As specified in the protocol, the study had three primary objectives:

- to determine the dose-response relationship of ibutilide for the conversion of atrial flutter or atrial fibrillation
- to assess the tolerance and safety of ibutilide in patients with atrial flutter or atrial fibrillation
- to determine a concentration-response relationship of ibutilide for the conversion of atrial flutter or atrial fibrillation

2.2.2 Secondary Objectives

The study had two prespecified secondary objectives:

- to assess the effects of ibutilide on heart rate and blood pressure
- to determine the pharmacokinetics of ibutilide in patients with atrial flutter or atrial fibrillation

2.3 Experimental Design

This was a randomized, double-blind, placebo-controlled study of a parallel design that was to be performed at multiple clinical centers in patients with sustained atrial flutter (AFl) or sustained atrial fibrillation (AF). The study was designed to evaluate the safety and effectiveness of single doses of ibutilide fumarate (0.005, 0.010, 0.015, or 0.025 mg/kg) administered as 10 minute infusions. A response was defined as "the termination of atrial flutter or atrial fibrillation."

The study was originally designed to have two successive tiers to allow for an interim safety evaluation. In Tier I, 50 patients, who were evenly stratified between sustained atrial flutter and sustained atrial fibrillation, were to be randomly allocated to treatment with one of the two *lower* doses of ibutilide or with placebo (in a ratio of 2:2:1). When safety was ascertained, Tier II was to be initiated and 50 more patients were to be randomly allocated to treatment with one of the two *higher* doses of ibutilide or with placebo (in a ratio of 2:2:1). After these first 100 patients were enrolled, the protocol was extended to include an additional 100 patients who were to be randomly allocated to treatment with *any of the four* doses of ibutilide or with placebo in a ratio of (1:1:1:1:1). See the diagram of the planned study design on the next page.

Planned Study Design

	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg
Original Protocol					
Tier I (n=60)	n=10	n=20	n=30		
Tier II (n=60)	n=10			n=20	n=30
Extension (n=100)	n=20	n=20	n=30	n=20	n=30

2.4 Drug Administration

Ibutilide (2.5 mg/ml) was to be diluted with 5% dextrose in water (D_5W) and was to be infused intravenously over ten minutes. The infusion was to be terminated for occurrence of any of the following: (a) conversion of atrial flutter of fibrillation to normal sinus rhythm; (b) a decrease in the systolic blood pressure to less than 90 mmHg; (c) a change in rhythm or atrioventricular conduction that was not hemodynamically tolerated or that threatened patient safety; (d) development of new bundle branch block; (e) an increase in the QRS duration by greater than 50%; (f) prolongation of the corrected QT interval (QT/√RR) to greater than 0.600 sec[a], or; (g) an adverse event that threatened patient safety.

2.5 Subjects

Patients in the trial were required to be between 18 and 80 years of age, to weigh less than 110 kg, and to have sustained atrial flutter[1] or atrial fibrillation.[2] Patients with atrial fibrillation for longer than three days were required to receive anticoagulant therapy for two weeks prior to enrollment. Patients were also required to be hemodynamically stable[3] and to have normal serum electrolytes with a serum potassium of at least 4.0 mEq/L. Women were required either to be surgically sterile or to be postmenopausal with at least 12 months without a menstrual period. Informed consent and review by an Institutional Review Board were stipulated.

Patients were to be excluded for any of the following conditions: (a) a myocardial infarction within the previous three months; (b) symptoms of angina or congestive heart failure; (c) serious pulmonary, hepatic, hematologic, metabolic, renal, gastrointestinal, CNS, or psychiatric decrease; (d) a serum creatinine of 2.0 mg/dl or greater; (e) liver enzymes greater than two times the maximum normal value, or; (f) signs or symptoms of digoxin toxicity.

2.6 Concomitant medications, and management of treatment failures

Concomitant use of class I or class III antiarrhythmic medications was prohibited. Moreover, if the patient had been receiving class I or class III antiarrhythmic medications, the medication was to be discontinued more than five elimination half-lives prior to enrollment. In contrast, the concomitant

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[1] Sustained atrial flutter was defined as a atrial flutter with a duration of at least three hours.

[2] Sustained atrial fibrillation was defined as atrial fibrillation with a duration of at least three hours but less than 90 days.

[3] Hemodynamically stable was defined as having a systolic blood pressure of at least 90 mmHg and diastolic blood pressure of less than 105 mmHg.

use of beta-adrenergic blocking agents, calcium-channel blocking agents, or of digoxin was permitted.

If atrial flutter or fibrillation persisted for one hour or more following completion of the infusion, pacing or electrical cardioversion could be performed as deemed appropriate by the investigator.

Use of additional antiarrhythmic drugs was to be delayed for four hours after the end of the infusion unless the investigator felt it was necessary to restore normal sinus rhythm sooner. In that case, drugs to facilitate conversion to normal sinus rhythm could be given one hour after the end of the infusion.

2.7 Evaluations

As shown in the Schedule of Events on page 4, pharmacokinetics, pharmacodynamics, efficacy, and safety were evaluated by serial monitoring of the following:

- blood samples for measurement of drug levels
- twelve-lead electrocardiograms (for measurement of duration of standard intervals, especially QRS duration and QTc)
- response rate (defined as "the termination of atrial flutter or atrial fibrillation")
- vital signs (supine blood pressure and pulse)
- blood and urine samples for safety laboratories (hematology, coagulation, chemistry, and urinalysis with microscopic examination)
- medical events

For the first 40 minutes (starting at the beginning of the infusion), the patients were monitored continuously by three-lead electrocardiography. From minute 40 until hour 24, patients were monitored by single-lead electrocardiography. In addition, all patients were to have a temporary right ventricular pacing wire or else have access to an external pacemaker.

2.8 Intended statistical analyses

As stated in the original protocol, the primary purpose of this study was to explore the dose-response relationship of ibutilide and not to test any pre-formulated hypotheses. Also, because the study examined both patients with atrial flutter and atrial fibrillation, all the analyses were to be conducted separately for patients with atrial flutter and patients with atrial fibrillation. The study was originally planned as a Phase II study, and the protocol was amended (2 March 1992) to increase the number of patients from 100 to 200 and to allow for the evaluation of all dose groups concurrently. Not much statistical detail was provided, but considering only the efficacy analyses, the following statements have been taken verbatim from the protocol:

Dose-Response Relationship: Defining the termination of atrial flutter or atrial fibrillation as a response, the analysis will focus on the relationship between the response rate and the ibutilide dose, and between the response rate and the ibutilide serum concentration. Graphic presentations will be made and curve-fitting will be attempted

Pharmacokinetic/pharmacodynamic evaluations: Descriptive analyses of plasma concentrations will be presented in graphic and tabular form. These will include plasma concentration versus time profiles (during and post infusion), and estimates of clearance and volume of distribution. In addition, the relationships between dose and plasma concentrations and the pharmacodynamic parameters of QTc interval prolongation and termination of atrial flutter/fibrillation will be assessed.

Schedule of Events

Activity	Screen	Time From Beginning of Infusion: Minutes											Hours								
		-10	-5	0	5	30	35	60	65	90	95	60	1	1.5	2	3	4	6	8	20	24
Informed Consent	x																				
History/Physical Exam	x																				
12 Lead ECG[1]	x	x											x								
Safety Labs	x																				x
Echocardiogram[2]																					
Three-Lead ECG Monitoring		—	—	—	—	—	—	—	—	—	—	—									
Single-Lead ECG Monitoring													—	—	—	—	—	—	—	—	—
Resting HHRR	x	x	x	x	x	x	x	x				x	x		x		x	x	x	x	x
Temporary Pacing Electrode		—	—	—	—	—	—	—	—	—	—	—									
Beatillo Infusion				—	—	—	—	—	—	—	—										
Beatillo Plasma Concentrations[3]		x				x	x			x			x	x	x	x					
Digoxin Levels (if applicable)		x											x								

3. RESULTS

3.1 Disposition of Subjects

The study was performed from April 1991 through January 1993 at nine study sites. Overall, 202 patients were assigned randomization numbers. Of these, two numbers (#2305 and #2331) were assigned to patients in the extension study who were never treated.[4]

Of the remaining 200 patients, 102 enrolled in the original protocol, and 98 in the extension. All 200 patients completed the study course. However, five of these 200 patients experienced medical events that caused discontinuation of the infusion (see the section on safety). Of these 200 patients, 197 were considered to be evaluable for efficacy: 100 in the original protocol, and 97 in the extension. See the top table on the next page.

Because the patients were stratified on the basis of their presenting arrhythmia, each phase of the study enrolled approximately equal numbers of patients with atrial fibrillation and with atrial flutter. Overall, approximately 40 patients were enrolled in each of the five dose groups; about 20 patients with atrial fibrillation and about 20 with atrial flutter were treated within each dose group. See the bottom table on the next page.

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[4] The sponsor states that the numbers were never reassigned and that this error was discovered after the protocol was terminated.

[redacted]

	Original Enrolled	Extension	Total
[redacted]			
AFI	49	51	100
AE	[redacted]	[redacted]	[redacted]
AFVAF	102	100	[redacted]
[redacted]			
AFI	49	51	100
AE	[redacted]	[redacted]	[redacted]
AFVAF	102	98	200
[redacted]			
AFI	49	51	99
AE	[redacted]	[redacted]	[redacted]
AFVAF	100	97	197

Number of Treated Patients in Each Dose Group (by Stratum)

	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg	Total
AFI	20	21	20	19	20	100
AE	21	20	20	19	20	100
AFVAF	41	41	40	38	40	200

3.2 Impact of Exclusions on the "Intention-to-Treat" Analysis

Three of the 200 treated patients were considered non-evaluable by the sponsor. Because this is such a small number, exclusion of these patients from the primary efficacy analyses will not likely alter any conclusions that are drawn. Furthermore, when these three cases are reviewed individually (see below), their exclusion from the final efficacy evaluation of "evaluable patients" does not appear to introduce much of a bias. Nonetheless, in this review I focus mainly on the characteristics and results from the sample of "all patient treated with study medication" (rather than on all "evaluable" patients) in order to approximate "intention-to-treat" analyses.

Patient #1201 (AFl) received a 15-minute infusion of 0.025 mg/kg for a total dose of 3.37 mg and had the arrhythmia successfully terminated. However, the sponsor considered this patient nonevaluable "since this was a dose-finding study and this patient received a dose of drug much higher than any of the doses defined in the protocol." This patient was replaced by Patient #1226 (AFl), who was assigned to the same treatment and also was successfully converted with the infusion. Thus, for purposes of the final efficacy evaluation of "evaluable" patients, one "success" among patients treated with ibutilide was replaced with another "success."

Patient #2116 (AF) received an unknown amount of intravenous study medication because the intravenous line came out of the vein and the drug was infused subcutaneously (a ten-minute infusion of 0.010 mg/kg for a predicted total dose of 0.96 mg). The arrhythmia failed to convert within 24 hours. This patient was replaced by Patient #2126 (AF) who was assigned to the same treatment (a ten-minute infusion of 0.010 mg/kg for a total dose of 1.14 mg). This patient's arrhythmia also failed to convert within 24 hours. Thus, for purposes of the final efficacy evaluation of "evaluable" patients, one "failure" among patients treated with ibutilide was replaced with another "failure."

Patient #2307 (AF) was treated according to the protocol (received a ten-minute infusion of placebo) but, as stated by the sponsor, was later found to have not been in atrial flutter or fibrillation and should not have been enrolled in the study. Nonetheless, on the final efficacy evaluation the patient was classified as a "failure," as the AF/AFl did not terminate during the 24 hours. This patient was not replaced. Thus, for purposes of the final efficacy evaluation of "evaluable" patients, one "failure" among the patients treated with placebo was not counted.

3.3 Demographics and Baseline Characteristics

3.3.1 Demographics

Of the 200 treated patients, 79% were classified as white, 18% as black, and 3% as hispanic. Eighty-eight percent (88%) were men and 12% were women. At baseline, the patients had a mean (± s.d.) age of 64.3 ± 9.5 years. The youngest patient was 25 years old, the oldest 82 years old. Over 55% of the patients were at least 65 years of age. The patients had a mean weight of 184.0 ± 32.0 lbs and a mean height of 69.2 ± 3.5 inches. Overall (i.e., considering the combined AFl/AF strata) and within each stratum (i.e., the AF stratum or the AFl stratum), the dose groups were similar for age, height, weight, and race/ethnicity. As shown in the table on the top of the next page, across dose groups the combined stratum (AFl/AF) and the AF stratum were balanced for sex. The individual AFl stratum, however, showed an imbalance in the distribution of men and women across dose groups (p=0.0496). Baseline characteristics of the patients are summarized in the table on pages 8 and 9.

Number of Men and Women in Each Dose Group (by Stratum)

	Placebo		0.005 mg/kg		0.010 mg/kg		0.015 mg/kg		0.025 mg/kg		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
AFI*	20	0	20	1	20	0	15	4	17	3	92	8
AE	18	3	17	3	18	2	18	1	17	3	88	12
AFI/AF	38	3	37	4	38	2	33	5	34	6	180	20

* Chi-square p=0.0496

3.3.2 Baseline blood pressure and pulse

At baseline, the 200 patients had a mean (±s.d.) systolic blood pressure of 133.3 ± 21.4 mmHg, a mean diastolic blood pressure of 80.3 ± 11.2 mmHg, and a mean pulse of 88.1 ± 23.6 beats/min. Across dose groups, the combined stratum (AFI/AF) was balanced for systolic blood pressure, diastolic blood pressure, and pulse.

3.3.3 Baseline electrocardiography

Overall for patients on whom baseline electrocardiographic data were available, the mean (±s.d.) QRS interval was 104.3 ± 25.0 msec, the mean QT interval was 383.6 ± 50.3 msec, the mean QTc interval was 431.85 ± 41.0 $sec^{\frac{1}{2}}$ (x 1000), and the mean atrial cycle length was 243.4 ± 39.3 msec. Overall in the combined AFI/AF stratum, and within each stratum, the dose groups were similar for duration of QRS, QT, and QTc intervals. The atrial cycle length was similar across dose groups for the combined AFI/AF stratum. As only nine patients had a baseline measurement of the PR interval, baseline similarity could not be assessed.

3.3.4 Baseline echocardiograms

Of the patients who had an echocardiogram at baseline, 74% (140 of 189) had an enlarged left atrium, 49% (89 of 180) had a decreased ejection fraction, and 59% (114 of 194) had a history of valvular heart disease.

3.3.5 Concomitant use of medications at baseline

Overall, 55% (111 of 200) of the patients were using concomitant digoxin, 41% (82 of 200) were using a concomitant calcium-channel blocking agent, and 18% (36 of 200) were using a concomitant β-adrenergic blocking agent.

3.3.6 History of atrial fibrillation or flutter, and symptoms at screen

Overall, 66.5% (133 of 200) of the patients had a history of atrial fibrillation or flutter (57% of the AFI patients and 78% of the AF patients). At screen, 41% (82 of 200 patients) reported symptoms consistent with atrial fibrillation or atrial flutter. The most frequent symptoms included shortness of breath, palpitations, dizziness, and fatigue.

Baseline Characteristics of Subjects by Dose Group

	Placebo (n=41)	Ibutilide (mg/kg) 0.005 (n=41)	0.010 (n=40)	0.015 (n=39)	0.025 (n=40)
Race (n) (W/B/O)[a]	32/9/0	29/12/0	25/14/1	27/10/1	30/9/1
Sex (n) (♂/♀)	38/3	37/4	38/2	39/5	34/6
Age (years) (mean±s.d.)	69.7 ±9.3	64.1 ±8.7	66.1 ±8.7	65.6 ±9.4	62.0 ±11.2
Weight (lbs) (mean±s.d.)	179.7 ±33.1	190.7 ±30.15	186.4 ±31.4	179.7 ±28.3	183.1 ±36.3
Systolic Blood Pressure (mmHg) (mean±s.d.)	132.7 ±21.8	133.85 ±25.0	135.8 ±23.65	135.1 ±17.2	129.3 ±18.3
Diastolic Blood Pressure (mmHg) (mean±s.d.)	80.9 ±11.2	81.1 ±12.3	80.7 ±11.0	80.0 ±11.5	78.8 ±10.2
Pulse (beats/min) (mean±s.d.)	90.2 ±26.7	84.9 ±23.6	85.1 ±22.2	87.2 ±19.6	92.9 ±25.4
12-Lead EKG Intervals					
PR (msec)[b]	--	--	--	--	--
QRS (msec)[c] (mean±s.d.)	105.8 ±25.4	111.45 ±27.4	100.8 ±24.35	102.1 ±24.1	101.3 ±23.4
QT (msec)[d] (mean±s.d.)	362.9 ±59.6	367.1 ±46.6	370.25 ±50.1	363.9 ±40.3	363.9 ±54.3
QTc (sec½ x 1000)[e] (mean±s.d.)	436.4 ±45.9	427.5 ±41.3	436.45 ±39.2	427.9 ±37.3	430.9 ±42.2
atrial cycle length[f] (mean±s.d.)	227.1 ±39.3	252.4 ±42.05	251.6 ±37.3	242.2 ±36.6	240.7 ±37.2

[a] Number of subjects by race/ethnicity: W/B/O = White/Black/Other
[b] The baseline PR interval was measured in only nine patients
[c] Total n=197 (n by dose group: placebo/0.005/0.010/0.015/0.025=36/40/40/38/40)
[d] Total n=191 (n by dose group: placebo/0.005/0.010/0.015/0.025=36/39/40/37/39)
[e] Total n=190 (n by dose group: placebo/0.005/0.010/0.015/0.025=36/39/40/36/39)
[f] Total n=91 (n by dose group: placebo/0.005/0.010/0.015/0.025=17/21/19/16/18)

Baseline Characteristics of Subjects by Dose Group (continued)

	Placebo (n=41)	Ibutilide (mg/kg) 0.005 (n=41)	0.010 (n=40)	0.015 (n=39)	0.025 (n=40)
Left Atrial Size (n)[a,c] (normal/enlarged)	10/20	10/20	7/21	11/18	11/25
Ejection fraction (n);[a,d] (normal/decreased)	19/23	18/19	20/13	13/20	16/14
Valvular heart disease (n)[a] (present/absent)	24/17	19/21	22/17	25/13	24/12
Duration of arrhythmia (days) (median; range)	9.6 0.5-1413.4	22.5 1.4-255.8	14.2 0.4-3122.4	12.6 0.5-647.4	9.1 0.2-669.9
Concomitant β-blocker (n);[b] (yes/no)	6/35	8/33	6/34	8/32	10/30
Concomitant digoxin (n);[b] (yes/no)	20/21	20/21	23/17	24/14	24/16
Concomitant calcium-channel blocker (n);[b] (yes/no)	16/25	16/25	17/23	18/20	15/25
History of AFl or AF (n); (yes/no)	29/12	22/19	33/7	25/13	24/16
Symptoms at screen (n); (yes/no)	15/26	19/22	17/23	17/21	15/25

[a] As reflected by the numbers, not all patients had baseline echocardiographic data.
[b] Concomitant use of a drug was defined as use within the 24 hours prior to infusion.
[c] Functionally, an "enlarged" left atrial diameter was defined as a left atrial diameter of a dimension outside of the range of normal for the evaluating echocardiographic laboratory.
[d] In the protocol, no standardized definition was provided for a "decreased" ejection fraction. Investigators made this determination independently.

3.4 Drug Exposure

Of the 200 patients treated with study drug, six either received the wrong dose or had difficulties with drug administration.[5] For purposes of analysis these patients were placed in the dose group consistent with the dose actually administered, rather than the dose group to which they were randomized. A seventh patient[6] may have received no active drug, although he was randomized

[5] These include Patients #1201 and #2118 (discussed above), and Patients #1124, #1223, #1344, and #2308 (each of whom received a dose different than that assigned by randomization).

[6] Patient #2213

to receive 0.025 mg/kg ibutilide. This patient's data were analyzed with the group to which he was randomized (0.025 mg/kg).[7]

3.4.1 Duration of the Infusion

The mean duration of the infusion in each dose group is shown in the table below. One-way analysis of variance (ANOVA) showed a significant difference among the mean durations of infusion in the AF stratum and in the combined AF/AFl stratum. Pairwise comparisons among the dose groups showed that the duration of infusion in the 0.025 mg/kg group was significantly shorter than in each of the other four dose groups. No other pairwise comparisons among dose groups were statistically significant.

Consistent with this observation, 8 of 19 (42%) of the patients in the 0.025 mg/kg group who successfully converted to normal sinus rhythm did not require the entire 10-minute infusion. This can be contrasted with the 15 of 55 (27%) of the patients overall who converted to normal sinus rhythm prior to completion of the entire 10-minute infusion. Hence, both shorter infusions and successful conversions appear to be represented disproportionately in the group that received 0.025 mg/kg of ibutilide compared to the other four treatment groups.

Mean Duration of Infusion (minutes)

	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg	Overall p value*
AFl	10.00	10.19	9.90	9.89	9.55	0.42
AF	10.00	9.90	9.70	10.00	8.80	0.007
AFl/AF	10.00	10.05	9.80	9.95	9.18	0.003

* From one-way ANOVA

[7] I evaluated these seven assignments and reassignments that were made by the sponsor. I felt that each was reasonable.

3.4.2 Total dose infused

The mean doses actually infused (based on body weight and the duration of the infusion) for successes and failures are shown in the table below:

Total Dose of Ibutilide Received by Patients with Successful or Unsuccessful Termination of Atrial Fibrillation or Atrial Flutter

	Successes		Failures	
Dose Group	N	Mean Total Dose (mg)	N	Mean Total Dose (mg)
Placebo	1	0.00	40	0.00
0.005 mg/kg	5	0.44	36	0.43
0.010 mg/kg	13	0.79	27	0.84
0.015 mg/kg	17	1.24	21	1.20
0.025 mg/kg	19	1.86	21	1.92
Total	55	1.25	145	0.71

3.5 PHARMACOKINETIC RESULTS[6]

Of the 200 patients treated with study medication, 159 were treated with ibutilide fumarate (i.e., 40 patients had been randomized to receive placebo, and one patient received placebo by mistake instead of ibutilide). Of these 159 patients with plasma concentration data, only 93 were included in the pharmacokinetic analysis. Concentration data from 66 patients were excluded from analysis for four major reasons: a) an insufficient number of observations for NONLIN fitting (n=21), b) analytical interference (n=19), c) erratic concentration-time profiles (n=18), and (d) inappropriate matrix for analysis (whole blood) (n=8).

In general, plasma concentrations of ibutilide decreased rapidly after the ibutilide infusion in a multi-exponential fashion. Plasma concentrations were typically around 1 ng/ml within one hour after the beginning of the 10-minute infusion (see the figures and table on page 13).

Because of the variability of the plasma concentration data, the estimates of the pharmacokinetic parameters were also highly variable. But overall, ibutilide had a large volume of distribution (mean=6.6 L/kg) and had a high systemic clearance (mean=37 ml min^{-1}/kg). The clearance of ibutilide was similar in patients with atrial fibrillation/flutter and in healthy volunteers. However, the

[6] For a complete assessment of the pharmacokinetic results, see the evaluation by the biopharmaceutical reviewer.

volume of distribution appeared to be lower in patients with atrial fibrillation/flutter than in healthy volunteers (see the top table below).[9]

The clearance and volume of distribution appeared to be independent of the dose of ibutilide fumarate (see the bottom table below). As shown in the table on page 14, the clearance and volume of distribution also appeared to be independent of the presenting arrhythmia (atrial flutter or atrial fibrillation), success or failure in terminating the arrhythmia, patient age (less than 65 years, or 65 years or older), sex, and concomitant treatment with either digoxin, calcium channel blockers, or beta-adrenergic blocking agents. Prolongation of the QTc interval (from baseline to Hour 1) did not correlate with clearance or with the volume of distribution.

Table 2. Ibutilide pharmacokinetic parameter estimates* following a single intravenous infusion of ibutilide fumarate: Comparisons of patients with atrial flutter or atrial fibrillation and healthy volunteers

Parameter	Patients	Healthy Volunteers†
Number of Subjects	96	28
Dose Range (mg/kg)	0.0045 to 0.0975	0.010 to 0.100
CL (mL min^{-1}/kg)	37 ± 16 (44%)	39 ± 7 (23%)
V_{ss} (L/kg)	6.6 ± 4.0 (61%)	11.5 ± 3.8 (33%)
Half-life Range (h)	1.0 to 11.1	4.3 to 12.2

* Data presented as the mean ± standard deviation (% coefficient of variation).
† Data from reference [10].

Table 3. Ibutilide pharmacokinetic parameter estimates* following a single intravenous infusion of ibutilide fumarate in patients with atrial flutter or atrial fibrillation: Relation to dose

Parameter	Dose Range (mg/kg)		
	0.0045 to 0.008	0.010 to 0.0175	0.020 to 0.0975
Number of Patients	18	51	24
CL (mL min^{-1}/kg)	33 ± 16	37 ± 17	39 ± 14
V_{ss} (L/kg)	7.1 ± 5.6	6.2 ± 3.6	6.9 ± 3.4
Half-life Range (h)	3.7 ± 2.6	3.0 ± 1.8	3.1 ± 1.7

* Data presented as the mean ± standard deviation (% coefficient of variation).

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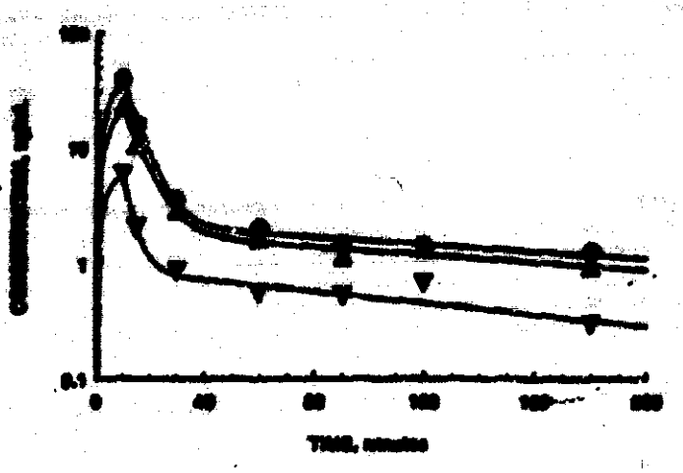
[9] As noted by the sponsor, this may be due in part to a difference in the blood sampling scheme, where samples were obtained through three hours after the infusion, whereas samples were obtained for 24 hours in the healthy volunteers. sampling for a shorter time may result in underestimating the AUC , as well as a larger fraction of the AUC being extrapolated to infinity.

Figure 1. [illegible] (symbols are the observed values and lines are the fitted curves)



Characteristics of Patients Illustrated in Figures 1 and 2

Symbol	Patient Number	Dose (mg/kg)	Arrhythmia	Arrhythmia Terminated ?	Cl, (mL min^{-1}/kg)	Vss (L/kg)
[illegible]						
●	[illegible]	[illegible]	Flutter	No	4.8	0.8
▲	[illegible]	[illegible]	Flutter	No	83.8	5.7
▼	[illegible]	[illegible]	Flutter	No	72.6	9.4
[illegible]						
●	[illegible]	[illegible]	Flutter	Yes	6.7	3.3
▲	[illegible]	[illegible]	Flutter	No	30.0	10.1
▼	[illegible]	[illegible]	Fibrillation	No	82.2	5.1

Figure 2. Plasma concentration profiles of ibutilide after a single intravenous infusion of ibutilide fumarate in female patients with atrial flutter or atrial fibrillation (symbols are the observed values and lines are the fitted curves)

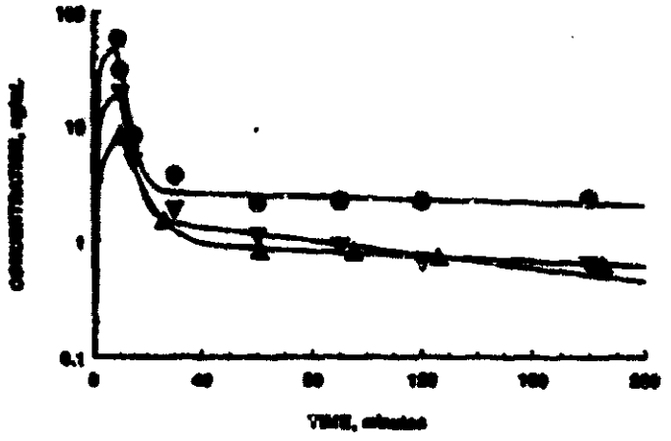


Table 4. Ibutilide pharmacokinetic parameter estimates (mean ± standard deviation) in various patient subpopulations following a single intravenous infusion of Ibutilide fumarate

Patient Population	n	Dose (mg/kg)	CL (mL min⁻¹/kg)	V_{ss} (L/kg)	$t_{1/2}$ (hr)
All patients combined	**99**	**0.0145 ± 0.0070**	**37 ± 16**	**6.6 ± 4.9**	**3.1 ± 1.9**
Arrhythmia					
Atrial Flutter	**51**	**0.0143 ± 0.0075**	**39 ± 17**	**6.9 ± 5.6**	**2.9 ± 1.6**
Atrial Fibrillation	**48**	**0.0146 ± 0.0072**	**36 ± 15**	**7.5 ± 4.3**	**3.4 ± 2.1**
Treatment Outcome					
Success	**28**	**0.0156 ± 0.0071**	**34 ± 16**	**5.4 ± 3.7**	**2.9 ± 2.0**
Failure	**75**	**0.0137 ± 0.0075**	**39 ± 16**	**7.2 ± 4.9**	**3.3 ± 1.8**
Sex					
Male	**81**	**0.0141 ± 0.0073**	**37 ± 16**	**6.5 ± 3.9**	**3.0 ± 1.9**
Female	**12**	**0.0172 ± 0.0071**	**34 ± 17**	**7.2 ± 4.7**	**3.3 ± 2.0**
Age					
< 65 years (56 ± 8 years)	**41**	**0.0136 ± 0.0077**	**35 ± 15**	**6.6 ± 4.3**	**3.3 ± 2.1**
≥ 65 years (71 ± 4 years)	**52**	**0.0151 ± 0.0071**	**38 ± 17**	**6.5 ± 3.3**	**3.0 ± 1.7**
Concomitant Medications					
Used digoxin	**55**	**0.0151 ± 0.0076**	**38 ± 16**	**6.3 ± 3.4**	**3.1 ± 2.0**
Did not use digoxin	**38**	**0.0136 ± 0.0070**	**35 ± 16**	**7.0 ± 4.8**	**3.3 ± 1.7**
Used calcium channel blockers	**35**	**0.0153 ± 0.0080**	**36 ± 18**	**6.3 ± 3.6**	**3.3 ± 2.1**
Did not use calcium channel blockers	**58**	**0.0140 ± 0.0070**	**38 ± 15**	**6.7 ± 4.3**	**3.0 ± 1.7**
Used β-blockers	**17**	**0.0128 ± 0.0074**	**43 ± 15**	**8.0 ± 3.8**	**3.0 ± 1.3**
Did not use β-blockers	**76**	**0.0149 ± 0.0073**	**36 ± 16**	**6.3 ± 4.0**	**3.2 ± 2.0**

3.0 EFFICACY RESULTS

3.0.1 All treated patients

Considering all 200 patients treated with study drug, the arrhythmia was successfully terminated in 34.0% (54 of 159) of the patients treated with ibutilide fumarate, but in 2.4% (1 of 41) of the patients treated with placebo. For the 100 patients with *atrial flutter* treated with study drug, the arrhythmia was successfully terminated in 38.75% (31 of 80) of the patients treated with ibutilide fumarate, but in 0.0% (0 of 20) of the patients treated with placebo. For the 100 patients with *atrial fibrillation* treated with study drug, the arrhythmia was successfully terminated in 29.1% (23 of 79) of the patients treated with ibutilide fumarate, but in 4.8% (1 of 21) of the patients treated with placebo. The following table and figure show the "success" rates by treatment group in all 200 patients treated with study drug:

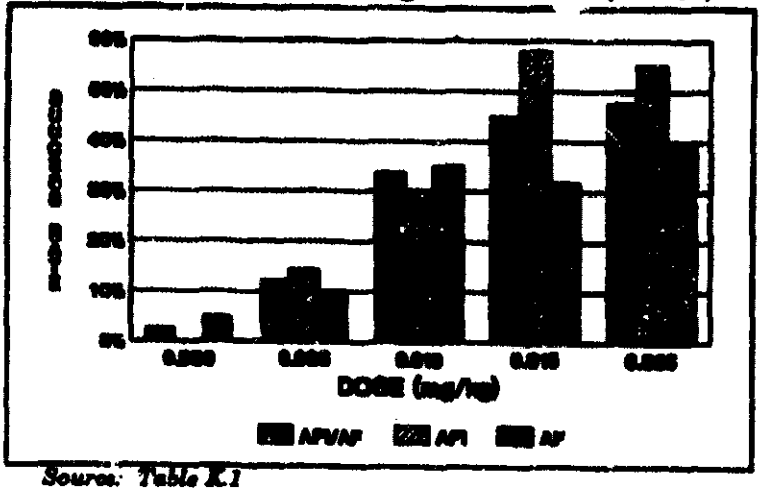
Principal Efficacy Results–All Treated Patients

Number (n) and Percent (%) of Success by Treatment Group in All Patients Treated With Study Drug (n=200)

	Placebo			Ibutilide fumarate (mg/kg) 0.005			0.010			0.015			0.025			p value*
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	
AFIAF†	41	1	2.4[A]	41	5	12.2[A]	40	13	32.5[B]	38	17	44.7[B]	40	19	47.5[B]	<0.0001
AFl†	20	0	0[A]	21	3	14.3[AB]	20	6	30.0[BC]	19	11	57.9[C]	20	11	55.0[C]	0.0003
AF†	21	1	4.8[A]	20	2	10.0[AB]	20	7	35.0[BC]	19	6	31.6[BC]	20	8	40.0[C]	0.0496

N = Total number of patients in group
n = Number of patients classified as a "success" on the final efficacy evaluation
* Chi-Square p value across dose groups
† Pairwise comparisons were only performed if the overall p value was ≤ 0.05. The letters "A," "B," and "C" show the results of pairwise comparisons. Groups with similar letters were not significantly different (p>0.05) from one another on pairwise comparison.

Termination of Atrial Flutter/Fibrillation in All Patients Receiving Medication (N=200)



Source: Table K.1

3.0.2 "Evaluable" patients

Considering the 197 evaluable patients treated with study drug, the arrhythmia was successfully terminated in 33.8% (53 of 157) of the patients treated with ibutilide fumarate, but in 2.5% (1 of 40) of the patients treated with placebo. For the 99 "evaluable" patients with *atrial flutter*, the arrhythmia was successfully terminated in 38.0% (30 of 79) of the patients treated with ibutilide fumarate, but in 0.0% (0 of 20) of the patients treated with placebo. For the 98 "evaluable" patients with *atrial fibrillation*, the arrhythmia was successfully terminated in 29.5% (23 of 78) of the patients treated with ibutilide fumarate, but in 4.5% (1 of 20) of the patients treated with placebo. The following table and figure show the "success" rates by treatment group in all 200 patients treated with study drug:

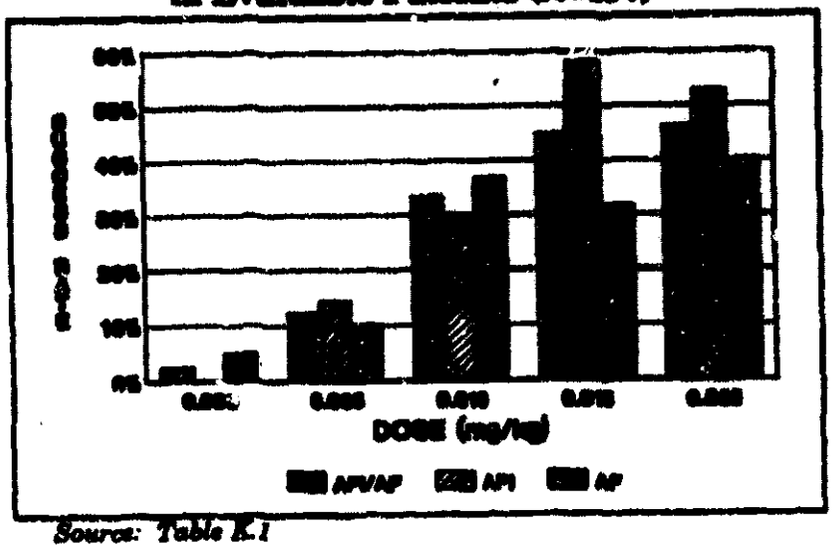
Principal Efficacy Results--All Evaluable Patients

Number (n) and Percent (%) of Successes by Treatment Group in All Evaluable Patients (n=197)

	Placebo			Ibutilide fumarate (mg/kg) 0.005			0.010			0.015			0.025			p value*
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	
AFl/AF*	40	1	2.5[A]	41	5	12.2[A]	39	13	33.3[B]	39	17	44.7[B]	39	18	46.15[B]	<0.0001
AFl*	20	0	0[A]	21	3	14.3[AB]	20	6	30.0[BC]	19	11	57.9[C]	19	10	52.6[C]	0.0004
AF*	20	1	5.0[A]	20	2	10.0[AB]	19	7	36.8[C]	19	6	31.6[BC]	20	8	40.0[C]	0.0001

N = Total number of patients in group
n = Number of patients classified as a "success" on the final efficacy evaluation
* Chi-Square p value across dose groups
* Pairwise comparisons were only performed if the overall p value was ≤ 0.05. The letters "A," "B," and "C" show the results of pairwise comparisons. Groups with similar letters were not significantly different (p>0.05) from one another on pairwise comparison.

Termination of Atrial Flutter/Fibrillation in Evaluable Patients (N=197)



Source: Table E.1

3.6.3 Efficacy Results at 24 hours: All treated patients

As noted in Section 3.6.1, overall the arrhythmia was successfully terminated within one hour of the end of the study-drug infusion in 34.0% (54 of 159) of the patients treated with ibutilide fumarate and in 2.4% (1 of 41) of the patients treated with placebo. At 24 hours, the results were slightly less favorable. That is, overall the arrhythmia was still classified as successfully terminated at 24 hours in 30% (48 of 159) of the patients treated with ibutilide fumarate and in 2.4% (1 of 41) of the patients treated with placebo:

Efficacy Results at 24 Hours--All Treated Patients

Number (n) and Percent (%) of Successes at 24 hours by Treatment Group in All Patients Treated with Study Drug (n=200)

	Placebo			Ibutilide fumarate (mg/kg) 0.005			0.010			0.015			0.025		
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
AF/AF	41	1	2.4	41	5	12.2	40	11[A]	27.5	38	16[B]	42.1	40	16[C]	40.0
AFl	20	0	0	21	3	14.3	20	6	30.0	19	11	57.9	20	9[C]	45.0
AF	21	1	4.8	20	2	10.0	20	5[A]	25.0	19	5[B]	26.3	20	7[C]	35.0

N Total number of patients in group
n Number of patients classified as a "success" on the final efficacy evaluation

[A] Two patients classified as "successes" in the primary analysis on page 15 (section 3.6.1) experienced alternating atrial fibrillation, atrial flutter, and normal sinus rhythm through hour 24, and therefore are reclassified as "failures" in this analysis (Patients #2345 and #2110).

[B] One patient classified as a "success" in the primary analysis on page 15 (section 3.6.1) experienced alternating atrial fibrillation, atrial flutter, sinus bradycardia, and normal sinus rhythm through hour 24, and therefore was reclassified as a "failure" in this analysis (Patient #2218).

[C] Three patients classified as "successes" in the primary analysis on page 15 (section 3.6.1) were not classified as successes through Hour 24: (a) Patient #1316 experienced termination of his atrial flutter 17 minutes after the infusion, but he also developed sustained polymorphic ventricular tachycardia requiring cardioversion. For purposes of the 24 hour evaluation, this patient is classified as a "failure." See the patient narrative in section 3.6.5.; (b) Patient #2221 (AF) developed alternating atrial fibrillation, atrial flutter, and normal sinus rhythm through hour 24, and therefore was reclassified as a "failure" in this analysis, and; (c) The rhythm in Patient #1226 (AFl) was unknown at Hour 24 and was therefore not considered a success.

These 24-hour results are of uncertain reliability as they were obtained through an indirect, piecemeal, retrospective assessment. The 24-hour results in this study were obtained (at the request of the FDA) through a retrospective chart review of the enrolled patients. In an attempt to determine whether patients who had converted to sinus rhythm remained free of their atrial arrhythmias through the 24 hour period, the sponsor was asked to evaluate the charts retrospectively and ended up reviewing miscellaneous notes about telemetry, miscellaneous 12-lead EKG data, information about the pulse gathered on the case report forms (e.g., "regular" vs. "irregular"), and data gathered occasionally from other sources (e.g., progress notes and discharge summaries).

By contrast, in the "Repeat Dose Study" (i.e., "Study 15" or Protocol P/7550/0015), each investigator was asked that question prospectively on the case report form. On the case report form in that study, investigators were asked to make the following assessment:

"For those patients whose atrial fibrillation/flutter terminated any time during the 24-hour study, from the time of termination the patient:

(1) Remained in normal sinus rhythm through Hour 24
(2) Remained in the rhythm he/she was in when atrial fibrillation/flutter terminated (other than NSR) through Hour 24
(3) Reverted to atrial fibrillation and remained in atrial fibrillation through Hour 24
(4) Reverted to atrial flutter and remained in atrial flutter through Hour 24
(5) Alternated between atrial fibrillation, atrial flutter, and normal sinus rhythm. Rhythm at Hour 24:
(6) Other:..."

3.6.4 Time to termination of arrhythmia

For the 55 of the 200 patients treated with study drug whose arrhythmia terminated successfully, the time to termination (as measured from the beginning of the infusion of study drug) ranged from 3 minutes to 70 minutes. The mean and median times to termination are shown in the table below.

Mean and Median Times for the Successful Termination of Arrhythmia Among Treated Patients (in minutes)

	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg	p value*
AFl (N=31)						
n	0	3	6	11	11	
mean	--	34.0	17.2	24.3	13.8	0.14
median	--	23.0	16.0	18.0	10.0	
AF (N=24)						
n	1	2	7	6	8	
mean	31.0	19.5	17.6	24.5	10.9	0.35
median	31.0	19.5	10.0	16.5	10.0	
AFlAF (N=55)						
n	1	5	13	17	19	
mean	31.0	28.2	17.4	24.35	12.6	0.05
median	31.0	23.0	15.0	18.0	10.0	

* From one-way ANOVA across dose groups

3.6.5 Relationship of Ibutilide Plasma Concentration to Termination of Atrial Flutter/Fibrillation[10]

Termination of the arrhythmia did not appear to be related directly to ibutilide plasma concentration. The range of ibutilide plasma concentrations in patients whose arrhythmia was not successfully terminated was similar to the range of concentrations in patients whose arrhythmias did terminate. Overall, the arrhythmia terminated in 55 of the 200 treated patients. Plasma concentrations were available for 48 of these patients, including one patient whose arrhythmia terminated after receiving placebo. The mean (±s.d.) plasma concentration at which the arrhythmia terminated in these 48 patients was 8.78 ± 11.34 ng/ml (coefficient of variation=129%), and the median was 4.1 ng/ml. The values ranged from 0.0 ng/ml (below the level of detection) to 59.8 ng/ml. High transient plasma concentrations occurred during and immediately following ibutilide infusion (the range was generally between 10 and 50 ng/ml at the end of the infusion) and usually dropped to near or below 1 ng/ml within an hour of the infusion.

3.6.6 Factors possibly influencing efficacy

3.6.6.1 Duration of arrhythmia

The duration of the arrhythmia was inversely related to the likelihood of successful cardioversion with ibutilide. Logistic regression demonstrated that in both the combined (AF/AF) and atrial flutter (AFl) strata, after adjusting for dose, the duration of arrhythmia was significantly related to the success rate (p=0.014 and p=039, respectively).[11] That is, the longer the duration of the arrhythmia, the lower the likelihood of success. In the atrial fibrillation (AF) stratum, however, the duration of the arrhythmia was not significantly related to the success rate (p=0.207).

In patients who had their arrhythmia successfully terminated, the median duration of the arrhythmia in the combined stratum (AF/AF) across all dose groups was 7.4 days, in the atrial flutter (AFl) stratum it was 6.5 days, and in the atrial fibrillation (AF) stratum it was 12.8 days. In contrast, in patients whose arrhythmia was not successfully terminated, the median duration of the arrhythmia in the combined stratum (AF/AF) across all dose groups was 22.1 days, in the atrial flutter (AFl) stratum it was 14.0 days, and in the atrial fibrillation (AF) stratum it was 26.2 days.

3.6.6.2 Ejection fraction

Logistic regression showed a significant association between ejection fraction (normal vs. decreased) and success rate only in patients with atrial flutter (AFl). After adjusting for dose, patients with atrial flutter and a normal ejection fraction had a higher success rate than patients with atrial flutter and a decreased ejection fraction (p=0.049). However, logistic regression demonstrated that in both the combined (AF/AF) and atrial fibrillation (AF) strata, after adjusting for dose, ejection fraction was not significantly related to the success rate.

3.6.6.3 Left atrial diameter, valvular heart disease

Neither left atrial diameter (normal vs. abnormal) nor valvular heart disease (present vs. absent) were related to the likelihood of successful cardioversion with ibutilide. That is, logistic regression

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[10] For a complete assessment of the pharmacokinetic results, see the evaluation by [redacted] biopharmaceutical reviewer.

[11] In this logistic regression, the duration of the arrhythmia was truncated at 90 days, and the interaction term of "dose by duration of arrhythmia" was eliminated (i.e., this interaction term had not been significant when it had been included in the logistic regression of "duration of atrial fibrillation/flutter").

analyses that were adjusted for dose neither demonstrated a significant association between left atrial diameter and the success rate, nor a significant association between valvular heart disease and the success rate.

3.6.6.4 Prolongation of QTc interval

The QTc interval was not prolonged from baseline preferentially either in patients who were "successes" or in patients who were "failures." That is, analyses of variance for changes from baseline in the QTc interval[12] did not demonstrate a significant difference between success and failure in any of the dose groups treated with ibutilide.

3.6.6.5 Concomitant use of other medications

3.6.6.5.1 Concomitant use of digoxin

Concomitant use of digoxin was associated with lower success rates in two of the three strata. Logistic regression demonstrated that in both the combined (AF/AF) stratum and the atrial flutter (AFl) stratum, after adjusting for dose, patients *not* receiving digoxin had a higher success rate than patients receiving digoxin (p=0.039 and p=0.050, respectively).[13] The overall success rate (excluding patients receiving placebo) was 43% (29 of 66) in the patients not receiving digoxin compared to 27% (25 of 91) in those receiving digoxin. In the atrial fibrillation (AF) stratum, however, the use of digoxin was not significantly related to the success rate (p=0.398).

For example, the figure below shows the success rates (by dose group) in the combined (AF/AF) stratum for patients who did and for patients who did not receive digoxin. Note that this figure considers only the 197 "evaluable" patients.

Ibutilide did not affect digoxin blood levels. Changes from baseline in digoxin levels were similar across all of the treatment groups (i.e., the placebo group and the four ibutilide treatment groups).

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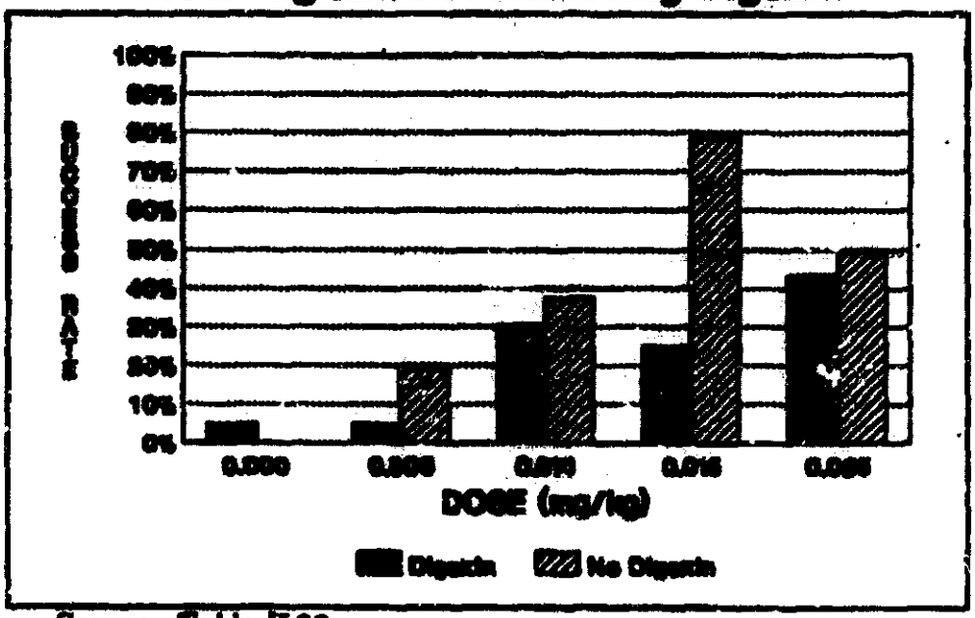
[12] Changes from baseline were calculated using the one-hour ECG because it was the only time point after the infusion that data were collected for both successes and failures.

[13] In this logistic regression, the interaction term of "dose by use of digoxin" was eliminated (i.e., this interaction term had been nonsignificant when it had been evaluated in the logistic regression of "no use vs. use of digoxin").

Termination of Arrhythmia in Patients Receiving and Not Receiving Digoxin



Source: Table K20

3.5.6.5.2 Concomitant use of β-adrenergic blocking agents

Logistic regression showed a significant association between use of β-adrenergic blocking agents and the success rate in patients with atrial flutter (AFl). After adjusting for dose, patients with atrial flutter who were taking β-adrenergic blocking agents had a higher success rate than patients with atrial flutter not taking β-adrenergic blocking agents (p=0.0045)[14]. The overall success rate in this stratum (excluding patients receiving placebo) was 79% (11 of 14) for those taking beta-adrenergic blocking agents compared to 30% (20 of 66) for those not using these agents. However, logistic regression demonstrated that in both the combined (AFl/AF) and atrial fibrillation (AF) strata, after adjusting for dose, use of beta-blockers was not significantly related to the success rate (p=0.075 and p=0.658, respectively). For example, the overall success rate (excluding patients receiving placebo) in the combined (AFl/AF) stratum was 50% (15 of 30) for those using beta-adrenergic blocking agents, compared to 30% (39 of 129) for those not using these agents.

3.5.6.5.3 Concomitant use of calcium-channel blocking agents

Concomitant use of calcium-channel blocking agents was not related to the likelihood of successful cardioversion with ibutilide. Logistic regression analyses that were adjusted for dose did not demonstrate a significant association between use of these agents and the success rate.

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[14] In this logistic regression, the interaction term of "dose by use of beta-blocker" was eliminated (i.e., this interaction term had been nonsignificant when it had been evaluated in the logistic regression of "no use vs. use of beta-blocker").

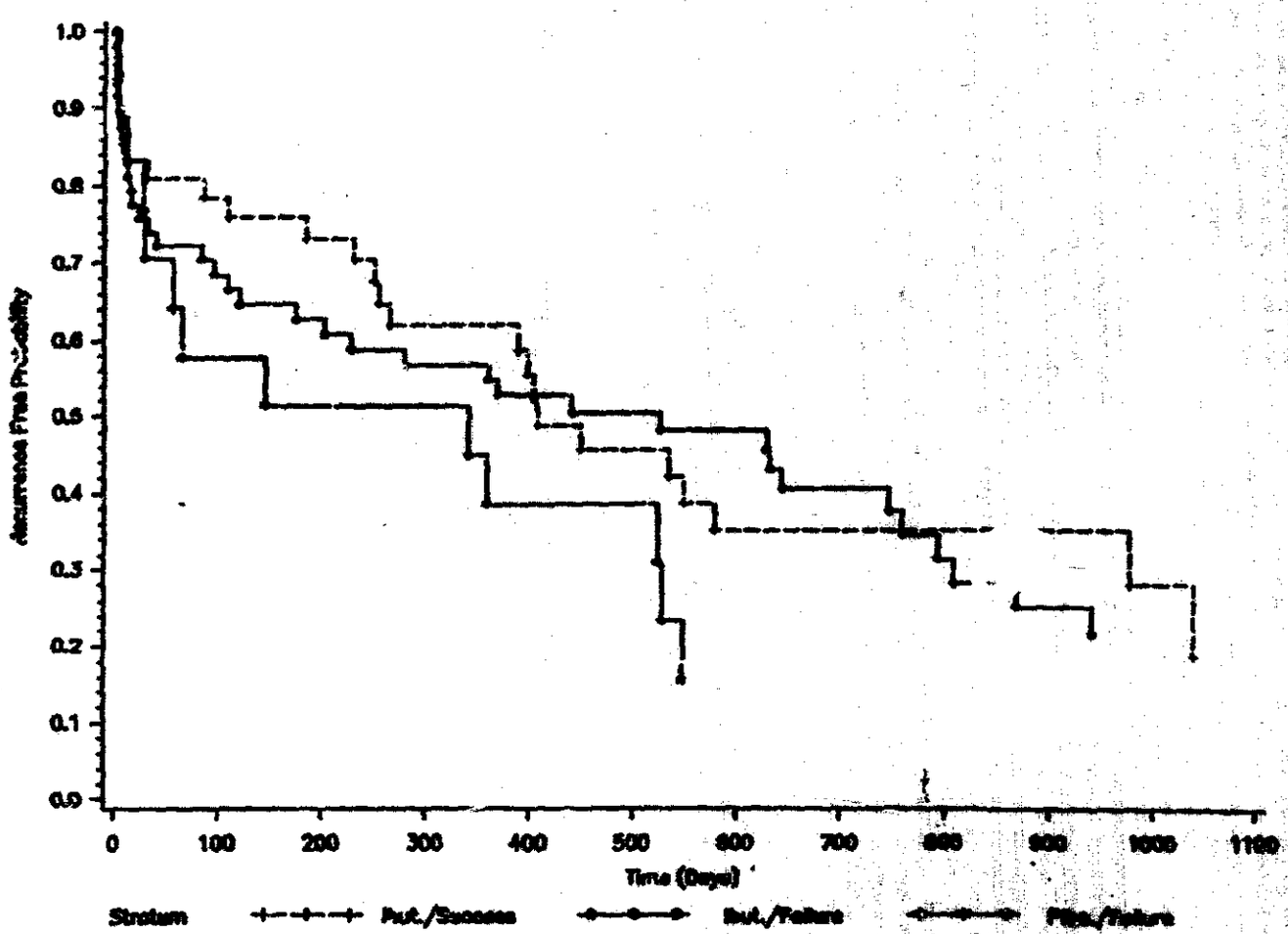
3.6.7 Long-term follow-up

At the request of the FDA, the sponsor performed a retrospective chart review to assess the long-term outcome of patients enrolled in the clinical trial. Kaplan-Meier curves were generated with the available data to show the length of time patients were free of atrial arrhythmias for three groups of patients that had been enrolled in the trial: (a) those successfully converted with ibutilide (n=49), (b) those who failed to be converted with ibutilide but who were then successfully converted by other means (n=30), and, (c) those who failed to be converted with placebo but who were then successfully converted by other means (n=20). Interpretation of these data are confounded by many factors (e.g., design issues, incomplete or sporadic follow-up, low statistical power, confounding medications, etc.). Nonetheless, the Kaplan-Meier curves are shown in the figure on the following page.

Atrial Arrhythmia-Free Curves

All Patients Receiving Medication (N=288)

Protocol P/7588/3014 Original/Extension Combined Ruffles (N=288)



Note: When the day of the month was unknown, the day following the infusion was used (Patient 1337)

3.7 PHARMACODYNAMIC RESULTS

3.7.1 Electrocardiographic effects[15]

3.7.1.1 PR intervals

PR intervals were difficult or impossible to measure at baseline when the patients were in atrial flutter or fibrillation. Accordingly, data assessing changes in the PR interval from baseline or comparing changes in the PR interval among dose groups were scant and not helpful.

3.7.1.2 QRS duration

The QRS duration at baseline was not significantly different across dose groups. The only significant change from baseline was in the 0.025 mg/kg dose group of the atrial fibrillation (AF) stratum. For the seven patients whose arrhythmia terminated during the infusion (and who also had the QRS duration measured at that time), the QRS duration increased from baseline by a mean of 4.86 msec. This was statistically significant (p=0.0467). Across dose groups, however, there were no significant differences in change of QRS duration from baseline to Hour 1. The change-from-baseline (CFB) "n" for these groups equals 192 patients.

3.7.1.3 Atrial cycle length

At baseline, the atrial cycle length (measured in patients in the atrial flutter stratum) was not significantly different across dose groups. The atrial cycle length increased significantly from baseline in all of the ibutilide treatment groups upon termination of the arrhythmia during infusion (CFB n=20). In contrast, the placebo group had no terminations of the arrhythmia during the infusion. These mean increases in the atrial cycle length ranged from 579 to 798 msec. The atrial cycle length was also significantly increased from baseline at Hour 1 in the 0.010, 0.015, and 0.025 mg/kg groups by 160, 424, and 280 msec, respectively (CFB n=49 in these three groups). In contrast, in the placebo group the atrial cycle length increased nonsignificantly (+12 msec; p=0.20) from baseline at 1 hour (CFB n=17).

Analysis of variance for change from baseline demonstrated a highly significant difference (p<0.0001) among dose groups. The pairwise comparisons showed a significant difference between the 0.015 mg/kg group and the placebo, 0.005, and 0.010 mg/kg groups, as well as between the 0.025 mg/kg group and the placebo and 0.005 mg/kg groups.

Ibutilide also significantly increased the atrial cycle length from baseline at Hour 1 in groups of patients whose arrhythmias did not terminate (i.e., "failures"). The cycle length increased significantly from baseline to Hour 1 in the 0.010 and 0.025 mg/kg groups by 18 and 43 msec, respectively (CFB n=21 in these two groups). In contrast, in the placebo group in which all of the patients were "failures," the atrial cycle length increased nonsignificantly from baseline at 1 hour (+12 msec; p=0.20).

3.7.1.4 QT interval

The duration of the QT interval at baseline was not significantly different across dose groups. For the 40 patients whose arrhythmia terminated during the infusion (and who also had changes from

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[15] Data in this section are for "evaluable" patients only (n=197).

baseline of the QT interval measured at that time), the QT interval increased significantly from baseline in each of dose groups treated with ibutilide. At the time of arrhythmia termination during the infusion in the four ibutilide treatment groups, the QT interval increased from baseline by means that ranged from 73 msec to 145 msec. In each of the four ibutilide-treatment groups at Hour 1 (CFB n=151), the QT interval increased from baseline by means that ranged from 22 msec to 73 msec. By contrast, at Hour 1 in the placebo group (CFB n=36) the QT interval had essentially not changed from baseline (decrease of 0.14 msec, p=0.97).

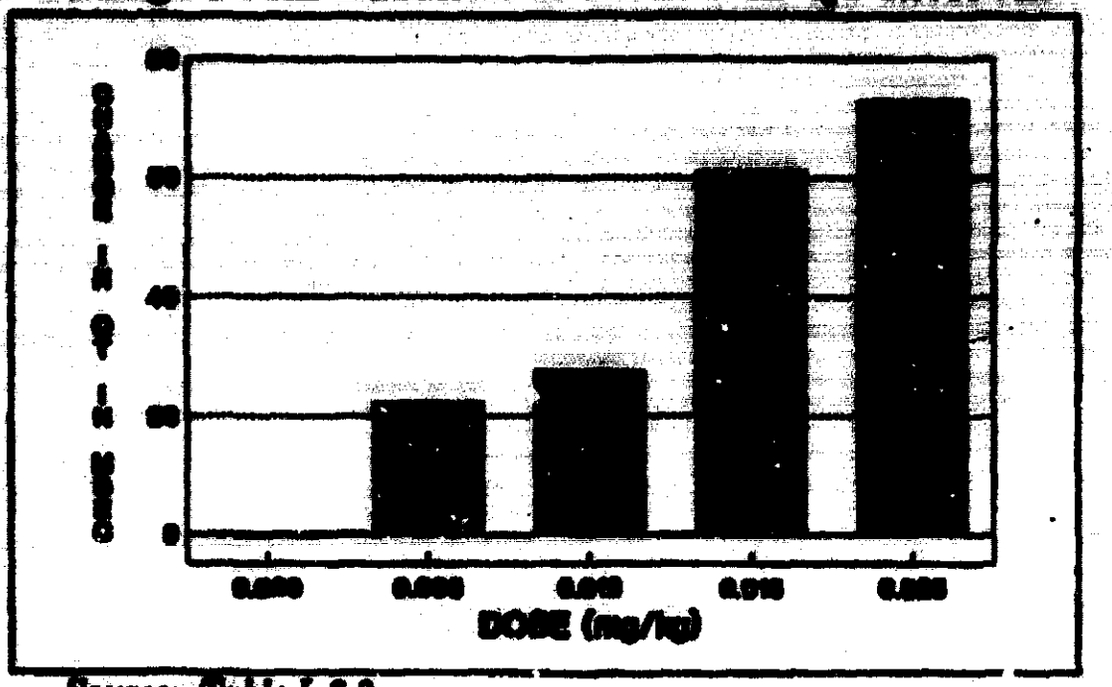
Analysis of variance indicated a highly significant difference (p<0.0001) among dose groups in the change of QT interval from baseline to Hour 1 in the combined (AF/AFl) stratum and in the atrial flutter (AFl) stratum. The difference was also statistically significant (p=0.0081) in the atrial fibrillation (AF) stratum. Pairwise comparisons are shown in the table below, and mean changes from baseline in the QT interval for the combined (AFl/AF) group are shown in the figure on the top of the next page.

Change from Baseline to Hour 1 in QT Interval (msec)

Stratum	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg	Overall P-Value
AFl/AF	-0.14‡	+22.18	+27.46*	+60.84*†‡	+72.79*†‡	<0.0001
AFl	-3.56	+17.79	+23.42	+75.68*†‡	+82.11*†‡	<0.0001
AF	+8.20	+26.35	+31.72	+45.22*	+64.40*†	0.0081

* Different from placebo group (P≤0.05)
† Different from 0.005 mg/kg group (P≤0.05)
‡ Different from 0.010 mg/kg group (P≤0.05)
Source: Tables L.3.3, L.4, and L.4A

Change From Baseline to Hour 1 in QT Interval



Source: Table L.3.3

3.7.1.5 QTc Interval

The length of the QTc interval at baseline was not significantly different across dose groups. For the 22 patients in the 0.010 and 0.025 mg/kg dose groups whose arrhythmia terminated during the infusion (and who also had changes from baseline of the QTc interval measured at that time), the QTc interval increased significantly from baseline by means of 31 and 51 $sec^{\frac{1}{2}}$ (x 1000), respectively. In each of the four ibutilide-treatment groups at Hour 1 (CFB n=149), the QTc interval increased from baseline by means that ranged from 19 to 52 $sec^{\frac{1}{2}}$ (x 1000). By contrast, at Hour 1 in the placebo group (CFB n=36) the QTc interval had changed little from baseline (decrease of 4.7 $sec^{\frac{1}{2}}$ (x 1000); p=0.29).

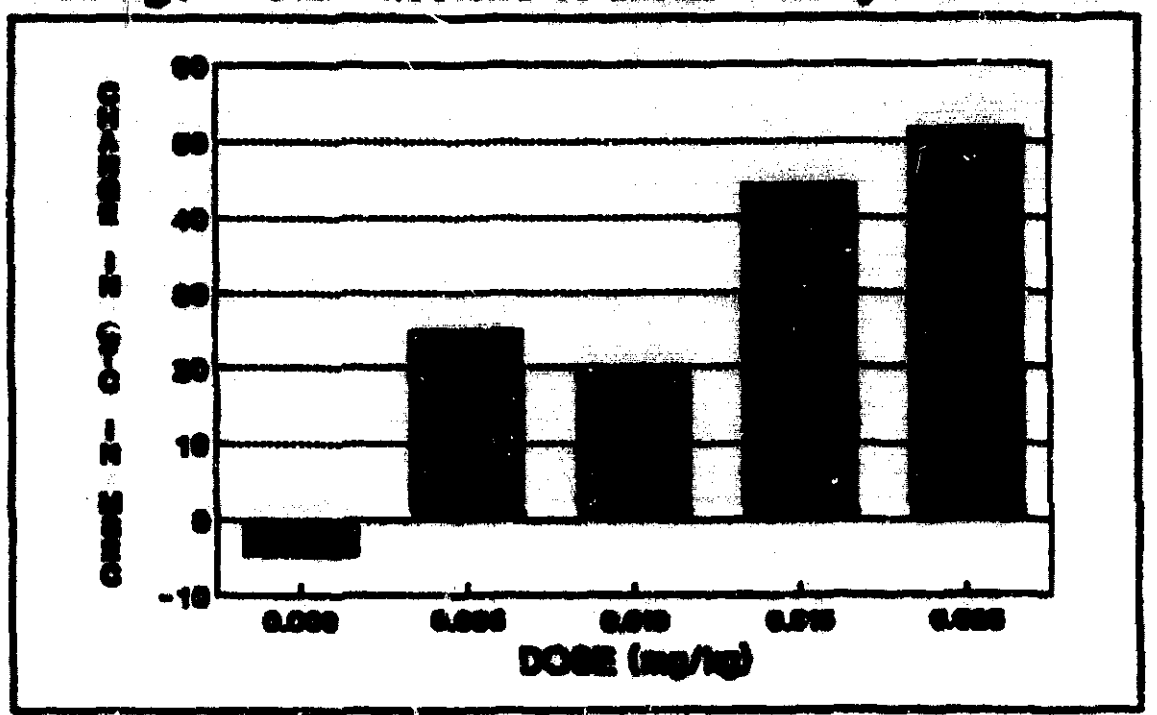
Analysis of variance indicated a highly significant difference among dose groups in the change of QTc interval from baseline to Hour 1 in the combined (AF/AFl) stratum (p<0.0001) and in the atrial flutter (AFl) stratum (p=0.0003). The difference was also statistically significant (p=0.0187) in the atrial fibrillation (AF) stratum. Pairwise comparisons are shown in the table on the next page, and mean changes from baseline in the QTc interval for the combined (AFl/AF) group are shown in the figure on the next page.

[illegible] Change from Baseline to Hour 1 in QTc Interval (msec)

Structure	Placebo	0.005 mg/kg	0.010 mg/kg	0.015 mg/kg	0.025 mg/kg	Overall P-Value
AP/AP	-4.07‡	+[illegible]*	+[illegible]*	+44.17*‡	+51.6]*‡	<[illegible]
AP1	-0.54	+[illegible]	+[illegible]	+[illegible]*‡	+57.78*‡	[illegible]
AF	+[illegible]‡	+[illegible]*	+[illegible]*	+[illegible]*	+46.16*	[illegible]

* Different from placebo group (P≤0.05)
† Different from 0.005 mg/kg group (P≤0.05)
‡ Different from 0.010 mg/kg group (P≤0.05)
Source: Tables L.3.4, L.4, and L.4A

Change From Baseline to Hour 1 in QTc Interval



Source: Table L.3.4

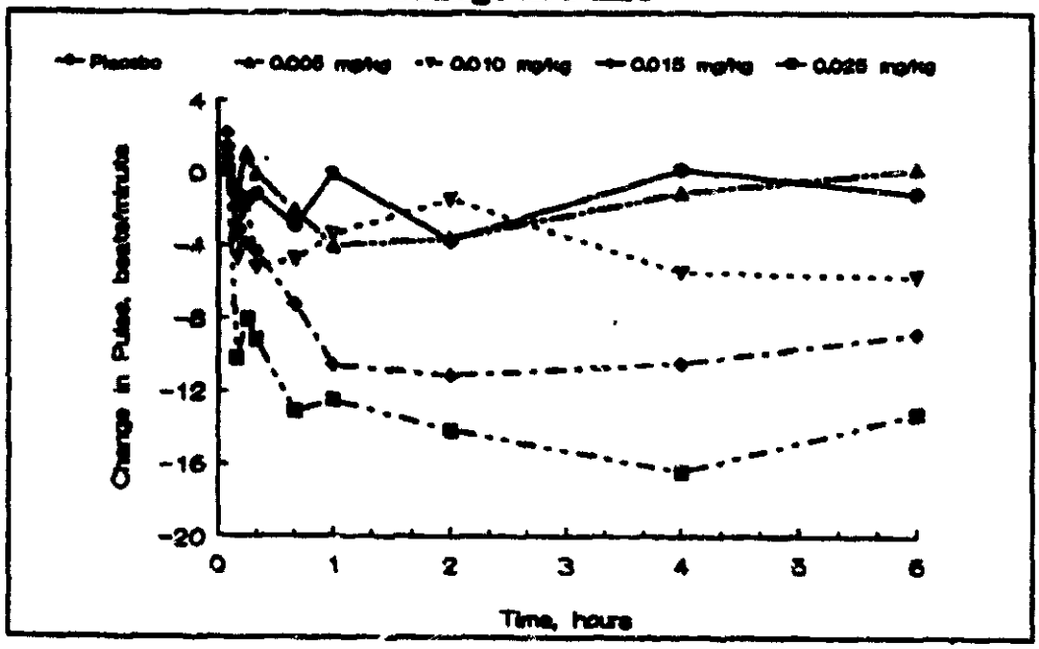
3.7.2 Effects on vital signs

Ibutilide did not appear to have any consistent, significant, dose-related, and persistent effects on systolic or diastolic blood pressure. The only statistically significant difference across groups in change from baseline occurred at Minute 40 in systolic blood pressure (p=0.0021). Pairwise comparisons showed that the -6.93 mmHg decrease from baseline in the 0.025 mg/kg group was significantly different from the change in the placebo group (+1.09 mmHg, pairwise p=0.0058), the change in the 0.005 mg/kg group (+0.63 mmHg, pairwise p=0.0097), and the change in the 0.010 mg/kg group (+3.53 mmHg, pairwise p=0.0004). At Minute 40, the 0.015 mg/kg group (-4.36 mmHg) also had a significantly greater decrease from baseline when compared with the 0.010 mg/kg group (+3.53 mmHg, pairwise p=0.0077).

In contrast, ibutilide had significant, persistent, and possibly dose-related effects on pulse. This effect can probably attributed to termination of the atrial arrhythmia. Analysis of variance indicated that there were significant differences among dose groups in change from baseline at Minute 10 and Hours 1, 2, 4, 8, and 16. Pairwise comparisons indicated that the differences were between the highest dose group (0.025 mg/kg) and the placebo, 0.005, and 0.015 mg/kg groups. The higher dose groups also experienced larger mean decreases in pulse than the lower dose groups or placebo. See the figure below.

Consistent with the notion that the decrease in pulse might be attributable to termination of the atrial arrhythmia, a change from baseline analysis was done at Hour 1 for failures only. Among the failures, there were no statistically significant changes from baseline in any of the dose groups.

Change in Pulse



Source: Table M.3.3

3.8 SAFETY RESULTS[16]

This summary of the safety results will emphasize major adverse events. These are summarized in the table on the next page. Narratives for patients who experienced major or notable adverse events are located in section 3.8.5.

3.8.1 Adverse Events

3.8.1.1 Most common adverse events

Fifty-four (54) of the 200 patients enrolled in the trial experienced at least one adverse event, half of whom experienced an adverse event of the cardiovascular system. That is, 27 of these patients experienced an adverse event of the cardiovascular system; 14 an adverse event of the body as a whole, and the remaining 13 experienced adverse events that were scattered among the other body systems. As shown in the table below, adverse events reported in three or more patients included hypotension, nonsustained monomorphic ventricular tachycardia (VT), headache, sustained polymorphic VT, and chest pain.

Number of Patients Experiencing the Most Frequent Medical Events

Medical Event	Placebo (N=41)	0.005 mg/kg (N=41)	0.010 mg/kg (N=40)	0.015 mg/kg (N=38)	0.025 mg/kg (N=40)	Total (N=200)
Hypotension		2		1	3	6
Nonsustained monomorphic VT		1	1	2	1	5
Headache	1		1	2	1	5
Sustained polymorphic VT			1	1	2	4
Chest pain			1	1	1	3

Source: Table P.3

3.8.1.2 Major adverse events

The table on the next page summarizes the major adverse events that occurred in the trial. No patients died during the course of the trial. Eight patients treated with ibutilide experienced serious adverse events, all of which were related to the cardiovascular system, including six cases of polymorphic ventricular tachycardia. No patients withdrew from the trial because of adverse events. However, the 10-minute infusion was discontinued in five patients because of adverse events of the cardiovascular system, including four cases of ventricular tachycardia. Eight patients experienced 11 adverse events of severe intensity, nearly all of which were related to the cardiovascular system. Overall, eleven patients experienced significant cardiac arrhythmias and six patients experienced hypotension. One patient experienced a notable increase in BUN and creatinine during the trial and died five days following the study.

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[16] Safety issues are discussed comprehensively in Dr. Gordon's review.

Major Adverse Events			
Category	n*	Patient ID	Dose Group
Deaths	0		
Serious Events	9	#1104 Atrial Arrhythmia, Extrasystoles Bigeminal	0.005
		#2225 Cerebrovascular Accident	PLA
		#2347 Dizziness, Hypotension	0.005
		#2125 Nonsustained Polymorphic Ventricular Tachycardia	0.010
		#2308 Sustained Polymorphic Ventricular Tachycardia	0.025
		#1106 Sustained Polymorphic Ventricular Tachycardia	0.010
		#2214 Sustained Polymorphic Ventricular Tachycardia	0.015
		#1316 Sustained Polymorphic Ventricular Tachycardia	0.025
		#2216 Sustained Polymorphic Ventricular Tachycardia	0.025
Withdrew from Trial	0		
Discontinued Infusion	5	#1304 QT Segment Prolonged	0.025
		#2323 Nonsustained Monomorphic Ventricular Tachycardia	0.005
		#2308 Nonsustained Polymorphic Ventricular Tachycardia	0.025
		#1106 Sustained Polymorphic Ventricular Tachycardia	0.010
		#2216 Sustained Polymorphic Ventricular Tachycardia	0.025
Severe	8	#1106 Sustained Polymorphic Ventricular Tachycardia	0.010
		#2214 Sustained Polymorphic Ventricular Tachycardia	0.015
		#2216 Sustained Polymorphic Ventricular Tachycardia, Hypotension	0.025
		#2347 Hypotension	0.005
		#2345 Chest Pain, Sinus Arrhythmia	0.010
		#1311 Bradycardia, Hypotension	0.025
		#1316 Sustained Polymorphic Ventricular Tachycardia	0.025
		#2308 Non-Sustained Polymorphic Ventricular Tachycardia	0.025
Proarrhythmia	11	#1106 Sustained Polymorphic Ventricular Tachycardia	0.010
		#1316 Sustained Polymorphic Ventricular Tachycardia	0.025
		#2214 Sustained Polymorphic Ventricular Tachycardia	0.015
		#2216 Sustained Polymorphic Ventricular Tachycardia	0.025
		#2125 Nonsustained Polymorphic Ventricular Tachycardia	0.010
		#2308 Nonsustained Polymorphic Ventricular Tachycardia	0.025
		#1341 Nonsustained Monomorphic Ventricular Tachycardia	0.025
		#2207 Nonsustained Monomorphic Ventricular Tachycardia	0.015
		#2113 Nonsustained Monomorphic Ventricular Tachycardia	0.010
		#2323 Nonsustained Monomorphic Ventricular Tachycardia	0.005
		#2330 Nonsustained Monomorphic Ventricular Tachycardia	0.015
Hypotension	6	#1124 Hypotension	0.005
		#1301 Hypotension	0.015
		#1311 Hypotension	0.025
		#2213 Hypotension	0.025
		#2216 Sustained Polymorphic Ventricular Tachycardia, Hypotension	0.015
		#2347 Hypotension	0.005
Other Notable Events	1	#1116 Increase in BUN and creatinine; subsequent death	0.005

* Patients may belong to more than one category

3.8.1.2.1 Deaths

No deaths occurred during this trial.

3.8.1.2.2 Serious adverse events

As shown in the table below and summarized in the table of major adverse events on page 30, 9 patients experienced 11 serious adverse events. Ten of these 11 serious adverse events occurred in patients randomized to treatment with ibutilide, and one to a patient randomized to placebo. Narratives for these patients may be found in section 3.8.5.

Notably, each of the serious adverse events in the patients treated with ibutilide were related to the cardiovascular system, including six cases of polymorphic ventricular tachycardia (four of which were sustained). These cases are discussed further in the section on proarrhythmia below. Finally, one patient treated with ibutilide (Patient #1104) developed sinus node abnormalities following overdrive pacing that included sinus arrest (five seconds) and sinus bradycardia (44 bpm). This was followed by a junctional rhythm with ventricular bigeminy. The patient was treated with temporary cardiac pacing for about 24 hours.

Number of Patients Experiencing Serious Medical Events

Medical Event	Placebo (N=41)	0.005 mg/kg (N=41)	0.010 mg/kg (N=40)	0.015 mg/kg (N=38)	0.025 mg/kg (N=40)	Total (N=200)
Atrial arrhythmia		1				1
Cerebrovascular accident	1					1
Dizziness		1				1
Extrasystoles bigeminal		1				1
Hypotension		1				1
Nonsustained polymorphic VT			1		1	2
Sustained polymorphic VT			1	1	2	4

Source: Table P.14

3.8.1.2.3 Withdrawals because of adverse events

No patients withdrew from the trial because of adverse events.

3.8.1.2.4 Adverse Events Causing Discontinuation of Infusion

As shown in the table below and summarized in the table of major adverse events on page 30, five patients experienced an adverse event that caused discontinuation of the infusion. Narratives for these patients may be found in section 3.8.5.

Each of these adverse events affected the cardiovascular system, and in three patients the events were considered to be serious (Patients ##2308, #1106, and #2216; see section 3.8.1.2.2 on page 31, above). In addition, after nine minutes of ibutilide infusion Patient #1304 developed marked prolongation of the QT interval (from 428 to 680 msec) and QTc interval (from 0.458 to 0.731 sec[½]). Finally, Patient #2323 developed nonsustained monomorphic ventricular tachycardia during the ibutilide infusion (i.e., a run of four beats and a run of eight beats).

Number of Patients with Medical Events Necessitating Discontinuation of Infusion

Medical Event	Placebo (N=41)	0.005 mg/kg (N=41)	0.010 mg/kg (N=40)	0.015 mg/kg (N=38)	0.025 mg/kg (N=40)	Total (N=200)
Sustained polymorphic VT			1		1	2
QT segment prolongation					1	1
Nonsustained monomorphic VT		1				1
Nonsustained polymorphic VT					1	1

Source: Table P.16

3.8.1.2.5 Severe adverse events

Overall, eight patients experienced 11 adverse events of a severe intensity, all of which occurred in patients randomized to and treated with ibutilide. Four of these events occurred in patients at the highest dose level (0.025 mg/kg). All eleven severe adverse events involved the cardiovascular system. These 11 severe adverse events included the following: chest pain (1 case), sinus arrhythmia (1 case), bradycardia (1 case), hypotension (3 cases), nonsustained polymorphic ventricular tachycardia (1 case), and sustained polymorphic ventricular tachycardia (4 cases).

As noted above in section 3.8.1.2.2, in six patients the adverse events were also classified as serious (Patients #1106, 2214, 2216, 2347, 1316, and #2308). In addition, at the end of the ibutilide infusion, Patient #1311 developed an abrupt increase in AV block, severe bradycardia (HR=47 bpm), and severe hypotension. These resolved without intervention. Finally, Patient #2345

developed severe sinus arrhythmia (sinus pauses) on the day of ibutilide treatment and severe chest pain the day after treatment with ibutilide.

3.8.1.2.6 Proarrhythmia

As shown in the table below and summarized in the table of major adverse events on page 30, 6.9% (11 of 159) of the patients treated with ibutilide experienced a proarrhythmic event. Sustained polymorphic ventricular tachycardia (VT) occurred in 2.5% (4 of 159) of the patients treated with ibutilide; nonsustained polymorphic VT occurred in 1.3% (2 of 159), and nonsustained monomorphic VT occurred in 3.1% (5 of 159). Narratives for these patients may be found in section 3.8.6.

Proarrhythmia

Arrhythmia	Placebo (N=41)	0.005 mg/kg (N=41)	0.010 mg/kg (N=40)	0.015 mg/kg (N=38)	0.025 mg/kg (N=40)	Total (N=200)
Sustained polymorphic VT			1	1	2	4
Nonsustained polymorphic VT			1		1	2
Nonsustained monomorphic VT		1	1	2	1	5

Source: Tables P.3-P.6

The mean (±s.d.) plasma concentration at which proarrhythmia occurred in these 11 patients was 7.46 ± 8.19 ng/ml and the median was 5.56 ng/ml. However, plasma concentrations of ibutilide were not obviously related to the occurrence of these proarrhythmic events. In part this was because the plasma levels were highly variable: the coefficient of variation was 110%, and the values ranged from 0.833 ng/ml to 29.0 ng/ml.

In healthy volunteers, each enantiomer of ibutilide (U-82208E and U-82209E) makes up approximately 50% of the racemic mixture. To make a comparison with patients who had experienced a proarrhythmic event, the sponsor determined the ratio of the two enantiomers that make up racemic ibutilide in all six of the patients who experienced polymorphic ventricular tachycardia (sustained: Patients #1106, #1316, #2214, and #2216; nonsustained: Patients #2125 and #2308). Twenty-six samples from these six patients were assayed using chiral-specific methodology. Results were expressed as the percent of total drug accounted for by the (+)-isomer of ibutilide fumarate, U-82208E. The average for the 26 plasma samples was 53.3±1.9% (%CV = 3.7%), suggesting that the ratio of enantiomers is not significantly skewed from 1:1 in these patients.

Five of the six patients who had episodes of polymorphic VT had a decreased ejection fraction. The ejection fraction was not reported for the sixth patient, but left ventricular function was described as "mildly decreased." Three of the six patients also had a history of congestive heart failure. Three of the six also had a QTc at baseline greater than 0.440 sec*.

All four episodes of sustained polymorphic ventricular tachycardia were classified as serious, all occurred either during the infusion or within 17 minutes after the end of the infusion. In two of these cases (Patients #1106 and #2216) the arrhythmia was associated with immediate adverse clinical consequences requiring cardioversion or defibrillation.[17] The two other patients also underwent cardioversion (Patients #2214 and #1316). Among the five patients that had episodes of nonsustained monomorphic VT, the longest episode was 11 beats.

3.6.1.2.7 Hypotension

As summarized in the table of major adverse events on page 30, six patients experienced hypotension reported as a medical event. Narratives for these patients may be found in section 3.6.5.

The mean (±s.d.) plasma concentration at which hypotension occurred in these six patients was approximately 7.51 ± 9.13 ng/ml (coefficient of variation=122%), and the median was approximately 4.29 ng/ml. The values ranged from 0.0 ng/ml (below the level of detection) to 22.7 ng/ml.

Of the six patients with hypotension reported as a medical event, one case was serious (Patient #2347) and three were of severe intensity (Patients #2347, #1311, and #2216). Three cases occurred in close temporal relationship to the infusion, and two were associated with arrhythmias: (a) Patient #2216 became hypotensive after developing sustained polymorphic VT during the infusion, (b) Patient #1311 developed abrupt AV block at the end of the infusion and became hypotensive; (c) Patient #2213 developed mild hypotension that resolved spontaneously five minutes after the infusion. In addition, Patient #1301 developed moderate hypotension associated with a decrease in heart rate (atrial flutter with variable conduction) one hour after the infusion.

Finally, several cases were confounded by administration of other medications: Patient #1124 developed mild hypotension after receiving furosemide; (b) Patient #1301 (see immediately above) developed moderate hypotension and was receiving diltiazem and nitroglycerin, and (c) Patient #2347 developed severe hypotension and was also receiving diltiazem, procainamide, and digoxin.

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[17] In Patient #1106 the polymorphic ventricular tachycardia spontaneously deteriorated to ventricular fibrillation that required electrical defibrillation. In Patient #2216 the polymorphic ventricular tachycardia resulted in severe hypotension. With DC cardioversion the patient developed ventricular fibrillation that required defibrillation.

3.8.2 Cardioversion

Several patients who failed to convert to normal sinus rhythm after receiving placebo or after receiving ibutilide subsequently underwent attempted cardioversion. These groups of patients were compared to assess whether ibutilide has an adverse impact on subsequent cardioversion. Given the variability of the data, the small numbers, and the way in which the data were gathered, the numbers nonetheless do not suggest an obvious adverse effect of ibutilide on subsequent cardioversion. See the table below and on the next page.

These results are of uncertain reliability as they were obtained through a retrospective chart review (at the request of the FDA). By contrast, in the "Repeat Dose Study" (i.e., "Study 15" or Protocol P/7550/0015), each investigator was asked prospectively to supply these data on the case report form. On the case report form in that study, investigators were asked specifically to supply the number of attempts at electrocardioversion and the number of joules used for each attempt.

Number of Electrocardioversion Attempts Required to Terminate Abnormal Rhythm: Prior to Hour 24 and After Hour 24

	N	Mean	Median	Min, Max
To terminate abnormal rhythm prior to Hour 24				
Flutter				
Placebo	6	1.0	1.0	1, 1
Ibutilide	12	1.0	1.0	1, 1
Total	18	1.0	1.0	1, 1
Fibrillation				
Placebo	9	1.78	2.0	1, 3
Ibutilide	21	1.62	1.0	1, 3
Total	30	1.67	1.0	1, 3
For abnormal rhythm not terminated during 24-hour study				
Flutter				
Placebo	-	-	-	-
Ibutilide	3	1.7	1.0	1, 3
Total	3	1.7	1.0	1, 3
Fibrillation				
Placebo	3	3.0	3.0	2, 4
Ibutilide	4	2.5	3.0	1, 3
Total	7	2.7	3.0	1, 4

Number of Doses Required to Terminate Abnormal Rhythm:
Prior to Hour 24 and After Hour 24

	N	Mean	Median	Min, Max
To terminate abnormal rhythm prior to Hour 24				
Flutter				
Placebo	6	166.3	150.0	50, 360
Ibutilide	12	108.3	100.0	50, 200
Total	18	126.3	100.0	50, 360
Fibrillation				
Placebo	9	433.3	300.0	200, 960
Ibutilide	21	350.0	200.0	100, 960
Total	30	375.0	250.0	100, 960
For abnormal rhythm not terminated during 24-hour study				
Flutter				
Placebo	–	–	–	–
Ibutilide	3	350.0	100.0	50, 900
Total	3	350.0	100.0	50, 900
Fibrillation				
Placebo	3	653.3	600.0	400, 960
Ibutilide	4	557.5	505.0	100, 920
Total	7	598.6	600.0	100, 960

3.8.3 12-lead electrocardiogram

Safety data from the 12-lead electrocardiograms did not demonstrate any consistently adverse effects of ibutilide related to AV conduction, bundle-branch block, Q-waves, T waves, ST segments, acute myocardial ischemia, old myocardial infarctions, or acute myocardial infarctions.

3.8.4 Laboratory values

Changes in safety laboratories were generally of uncertain clinical significance. For example, decreases from baseline in hemoglobin and hematocrit occurred in the ibutilide groups and in the placebo group. Similarly, about 10%-12% of patients had normal hematocrits and hemoglobin values prior to the infusion, but decreased hematocrits and hemoglobin values afterwards. Most likely these were related to frequent blood sampling, hydration of the patients, or both.

Creatine kinase increased markedly from baseline in several patients. These increases were readily explained by electrical cardioversion.

As noted in the table of major medical events on page 30 (under "other notable events") Patient #1116 had undergone a heart transplant about five years prior to the study and was experiencing mild rejection. During the trial, he experienced an increase in BUN and creatinine and died five days following the study. The investigator felt the death was unrelated to the infusion. Further information is provided in the patient narratives (section 3.8.5).

3.8.5 Patient Narratives

These narratives provide detail on patients who experienced major or notable adverse events, as listed in the table on page 30. The narratives are organized by Patient ID number

Patient #1104; *Atrial Arrhythmia, Extrasystoles Bigeminal* (Investigator description: sinus arrest, ventricular bigeminy): This 65-year-old man with AFl received a ten-minute infusion of ibutilide (0.005 mg/kg). The drug did not terminate the AFl. One hour and six minutes after the end of the infusion the patient was paced out of AFl. He developed sinus bradycardia (approximately 44 bpm) and had a five-second pause (sinus arrest) following conversion. This was followed by junctional rhythm with ventricular bigeminy. The post-termination junctional bradycardia lasted approximately 30 minutes. Temporary pacing was utilized as the drug effect on rhythm wore off. Temporary pacing was continued for approximately 24 hours while the patient was given procainamide. The pacemaker was removed and the patient recovered. Both the sinus arrest and ventricular bigeminy were considered to be serious and of moderate intensity. (Total dose=0.43 mg ibutilide fumarate)

Patient #1106; *Sustained Polymorphic Ventricular Tachycardia* (Investigator description: Sustained Polymorphic VT): This 65-year-old man with AFl had a history of CHF and aortic valve replacement. He was randomized to a ten-minute infusion of ibutilide fumarate (0.010 mg/kg). His QTc at Minute -10 was 0.417 $sec^{\frac{1}{2}}$. After seven minutes of the infusion he had significant prolongation of the QT interval to 660 msec (baseline = 400 msec), frequent premature ventricular contractions, and seven runs of 3-4 beats of nonsustained VT. The infusion was discontinued and he immediately developed polymorphic VT which degenerated to ventricular fibrillation. The patient was rapidly cardioverted with restoration of AFl/AF with frequent couplets. His QTc at Hour 1 was 0.474 $sec^{\frac{1}{2}}$. This adverse event was classified as serious and of severe intensity. (Total dose = 0.66 mg ibutilide fumarate)

Patient #1116; *Increased BUN and creatinine; subsequent death*: This 54 year-old man had a heart transplant prior to the study and was in mild rejection. He had no prior history of AFl or AF. At baseline his BUN was 23 mg/dl (normal range: 9-21 mg/dl), with a creatinine of 1.7 mg/dl (normal range: 0.8-1.5 mg/dl). He was treated with ibutilide fumarate (0.005 mg/dl) for nine minutes, at which time he converted to NSR. Following the infusion his BUN rose to 51 mg/dl, with a creatinine of 2.2 mg/dl. The patient died five days following the study. The investigator felt the death was definitely unrelated to the infusion. (Total dose=0.54 mg ibutilide fumarate)

Patient #1124 *Hypotension* (Investigator description: Hypotension): This 61 year-old man had a history of coronary artery disease, CHF, hypertension, COPD, and non-insulin dependent diabetes mellitus, and gout. The patient was randomized to ibutilide fumarate (0.005 mg/kg) for conversion of atrial flutter. At Minute -10, Minute -5, and Time 0, his blood pressures were 107/63, 101/68, and 107/63 mmHg, respectively. He received the entire ten-minute infusion, and converted one hour following the infusion. Nine hours following the beginning of the infusion the investigator reported hypotension lasting for 11 hours. The blood pressures recorded during that time period were 89/61, 97/52, 87/52, and 120/70 mmHg. The investigator felt the hypotension could have been due to study treatment or to a high dose of intravenous lasix given an hour prior to the hypotension. The hypotension was not classified as serious and as of mild intensity. (Total dose=0.54 mg ibutilide fumarate)

Patient #1301 *Hypotension* (Investigator description: Decrease in Blood Pressure). This 73 year-old woman had a history of myocardial infarction, pacemaker for bradycardia, two-vessel coronary artery disease, PTCA x 3, and atrial flutter. She was enrolled in the protocol for conversion of atrial flutter and was randomized to ibutilide fumarate (0.015 mg/kg). At Minute -10, Minute -5, and Time 0, her blood pressures were 122/80, 117/70, and 121/79 mmHg, respectively. She received

the entire ten-minute infusion and remained in atrial flutter. At Hour 1 she developed hypotension lasting for 6½ hours. The blood pressures recorded during that time period were 69/54, 100/60, 84/60, and 90/62 mmHg. Fluids were given and the patient's Cardizem and NTP were held. The patient remained asymptomatic. The investigator noted that after Minute 20 the patient's rate began to slow and the ECG illustrated atrial flutter with variable conduction. The patient's blood pressure decreased with the decrease in heart rate. The adverse event was not classified as serious and was of moderate intensity. (Total dose=1.01 mg ibutilide fumarate)

Patient #1304; *QT Segment Prolonged* (Investigator description: Prolonged QT): This 67 year-old woman with AFl had a history of prolonged QT interval secondary to quinidine and a history of torsades de pointes secondary to hypokalemia and hypomagnesemia. She was randomized to ibutilide (0.025 mg/kg) and received nine minutes of the infusion at which time the infusion was discontinued because the QT interval had increased from 428 to 680 msec, and the QTc interval had increased from 0.458 to 0.731 $sec^{\frac{1}{2}}$. At Hour 1 the QT had decreased to 600 msec and the QTc had decreased to 0.652 $sec^{\frac{1}{2}}$. The patient was cardioverted to sinus rhythm (paced) an hour after the end of the infusion. This QT prolongation was not classified as serious and was of mild intensity. (Total dose=1.42 mg ibutilide fumarate)

Patient #1311 *Hypotension, Bradycardia NOS* (Investigator description: Hypotension, Bradycardia): This 53 year-old man had a history of myocardial infarction, coronary-artery-bypass-graft surgery, cerebrovascular accident, and atrial fibrillation/flutter. The patient was randomized to ibutilide fumarate (0.025 mg/kg) for conversion of atrial flutter. At Minute -10, Minute -5, and Time 0, his blood pressures were 121/92, 127/97, and 130/95 mmHg, respectively. He received the entire ten-minute infusion, and remained in AFl. At the end of the infusion there was an abrupt increase in AV block with a heart rate of 47 beats per minute and blood pressure decreasing transiently to 64/42 mmHg. Within 1-2 minutes the ventricular response returned to 90 beats per minute and the blood pressure increased to 88/69 mmHg without intervention. The reported hypotension lasted for two hours, with blood pressures recorded during that period of 94/69, 92/72, 98/75, and 112/76 mmHg. Neither the hypotension nor the bradycardia were classified as serious; both were classified as of severe intensity. (Total dose=1.98 mg ibutilide fumarate)

Patient #1316; *Sustained Polymorphic Ventricular Tachycardia* (Investigator description: Sustained Polymorphic VT): This 45-year-old man had a history of congestive heart failure, hypertension, cardiomyopathy, and mitral valve disease with a mitral valve replacement. He entered the trial in AFl. His magnesium level was 1.6 mg/dl (1.8 mg/dl = low normal). He received supplemental magnesium, resulting in a 2.2 mg/dl level prior to infusion. His QTc at Minute -10 was 0.448 $sec^{\frac{1}{2}}$. He received a ten-minute infusion of ibutilide fumarate 0.025 mg/kg. Seventeen minutes after the end of the infusion his AFl terminated and he developed polymorphic VT requiring cardioversion with 360 joules. His QTc at Hour 1 was 469 $sec^{\frac{1}{2}}$. This adverse event was considered to be serious and of severe intensity. (Total dose =1.84 mg ibutilide fumarate)

Patient #1341 *Nonsustained Monomorphic Ventricular Tachycardia* (Investigator description: Nonsustained Monomorphic VT): This 52-year-old man had a history of moderate pulmonary hypertension, global left ventricular dysfunction, and significant mitral regurgitation. His QTc at Minute -10 was 0.410 $sec^{\frac{1}{2}}$. He was randomized to ibutilide fumarate (0.025 mg/kg) for conversion of atrial flutter. He received the entire ten-minute infusion and remained in AF. At Hour 1 his QTc was 0.494 $sec^{\frac{1}{2}}$. One hour and five minutes after the end of the infusion the patient had a run of nonsustained monomorphic VT. The investigator indicated that the patient had runs of VT throughout the admission, but indicated he felt this episode could have been due to the study medication. This adverse event was not classified as serious and was considered to be of mild intensity. (Total dose=1.98 mg ibutilide fumarate)

Patient #2113 *Nonsustained Monomorphic Ventricular Tachycardia* (Investigator description: Nonsustained Monomorphic VT): This 79-year-old man with a history of hypertension, hypertrophic cardiomyopathy, CHF, and coronary artery disease. At Minute -10 his QTc was 0.441 sec$^{\frac{1}{2}}$. He was treated with ten-minute infusion of ibutilide fumarate (0.010 mg/kg) for conversion of AF, which was successful. At one hour his QTc was 0.476 sec$^{\frac{1}{2}}$. Two hours postinfusion he had an 11-beat run of monomorphic VT. This adverse event was not classified as serious and was considered to be of mild intensity. (Total dose=0.84 mg ibutilide fumarate)

Patient #2125; *Nonsustained Polymorphic Ventricular Tachycardia* (Investigator description: Nonsustained Polymorphic VT): This 74-year-old man with a history of two myocardial infarctions, a coronary artery bypass graft, and both AF and AFl enrolled in the study with AF. He received a ten-minute infusion of ibutilide (0.010 mg/kg). His QTc at Minute -10 was 0.469 sec$^{\frac{1}{2}}$. He had some ventricular ectopy at baseline. One minute after completing the ten-minute infusion he developed a few short runs of self-terminating polymorphic VT (longest run 15 seconds). He remained in AF. His QTc at Hour 1 was 0.491 sec$^{\frac{1}{2}}$. The nonsustained polymorphic VT was considered serious and of moderate intensity. (Total dose = 0.63 mg ibutilide fumarate)

Patient #2207 *Nonsustained Monomorphic Ventricular Tachycardia* (Investigator description: Nonsustained Monomorphic VT): This 68-year-old man with AF was randomized to ibutilide fumarate (0.015 mg/kg). At Minute -10 his QTc was 0.468 sec$^{\frac{1}{2}}$. He had a 5-beat run of monomorphic VT at Minute 8 of the infusion. The infusion was completed and the patient converted at Minute 20. At one hour his QTc was 0.492 sec$^{\frac{1}{2}}$. The investigator felt the VT was either due to ibutilide or pacer stimuli. This adverse event was not classified as serious and was considered to be of moderate intensity. (Total dose=1.29 mg ibutilide fumarate)

Patient #2213 *Hypotension* (Investigator description: Hypotension): This 45 year-old man had a history of atrial fibrillation. He was randomized to ibutilide fumarate (0.025 mg/kg) for conversion of atrial fibrillation. At Minute -10, Minute -5, and Time 0, his blood pressures were 154/86, 138/92, and 124/74 mmHg, respectively. He received the entire ten-minute infusion, and remained in AF. Five minutes after the end of the infusion his blood pressure dropped to 69/55 mmHg. Five minutes later it returned to 123/71 mmHg. The hypotension was not classified as serious and was considered to be of mild intensity. (Total dose=2.23 mg ibutilide fumarate)

Patient #2214; *Sustained Polymorphic Ventricular Tachycardia* (Investigator description: Sustained Polymorphic VT): This 67-year-old man with a history of hypertension entered the study in AF and with a QTc of 0.385 sec$^{\frac{1}{2}}$. He completed the ten-minute infusion of ibutilide fumarate (0.015 mg/kg) and immediately developed 30 seconds of ectopy, followed by polymorphic VT. He was DC cardioverted with 200, 300, and 360 joules and was simultaneously given one gram of magnesium sulfate. The VT was terminated within two minutes and the patient remained in sinus rhythm. His QTc at Hour 1 was 0.360 sec$^{\frac{1}{2}}$. This adverse event was classified as serious and of severe intensity. (Total dose = 1.37 mg ibutilide fumarate)

Patient #2216; *Sustained Polymorphic Ventricular Tachycardia, Hypotension* (Investigator description: Sustained Polymorphic VT, Hypotension): This 40-year-old man had a history of hypertension and congestive heart failure. He was admitted with AF, and was randomized to a ten-minute infusion of ibutilide fumarate (0.025 mg/kg). He had a QTc of 0.384 sec$^{\frac{1}{2}}$ at Minute -10. At Minute -10, Minute -5, and Time 0 his blood pressure was 118/94, 128/87, and 136/94 mmHg, respectively. After six minutes of the infusion he developed increased premature ventricular contractions and went into sustained polymorphic VT. His blood pressure dropped to 49/29. With DC cardioversion he was converted into ventricular fibrillation, and then was cardioverted again to normal sinus rhythm (QTc = 0.551$^{\frac{1}{2}}$). Following DC cardioversion his blood pressure was 150/120 mmHg. The sustained polymorphic ventricular tachycardia was considered to be serious

and of severe intensity; the hypotension was not considered to be serious and was of severe intensity. (Total dose = 1.86 mg ibutilide fumarate)

Patient #2225; *Cerebrovascular accident* (Investigator description: CVA). This 52-year-old man with new-onset AF received anticoagulation with heparin and the next day received a 10-minute infusion of placebo. One hour after the infusion he was DC cardioverted to normal sinus rhythm. The next morning he was ambulatory and oriented. However, he suddenly developed expressive aphasia and right-sided weakness. His initial CT scan revealed no evidence of bleeding and no acute infarct. His symptoms of right hemiplegia and expressive aphasia improved. (Total dose = 0 mg ibutilide fumarate)

Patient #2306; *Nonsustained Polymorphic Ventricular Tachycardia* (Investigator description: Nonsustained Polymorphic Ventricular Tachycardia): This 65-year-old man with AF was randomized to receive a ten-minute infusion of ibutilide fumarate (0.010 mg/kg). The pharmacist inadvertently mixed the drug for a 0.025 mg/kg infusion. After three minutes the infusion was discontinued because of polymorphic VT. The nurse delivered a precordial thump with no effect. The VT terminated spontaneously 4 seconds later and he remained in AF. His QTc at Minute -10 was 0.453 sec[½] and at Hour 1 was 0.464 sec[½]. The nonsustained polymorphic VT was considered serious and of severe intensity. (total dose = 0.54 mg ibutilide fumarate)

Patient #2323: *Nonsustained Monomorphic Ventricular Tachycardia* (Investigator description: Nonsustained Monomorphic VT): This 67 year-old woman with AF was randomized to 0.005 mg/kg ibutilide fumarate. At Minute -10 her QTc was 0.381 sec[½]. At Minute 8 of the ten-minute infusion a four-beat run of VT was noted. At Minute 9 the patient had an 8-beat run of VT and the infusion was stopped. Two grams of magnesium sulfate were given and no other ectopy was seen. The patient remained in AF. At Hour 1 her QTc was 0.480 sec[½]. This adverse event was not classified as serious and was of moderate intensity. (Total dose=0.42 mg ibutilide fumarate)

Patient #2330 *Nonsustained Monomorphic Ventricular Tachycardia* (Investigator description: Nonsustained Monomorphic VT): This 59-year-old woman had a history of chronic angina, hypertension, CHF, and mitral regurgitation. She was randomized to a ten-minute infusion of ibutilide fumarate (0.015 mg/kg) for conversion of AFl. At baseline her QTc was 0.409 sec[½]. She converted to normal sinus rhythm at Minute 3 of the infusion. Eleven minutes after the end of the infusion she had a 4-beat run of monomorphic VT. She was given two grams of magnesium sulfate and no other VT was seen. At one hour her QTc was 0.464 sec[½]. This adverse event was not classified as serious and was considered to be of moderate intensity. (Total dose=1.01 mg ibutilide fumarate)

Patient #2347; *Dizziness, hypotension* (Investigator description: dizziness, hypotension). This 72-year-old man with AF had mild dizziness during the screening phase of the study. He received a ten-minute infusion of ibutilide fumarate (0.005 mg/kg). The AF was not terminated by the infusion and he was electrically cardioverted to sinus bradycardia. The day following the infusion he was too dizzy to walk and was hypotensive (62/30 mmHg) at the time of the Hour 24 vital signs. His blood pressure had been 120/77 mmHg at Minute -10 and 120/74 mmHg at Time 0 and remained in the same range through Hour 24, when the hypotension was apparent. He was given intravenous fluid and his blood pressure increased to 110/70 mmHg within 30 minutes. His hospitalization was prolonged until the dizziness subsided to the baseline level. Other medications included digoxin, procainamide, and diltiazem. The hypotension was considered to be serious and of severe intensity. The dizziness was considered to be serious and of moderate intensity. (Total dose = 0.52 mg ibutilide fumarate)

4. REVIEWER'S ASSESSMENT AND COMMENTS

4.1 Trial design

This was a randomized, double-blind, placebo-controlled trial of a parallel design (five arms) performed by nine principal investigators. The study enrolled 202 patients with sustained atrial flutter or fibrillation, about 40 per treatment arm, and was executed over about 20 months. Each patient received a single dose of ibutilide fumarate (0.0, 0.005, 0.010, 0.015, or 0.025 mg/kg) administered as a ten-minute intravenous infusion. In the protocol an efficacy response was defined as "the termination of atrial flutter or atrial fibrillation." In the case report form, however, successful conversion was operationally defined as termination of the arrhythmia during the infusion or within one hour following the infusion. Follow-up in the trial was nearly complete. Two hundred patients actually received study drug, and 197 were considered "evaluable" by the sponsor. The treatment groups were generally similar at baseline.

The study was originally planned as a Phase II study, and because of safety concerns the study was initially designed to have two Tiers, each to include about 50 patients. Later an additional Extension was added that included about 100 more patients. Within each of these three periods, patients were randomly allocated to treatment with placebo or a specified dose of ibutilide. For purposes of analysis, placebo patients from each period were pooled into a single "placebo group."

As a consequence of the design, none of the active-treatment groups (ibutilide-treatment groups) was represented in all three periods of the study, even though each was included in two of the periods. This increases the possibility of confounding period effects. These possible period effects were not formally discussed or analyzed in the body of this review. However, the lack of concurrent treatment with study drug for the entire duration of the trial for each of the five dose groups will not likely alter any of the major conclusions about efficacy or safety. In addition, in the last period (the Extension) patients were randomly allocated to concurrent treatment in each of the five dose groups.

Overall, the trial appears to have been designed adequately, was of a sufficient size, and was executed satisfactorily to reduce the likelihood of bias.

4.2 Representation of various groups in the trial

Women were under-represented in the trial, only 24 were included among the 200 treated patients, but this is almost certainly because the majority of the participating centers were affiliated with the Veterans' Administration. The elderly were well represented: over 55% of the treated patients were at least 65 years of age. In contrast, pediatric patients were excluded from the trial; the youngest patient was 18 years of age.

The sponsor's study report emphasizes the percentages of patients with enlarged left atria, decreased ejection fractions, and valvular heart disease. But reliance on these surrogate physiological measures as indices of clinically-meaningful cardiac impairment overstates the extent of cardiac disease in this patient sample. In fact, patients with congestive heart failure, angina pectoris, or a recent myocardial infarction were all specifically *excluded* from this trial. Similarly, patients were required to have a serum K^+ of at least 4.0 mEq/L, a serum creatinine of less than 2.0 mg/dl, and hepatic enzymes not more than twice the maximal normal value. Patients with serious diseases of other body systems were excluded from participation.

Consequently, the generalizeability of this trial is limited to relatively healthy adult male patients with atrial fibrillation or atrial flutter. The lack of data on the effects of intravenous ibutilide in

patients with substantial mechanical cardiac impairment or with substantial electrical cardiac impairment are major shortcomings both for this trial and for the overall development program of the drug. For example, it would be of great practical value to know how patients with congestive heart failure of New York Heart Association (NYHA) functional class IV, patients with sick sinus syndrome, or patients with advanced degrees of heart block respond to or handle the drug. In the absence of data, the relative safety and effectiveness of this drug in these populations remain largely speculative, as do instructions for use in these populations.

4.3 "Efficacy"

Overall, atrial fibrillation or atrial flutter terminated within seventy minutes[18] in about one-third of patients (i.e., 54 of 159) treated with infusions of ibutilide at the doses used in this study. In contrast, infusions of placebo were associated with only about a 2% conversion rate within seventy minutes (i.e., 1 of 41 patients). By treatment group, the conversion rates in the groups treated with ibutilide (0.005, 0.010, 0.015, and 0.025 mg/kg) were 12.2, 32.5, 44.7, and 47.5%, respectively. For patients successfully converted in this study with ibutilide, doses of 0.005, 0.010, 0.015, and 0.025 mg/kg corresponded to average absolute doses of 0.44, 0.79, 1.24, and 1.88 mg, respectively.

At the doses used in the study, these approximations probably overestimate the "efficacy" of ibutilide for at least two reasons:

- First, after initial successful conversion, the protocol did not provide for systematic evaluations of early recurrences of the arrhythmia. Clinically, these early relapses would be regarded as therapeutic failures. But for purposes of the protocol they were counted as "successes." Stated differently, if the atrial arrhythmia recurs within a short time, particularly within a matter of hours (i.e., a clinical failure despite initial successful cardioversion), then the patient hasn't experienced much of a benefit.

  At the request of the FDA, therefore, the sponsor performed a retrospective chart review to get some estimate of the acute relapse rate. In this analysis, the overall estimates of "efficacy" were slightly lower at the 24 hour follow-up than those seen immediately within an hour of the termination of the infusion (see section 3.6.3 on pages 17-18). Unfortunately, these data were difficult to assess and were incomplete because the sponsor was forced to rely on indirect and retrospective measures to assess the rhythm for the full 24 hours.

- Second, the protocol did not allow for a good estimate of the spontaneous conversion rate over 24 hours in placebo-treated patients, a more meaningful number than the spontaneous conversion rate over seventy minutes, as measured by the study. That is, often patients randomized to placebo whose arrhythmia did not terminate within the first seventy minutes of the infusion of study drug shortly thereafter underwent electrical cardioversion, pharmacological cardioversion, or pacing. Stated differently, if the atrial arrhythmia would resolve spontaneously within a short time in non-treated patients, then there is less clinical value in treating patients with drug rather than adopting a "wait and see" approach.

In summary, in this trial the treatment effect was probably overestimated somewhat because early relapse rates in ibutilide-treated patients were not systematically recorded. Similarly, the treatment effect was also probably overestimated somewhat because of a second, independent reason: spontaneous conversions (as measured in the placebo-treated patients in the trial) were not

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[18] Measured from the onset of the 10-minute infusion

measured beyond seventy minutes. That is, the protocol was not designed to capture either of these rates beyond seventy minutes, and therefore the results reflect a somewhat optimistic estimate of the effects of ibutilide. These rates were only gathered retrospectively and indirectly.

4.4 Factors possibly influencing "efficacy" or safety

Certain features appeared to be correlated with the ability of ibutilide to terminate atrial fibrillation or flutter. For example, ibutilide appeared to be less effective in terminating long standing atrial fibrillation or atrial flutter, and it may be less effective in terminating atrial fibrillation or atrial flutter in patients receiving digoxin, or in patients *not* receiving β-adrenergic blocking agents. These various subgroup analyses provide many hypotheses that could be evaluated in future studies (e.g., as part of formal interaction studies).

In the development program for ibutilide, few (if any) formal studies were performed to assess whether the safety, efficacy, or instructions for use of ibutilide differ in specific populations or under different conditions. For example, adverse hemodynamic effects of ibutilide could have been prospectively evaluated in a study of patients with NYHA Class III or IV heart failure. Similarly, adverse electrophysiological effects of ibutilide could have been prospectively evaluated in studies of patients with sick sinus syndrome, atrio-ventricular block, or inducible ventricular tachycardia. Formal drug-interaction studies could have evaluated potential pharmacokinetic or pharmacodynamic interactions of ibutilide with β-adrenergic blocking agents, digoxin, or calcium channel blockers. Similarly, formal studies could have assessed the pharmacokinetics and pharmacodynamic characteristics of ibutilide and its metabolites in patients with significant hepatic impairment, or in patients with significant renal impairment. Such studies were not performed.

Instead of formal prospective studies to evaluate these possible interactions, the application relies heavily on the limited inferences that can be drawn from the retrospective analyses of the patients that were enrolled in the major clinical trials. Yet the enrollment criteria for these major studies generally excluded patients with the most significant pathology or with the greatest physiological impairment. For example, even though 49% (89 of 180) of the patients enrolled in this trial had decreased ejection fractions, this does not allow firm conclusions to be made about any possible hemodynamic effects of ibutilide in patients with mechanically "sick" hearts because patients with congestive heart failure were excluded from the trial.

Similarly, in this trial patients were required to have a serum creatinine of less than 2.0 mg/dl and to have "hepatic enzymes" that did not exceed twice the maximum normal value. Accordingly, results from this trial can not be extrapolated from this trial to patients who may have greater degrees of renal or hepatic impairment.

4.5 Dose-response, concentration-response, and duration of infusion

This study demonstrated a dose-response relationship in the termination of atrial fibrillation and flutter by ibutilide, and the results also suggest a dose response for the induction of proarrhythmia. However, plasma levels of ibutilide did not appear to be correlated either with "efficacy" or with safety in this study. For example, plasma levels in patients in whom conversion occurred overlapped extensively with plasma levels in patients in whom conversion failed to occur. Likewise, plasma concentrations of ibutilide were not obviously related to the occurrence of proarrhythmic events. However, plasma levels were quite variable.

But in addition to highly variable plasma-concentration data, the duration of the infusion may have also contributed to the lack of a correlation between concentration and response. That is, the drug was administered relatively quickly over 10 minutes, yet the median and mean times for the

successful termination of the arrhythmia were never less than 10 minutes (see the table on page 18 in section 3.6.4). Hence, the full dose of the drug had already been administered before the majority of patients successfully converted. If the drug had been infused more slowly, then concentration-response relationships might have been demonstrated.

The duration of the ibutilide infusion was generally not evaluated in the drug development program. For example, had ibutilide been infused over an hour (or several hours) instead of over 10 minutes, concentration-responses both for conversion of the arrhythmia and for safety might have been demonstrated. Moreover, these concentration-responses might *not* have overlapped: longer infusions might have allowed for a dissociation between the "desirable" effects of ibutilide (i.e., conversion of atrial fibrillation or flutter to sinus rhythm) and the adverse effects of the drug (e.g., proarrhythmia). For example, had the drug been given over several hours, similar conversion rates might have been achieved in the absence of proarrhythmic events. As this suggests the possibility of safer drug-administration regimens, this issue could impact on the possibility of drug approval.

4.6 Normal Sinus Rhythm--a surrogate endpoint?

Despite the popular clinical feeling that "all patients deserve at least one chance to be in normal sinus rhythm," the endpoint evaluated in this study (i.e., "the termination of atrial flutter or atrial fibrillation") may be viewed as an endpoint of uncertain clinical benefit to the patients enrolled. This endpoint is an electrocardiographic observation, not a clinical one, the correction of which is of uncertain benefit to the patients enrolled in the study.

In the harshest view, ibutilide may be used in some patients to convert the cardiac rhythm from atrial flutter or fibrillation to normal sinus rhythm (an uncertain clinical benefit) for a length of time that is not well characterized. Yet, these same patients will be exposed to tangible and serious risks--most of which, like proarrhythmia, involve the cardiovascular system, and some of which are potentially fatal if not properly detected and treated.

Several recent experiences demonstrate that mere correction (or improvement) of physiological abnormalities may not translate into a direct clinical benefit for the patient. The CAST trial, for example, tested the physiologically reasonable idea that suppression of premature ventricular depolarizations (with flecainide, encainide, or moricizine) in patients with a prior myocardial infarction might reduce the incidence of sudden arrhythmic death. Instead, all three drugs had an adverse effect on survival in this population. Similarly, the PROMISE trial evaluated the effects on survival of milrinone, a drug known to improve invasive hemodynamic indices in symptomatic patients with congestive heart failure. Despite a prior expectation that milrinone might be of benefit because of its hemodynamic effects, the drug had an adverse effect on survival.

Thus with ibutilide, those who propose the idea that "conversion to normal sinus rhythm" is--in and of itself--a benefit to patients must also convincingly articulate how a transient correction of an electrocardiographic abnormality differs from these other surrogate endpoints. Stated simply: how is "conversion to sinus rhythm" different from other surrogate endpoints such as the suppression of premature ventricular depolarizations or the improvement of invasive hemodynamic indices?

4.7 Clinical benefit

The clinical benefit of conversion to normal sinus rhythm would be less in question if two conditions had been met: (a) if the trial had enrolled severely symptomatic patients, patients in extremis, or patients who remained significantly symptomatic despite optimal therapy for "ventricular rate

control," and; (b) if conversion to normal sinus rhythm had been associated with improvement in these symptoms.

- At baseline, the majority (i.e., 59%) of the patients enrolled in the trial did not appear to be symptomatic from the arrhythmia. That is, at the initial screen about 41% of the patients reported symptoms consistent with atrial fibrillation or atrial flutter such as shortness of breath, palpitations, dizziness, or fatigue. In addition, patients with congestive heart failure, angina pectoris, or a recent myocardial infarction were all specifically excluded from this trial. Furthermore, some of the symptoms present at screen may have resolved with attempts to control ventricular rate rather than cardioversion. Thus, the clinical benefit of cardioversion may be questionable in this largely asymptomatic or mildly symptomatic group of patients.

  Stated differently, use of cardioversion is difficult to dispute in severely symptomatic patients or patients in extremis. Despite the potential risks, the benefit is clear even if the conversion may be brief. On the other hand, in asymptomatic or mildly symptomatic patients the acceptable risk is less, especially when alternative therapies (such as ventricular rate control and anticoagulation) are available and particularly when the conversion to normal sinus rhythm might be transient. This trial provides data only on the latter group of patients.

- Symptoms were evaluated at baseline (screen) in this trial, but no evaluations of symptoms were made after treatment. Hence, it is unknown whether conversion to normal sinus rhythm actually resulted in symptomatic improvement in any of the patients, or whether patients in the ibutilide-treatment groups actually had a greater symptomatic improvement than those in the placebo group. That is, direct clinical benefit was *not* specifically assessed in this trial. Risk was clearly demonstrated in the trial, but benefit can only be assumed.

4.8 Safety

In this trial, treatment with ibutilide was associated with significant toxicity. Eight patients treated with ibutilide experienced serious adverse events, all of which were related to the cardiovascular system. These included six cases of polymorphic ventricular tachycardia. Overall, eleven patients experienced proarrhythmia and six patients experienced hypotension identified as adverse events.

In the patients evaluated in this trial, atrial fibrillation and atrial flutter were not acutely life-threatening arrhythmias. Yet treatment with ibutilide induced life-threatening arrhythmias in some patients. Therefore, for marketing approval a judgment must be made whether these risks generally exceed the benefits--at least in some patients, at some doses of ibutilide, or under certain conditions.

On the one hand, the risks of arrhythmias such as polymorphic ventricular tachycardia or of torsades de pointes should never be underestimated. Each case in this trial ultimately resolved without permanent sequelae, but a clinical trial such as this is an artificial environment in which patients are systematically scrutinized (with a certain amount of redundant monitoring) by highly trained personnel. With the widespread use of ibutilide in less controlled circumstances, adverse outcomes from these arrhythmias are more likely to occur. For example, adverse outcomes from these arrhythmias are more likely to occur on a general medical ward or in a busy emergency room than on a cardiac ward with telemetry that is staffed by cardiologists and electrophysiologists.

On the other hand, the risks of these arrhythmias may be manageable if they are detected and properly handled by trained personnel. The key for safety, then, is to ensure that cardiac status

and rhythm are monitored adequately and appropriately, and to ensure that trained personnel and appropriate equipment (e.g., defibrillators, pacing equipment) are immediately accessible.

The duration of monitoring is also an important consideration. Although all four episodes of sustained polymorphic ventricular tachycardia occurred during the infusion or within 17 minutes after the end of the infusion, proarrhythmic events occurred over a wide range of plasma concentrations of ibutilide. Thus, plasma concentrations of ibutilide do not appear to be obviously related to the occurrence of the proarrhythmia. Because any plasma level of ibutilide may be associated with proarrhythmia, a conservative recommendation would be to monitor patients for at least five elimination half-lives after drug administration. For the purposes of this calculation, it should be noted that the mean elimination half-life as estimated in this trial is probably artificially short because of the truncation of blood sampling three hours after drug administration (see section 3.5 on pages 11-14). Hence, more accurate estimates of the elimination half-life should be used in the calculation. In patients with hepatic impairment, renal insufficiency, or with prolonged elimination of the drug from any cause, the duration of monitoring should be correspondingly increased.

An additional risk of ibutilide therapy is the possible need for emergency defibrillation, which generally requires more energy (joules) than synchronized cardioversion. Two patients in this trial required emergency defibrillation because of the development of ventricular fibrillation (see section 3.8.1.2.6 on pages 33-34; Patients #1106 and #2216). In this way, ibutilide treatment differs substantially from DC cardioversion for atrial arrhythmias. Unlike elective DC cardioversion for atrial fibrillation or flutter in which the patient is sedated and the staff is prepared, the treatment of a hemodynamically unstable proarrhythmic event such as ventricular fibrillation requires immediate intervention regardless of whether or not the patient and staff are optimally prepared. Hence, the risk of fibrillation is more of an issue with pharmacological treatment using ibutilide than it is with DC cardioversion because of the different circumstances surrounding the administration of the electrical shock (i.e., emergency vs. controlled). Even if the electrical shocks in these two situations are of equivalent energy (in joules), they may not be of equal risk (or comfort) to the patient. On a related note, the safety of electrical cardioversion after administration of ibutilide is difficult to assess from this study because the data were not gathered prospectively.

Finally, several medical events in this study (sinus arrest, severe AV block, severe bradycardia) confirm that the adverse electrophysiological properties of ibutilide are not limited to the induction of ventricular tachycardia. These electrophysiological effects may produce profound hemodynamic instability. Patients with diseased sinus nodes, diseased atrio-ventricular nodes, or with pre-existing heart block may be particularly susceptible to these effects.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 12, 1995

FROM: Maryann Gordon, MD MAG

SUBJECT: Ibutilide NDA#20-491

TO: Files

The sponsor, upon our request, has submitted the randomization groups (attached) for the 33 patients in protocol 0015 who were randomized but received no study drug because they had spontaneously converted to sinus rhythm prior to drug administration.

An intent to treat analysis including these 33 patients (10 placebo, 15 ibutilide 1/0.5, 8 ibutilide 1/1) was conducted by James Hung (attached). The conclusions about the efficacy of ibutilide for study 0015 remains unchanged.

cc
HFD-110/D. Willard

Numbers - Mixed and not Used
Prot 0015

1041	1mg/.5mg	2118	1mg/.5mg
1066	1mg/.5mg	2126	Placebo
1076	1mg/.5mg	2160	1mg/1mg
1085	Placebo	2169	1mg/.5mg
1087	1mg/.5mg	2174	1mg/.5mg
1119	1mg/1mg	2187	1mg/.5mg
1146	1mg/1mg	2189	1mg/1mg
1158	1mg/.5mg	2195	Placebo
1161	Placebo	2209	Placebo
1162	1mg/.5mg	2236	Placebo
77	1mg/.5mg		
1	1mg/.5mg		
1200	1mg/1mg		
1211	Placebo		
1215	1mg/.5mg		
1219	Placebo		
1235	1mg/.5mg		
1236	Placebo		
1242	1mg/1mg		
2004	1mg/1mg		
2017	1mg/1mg		
2104	1mg/.5mg		
2117	Placebo		

Table A. Success rates for the evaluable patients (N=275) [Study 15]

Stratum	Placebo			Ibutilide						p-value
				1 mg/0.5 mg			1 mg/ 1mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	91	12	13	94	50	53	90	48	53	<0.0001

P-value is computed using Pearson's chi-sqare test.

Table B. Success rates for all randomized patients (N=299) [Study 15]

Stratum	Placebo			Ibutilide						p-value
				1 mg/0.5 mg			1 mg/ 1mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	96	12	13	101	54	53	102	50	53	<0.0001

P-value is computed using Pearson's chi-sqare test.

$p < 0.0001$ for the difference between each ibutilide dose regimen and placebo

C50

NDA-
#20-491

OCT 12 1995

(1)

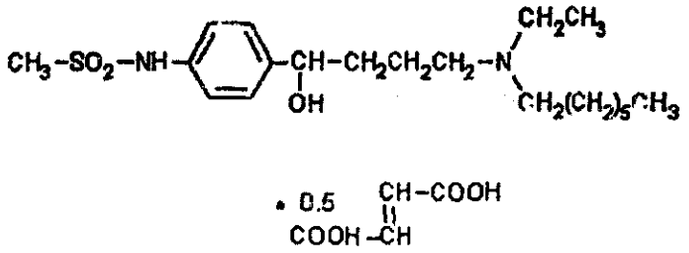
REVIEW OF PROTOCOL 0015

Study Title:	**A Study of the Conversion Efficacy and Safety of Repeated Intravenous Doses of Ibutilide Fumarate in Patients with Atrial Flutter or Atrial Fibrillation (Protocol P/7550/0015)**
Date of Protocol	**June 30, 1992**
Study Design.	**Double-blind, placebo-controlled, randomized, dose-response study**
Subject Type:	**Patients with a rhythm of sustained atrial flutter or atrial fibrillation with a duration of 3 hours to 45 days**
Number of Subjects Planned/Enrolled:	**240/266 patients (86 received placebo, 180 received ibutilide)**
Study Drugs/ Route of Admin:	**Ibutilide or placebo/ intravenous infusion**
Dosage:	**Ten-minute infusion of 1 mg ibutilide or placebo. If termination did not occur within 10 minutes after the end of the first infusion, a second infusion of 1 mg or 0.5 mg was given to patients randomized to ibutilide and another placebo infusion was given to those randomized to placebo. (Patients weighing less than 60 kg received 0.005 mg/kg instead of 0.5 mg and 0.010 mg/kg instead of 1 mg.)**
Primary Objective:	To demonstrate the effectiveness of 1 mg (or 0.01 mg/kg in patients weighing less than 60 kg) of ibutilide in the termination of atrial flutter or atrial fibrillation. Treatment was considered successful if the atrial arrhythmia terminated, for any length of time, by Hour 1.5; and to investigate whether a second dose of 1 mg (or 0.01 mg/kg in patients weighing less than 60 kg) or 0.5 mg (or 0.005 mg/kg in patients weighing less than 60 kg) would increase the termination rate.

I. Summary

Ibutilide, a class III antiarrhythmic, acts by increasing an inward depolarizing sodium current which, in turn, prolongs the duration of the action potential of the atrial and ventricular myocytes. Ibutilide is being developed for the acute termination of atrial flutter and atrial fibrillation. The drug is to be administered by intravenous infusion.

The structure of ibutilide fumarate is as follows:



Protocol 0015 was a double blind, randomized, placebo controlled, multicenter study evaluating the efficacy of intravenous ibutilide in terminating atrial flutter or atrial fibrillation of recent onset (3 hours to 45 days). A total of 266 patients were enrolled with 180 receiving ibutilide and 86 receiving placebo. Patients randomized to ibutilide received 1 mg ibutilide for the first 10-minute infusion and, if their arrhythmia was not terminated, received either 1 mg or 0.5 mg ibutilide for the second 10-minute infusion. Patients randomized to placebo received placebo for the first infusion and, if their arrhythmia was not terminated, received a second dose of placebo. Note: patients weighing less than 60 kg received ibutilide infusions of 0.01 mg/kg or 0.005 mg/kg rather than 1 mg or 0.5 mg, respectively.

Efficacy

Success was defined by the protocol as termination of arrhythmia for any length of time within 1.5 hours of receiving study drug.

The success and failure rates as defined by the protocol for all patients combined were as follows:

	all patients randomized (n=266)			
	ibutilide (n=180)		placebo (n=86)	
	n	%	n	%
success	78	43	2	2
failure	102	57	84	98

p < 0.0001 for the difference in the success rate between placebo and ibutilide.

The success rates for the subgroup of patients who had atrial flutter at baseline were:

	atrial flutter patients (n=133)			
	ibutilide (n=90)		placebo (n=43)	
	n	%	n	%
success	50	43	1	2
failure	40	57	42	98

p < 0.0001 for the difference in the success rate between placebo and ibutilide.

The success rates for the subgroup of patients who had atrial fibrillation at baseline were:

	atrial fibrillation patients (n=133)			
	ibutilide (n=90)		placebo (n=43)	
	n	%	n	%
success	28	31	1	2
failure	62	69	42	98

p= 0.0011 for the differences in success rate between placebo and ibutilide.

Safety:

The most common medical events reported were the ventricular tachycardias (including sustained and nonsustained polymorphic and monomorphic VT). The incidence rates for the all ibutilide group and placebo

group were 13.3% (24/180) and 1.2% (1/86), respectively. The rates by dose group were similar (13.8% and 12.7% for 1mg/1mg and 1mg/0.5 mg, respectively).

Compared to male patients, female patients had a much greater propensity to experience proarrhythmic events. The rates for sustained polymorphic VT for females and males were 5.1% and 0.7%, respectively, and the rates for nonsustained polymorphic VT were 15.4% and 5.0%, respectively.

There is some indication that ibutilide causes more headaches and nausea compared to placebo. There was one death and it was in the placebo group. There is no evidence that ibutilide affects any laboratory value.

In conclusion, ibutilide given in 1 or 2 short term infusions at doses 1 mg/1mg and 1mg/ 0.5mg, is able to terminate atrial flutter and, to a lesser extent, atrial fibrillation compared to placebo. Provided the rest of the studies support this finding, the drug is a reasonable alternative to using DC shock in patients for whom being in sinus rhythm is worth the risk of stroke. The adverse events caused by ibutilide are limited primarily to sustained and nonsustained ventricular tachycardia and almost all of these events occurred while ibutilide was being infused (or shortly after) and while the patient was under close observation. Sustained ventricular tachycardia and ventricular fibrillation was reversed with electroversion and there is no indication that, given proper equipment, all of these life threatening arrhythmias cannot be successfully terminated. Females, for unknown reasons, are particularly susceptible to ventricular tachycardia (see safety review) and since the benefit is marginal for patients with atrial fibrillation (24 hour conversion rate was 1.9% for males and females combined), the package labeling must carefully define the higher risk reduced benefit ratio according to gender.

A complete description of Protocol 0015 is found in appendix A.

II. Results

Enrollment

A total of 266 patients entered the study. Patients were randomized at baseline to either placebo\placebo (n=86), ibutilide 1mg/ibutilide 0.5mg (n=86), or ibutilide 1mg/1mg (n=94). If the patient converted with the first infusion, the second one was not given. Unless noted, the tables in this report show results for patients in the group to which they were randomized, regardless of whether they received the second infusion.

Demographic Variables

Age, Height, Weight, Temperature, Respiration

Patients were similar for age, height, respiration, temperature and weight across treatment groups. The mean age was 67 years with the range from 29 years to 90 years and mean weight was 83 kg, with a range from 44 kg to 141 kg. (*data from vol 1.70, 08/19 table F.1 page 186 and table F.3, page 188*)

Race and Sex

The table below shows the distribution of race and sex by dose.

Demographic Variable		Dose							
		PLB/PLP (n=86)		1 mg/0.5 mg (n=86)		1 mg/1 mg (n=94)		Total (n=266)	
		n	%	n	%	n	%	n	%
Race	Black	9	10.5	17	19.8	14	14.9	40	15.0
	Hispanic	-	-	-	-	4	4.3	4	1.5
	White	77	89.5	69	80.2	76	80.9	222	83.5
Sex	Female	14	16.3	16	18.6	23	24.5	53	19.9
	Male	72	83.7	70	81.4	71	75.5	213	80.1

from table F.7, vol. 1.70, 08/19/194

Of the 266 patients, 40 were black, 4 were Hispanic and 222 were white. The majority of patients (80.1%) were male. The treatment groups were fairly well balanced.

Medical History

Current arrhythmia

Since the patients were stratified based on baseline arrhythmia, there was no difference in the distribution of AFL or AF patients across dose groups (133 patients per group).

Patient characteristics

Patient characteristics (including previous history of atrial arrhythmia, heart disease, other medical history, and whether symptoms of atrial arrhythmia are present or not) are shown in the table below.

Patient Characteristics+		Dose							
		PLB/PLB n=86		1 mg/0.5 mg n=86		1 mg/1 mg n=94		Total N=266	
		n	%	n	%	n	%	n	%
History of AFL/AF	No	40	46.5	40	46.5	50	53.2	130	48.9
	Yes	46	53.5	46	53.5	44	46.8	136	51.1
History of heart disease	No	24	27.9	17	19.8	24	25.5	65	24.4
	Yes	62	72.1	69	80.2	70	74.5	201	75.6
Other medical history	No	6	7.0	5	5.8	10	10.6	21	7.9
	Yes	80	93.0	81	94.2	84	89.4	245	92.1
Symptoms of arrhythmia present?++	No	33	38.4	31	36.0	29	30.9	93	35.0
	Yes	53	61.6	55	64.0	65	69.1	173	65.0

+data for all categories except symptoms of arrhythmia from table G.1, vol. 1.70, 08/19/209
++from table 1S.1 informational amendment 004 received Jan 6, 1995.

Slightly over half of all patients had history of AFL/AF and 75.6% had heart disease. Most patients had "other medical history," and 65% of patients reported symptoms associated with their arrhythmia. The groups were well balanced.

History of heart disease

The number of patients who reported the following heart diseases is listed below. Note: conditions reported for less than 9 patients have been omitted from the table.

History+	placebo (n=86)	ibutilide		total (n=266)
		1 mg/0.5 mg (n=86)	1 mg/1 mg (n=94)	
Any histo. described	62	69	70	201
CAD	26	21	23	70
MI	22	19	22	63
CHF	12	19	26	57
CABG	17	13	22	52
HTN	17	19	15	51
mitral valve disease	11	13	12	36
aortic valve disease	9	5	10	24
cardio-myopathy	6	9	9	24
angina	6	6	4	16
angioplasty	6	3	4	13
pacemaker	6	3	3	12
rheumatic fever	3	3	3	9
ventricular tachycardia	3	4	2	9

+data were collected retrospectively

from information amendment 009 page 6 received Feb 3, 1995.

The most common heart diseases were coronary artery disease, myocardial infarction, congestive heart failure, and coronary artery by-pass grafting. Mitral and aortic valve diseases were also relatively common. Rheumatic fever was reported by 9 patients.

Etiology of Atrial Arrhythmia

The was no attempt by the sponsor to prospectively determine etiology

of patients' atrial arrhythmia. The following table was prepared with data gathered after the study was analyzed. From a total of 266 patients randomized, information was obtained from 98.5% (262).

presumed etiology+	placebo n=86		ibutilide 1/0.5 mg n=84		ibutilide 1/1mg n=92	
	n	%	n	%	n	%
rheumatic valvular disease	5	5.8	5	6.0	5	5.4
nonrheumatic valvular disease	29	33.7	27	32.1	32	34.8
CAD	37	43.0	34	40.5	36	39.1
hypertension	37	43.0	47	56.0	42	45.7
CHF	29	33.7	30	35.7	33	35.9
S/P cardiac Sx	11	12.8	6	7.1	20	21.7
"lone"	4	4.7	5	6.0	4	4.4
hyperthyroid	0	0	1	1.1	1	1.1
pulmonary disease	16	18.6	16	19.1	19	20.7
other	26	30.2	25	29.8	32	34.8
unknown	5	5.8	2	2.4	3	3.3

from [illegible]national amendment 022, vol 3 page 11 received March 15, 1995
+pat[illegible]ould have more than one presumed etiology

The groups were well balanced regarding the presumed etiology of the atrial arrhythmia. The most common causes were nonrheumatic valvular disease, coronary artery disease, hypertension, congestive heart failure and other. The least common causes were hyperthyroid, rheumatic valvular disease, "lone" atrial arrhythmia, and unknown.

Symptoms Related to Current Episode of Atrial Flutter/Fibrillation

The table below displays the number of patients reporting one or more symptoms. The sponsor did not attempt to elaborate on the degree of severity.

symptom	placebo (n=86)	ibutilide		total (n=266)
		1 mg/0.5 mg (n=86)	1 mg/1 mg (n=94)	
any symptom described	53	55	65	173
SOB	32	38	49	119
palpitations	20	15	18	53
chest tightness/pain	6	7	12	25
dizziness	9	6	10	25
weakness	5	6	10	21
edema	1	13	4	18
fatigue	3	5	10	18
rapid heart beat	4	5	7	16
diaphoresis	2	2	6	10
orthopnea	1	8	1	10
PND	2	5	1	8
nausea	2	3	2	7
syncope	0	1	3	4
irregular pulse	0	3	0	3
vomiting	2	1	0	3
cough	1	0	1	2
headache	2	0	0	2
CHF	0	1	0	1

from table G.3, vol. 1.70, 08/19/254

Only 65% (173/266) of patients reported symptoms related to their arrhythmia. The most common symptoms were shortness of breath and palpitations followed by chest tightness/pain, dizziness, and weakness.

Follow up

Patients were to be followed up for at least 72 hours but only if a medical event occurred. Of the 3 patients who had a medical event but were not followed up, there was 1 placebo patient (#1217)who died of respiratory failure during the study; 1 placebo patient (#2002) who developed increased agitation

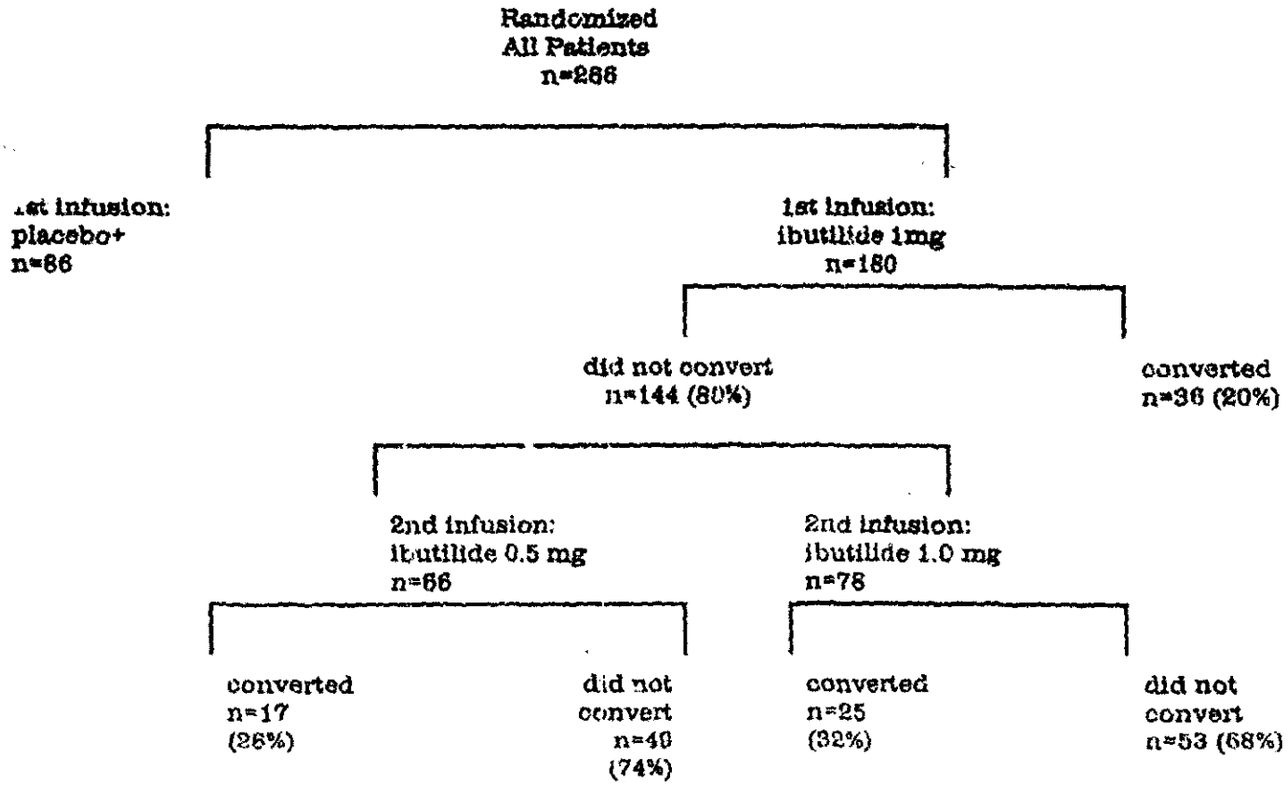
and confusion, required electrical cardioversion and was sent to an out-of-town nursing home before the 72 hour evaluation could be completed; and 1 ibutilide 1 mg/1 mg patient (#1062) who developed dizziness and did not have the 72 hour follow-up.

III. Efficacy

Primary endpoint (as specified in the protocol)

All patients

The definition of success as defined by the protocol was termination of atrial arrhythmia for any length of time, but before 1.5 hours after start of study drug. Using this definition, the following figure gives results for all patients combined regardless of baseline arrhythmia. The results for the placebo group (only 2 out of 86 patients were successes) have been omitted from the figure.



+ Since only 2/86 placebo patients converted, results for placebo are not shown in the above diagram. The 2 placebo patients who converted did so with the second infusion.

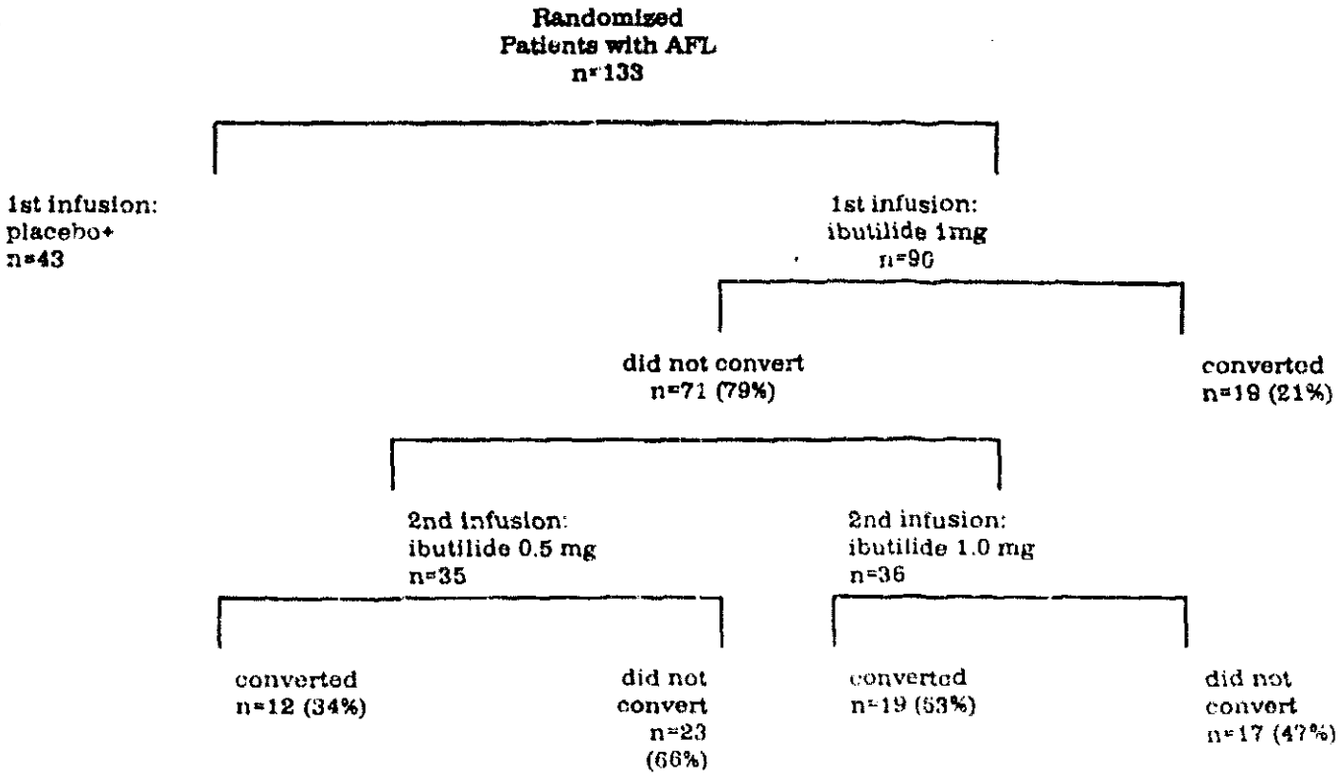
Of the patients who were randomized to ibutilide, 43% (78/180) converted with either the first or second infusion compared to 2% (2/86) of the placebo patients ($p < 0.0001$ for difference in success rates between ibutilide and placebo). Of the 78 patients who converted, 20% (36/180) converted with the first infusion and 29% (42/144) converted with the second infusion.

Of the 42 patients who converted with the second infusion, 26% (17/66) converted with the low dose (0.5 mg) and 32% (25/78) converted with the high dose (1.0 mg). There was no statistically significant difference in the success rates between the two dose groups.

Patients were stratified according to their baseline arrhythmia. The sections below discuss the success and failure rates according to the patients' baseline arrhythmia.

Atrial flutter (AFL)

The results for the 133 patients who were exhibiting AFL at baseline are shown in the figure below. Only 1 placebo patient converted so the results of the placebo group have been omitted from the figure ($p < 0.0001$ for difference in success rates between ibutilide and placebo).



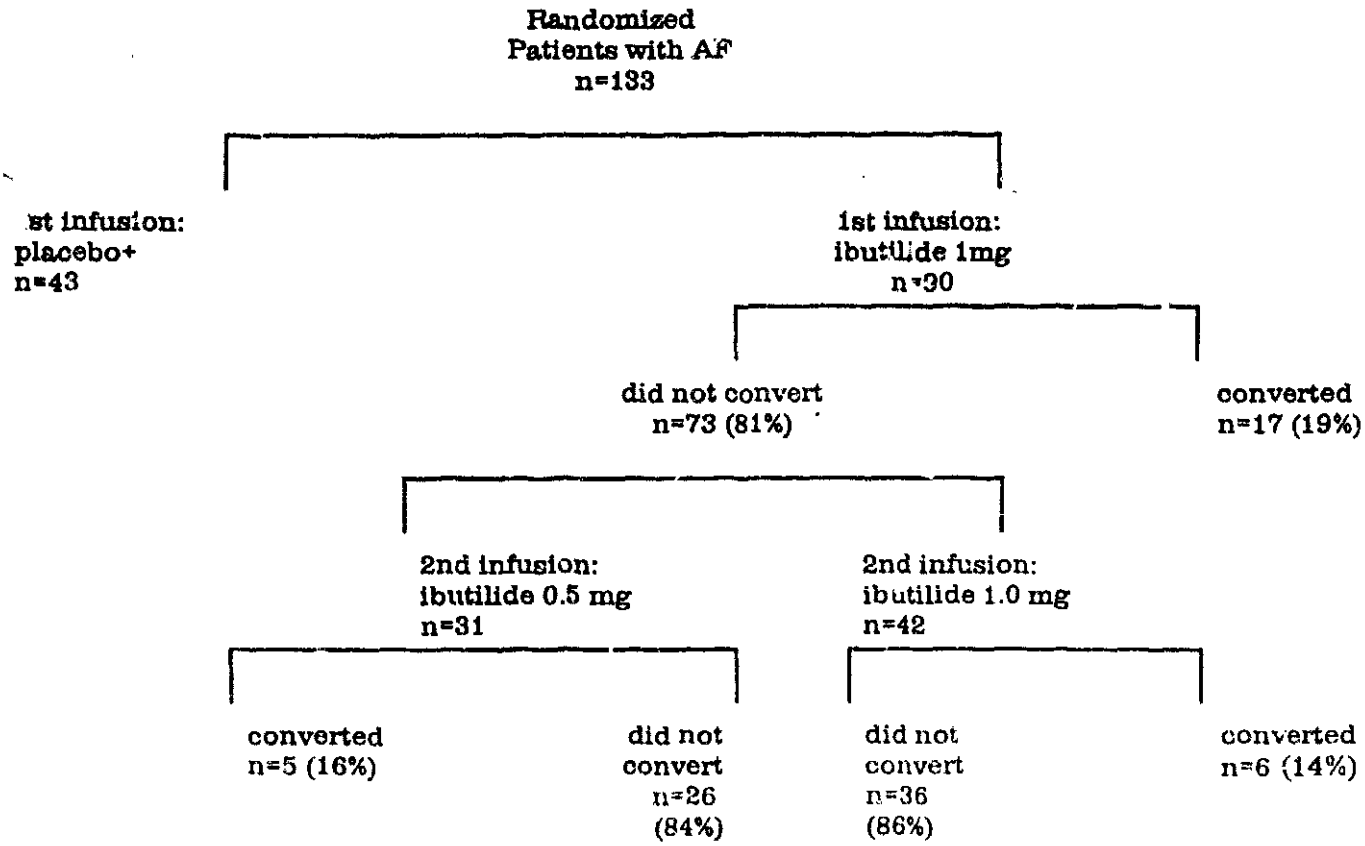
+results for the placebo group have been omitted from the figure.
Tables K.1, K.2, K.5 Vol 1.71, 08/20

Of the AFL patients who received ibutilide, 56% (50/90)had their arrhythmia terminated; 21% (19/90) converted with the first infusion and 44% (31/71) converted with the second infusion.

Of the AFL patients who converted with the second infusion, 34% (12/35) converted with the low dose (0.5 mg) and 53% (19/36) converted with the high dose (1.0 mg). There was no statistically significant difference between the success rates for the 2 dose groups.

Atrial Fibrillation (AF)

The results for the 133 patients who were exhibiting AF at baseline are shown in the figure below. Only 1 placebo patient converted so the results of the placebo group have been omitted from the figure (p=0.0011 for the difference in success rates between ibutilide and placebo).



+results for the placebo group have been omitted from the figure.
from Tables K.1, K.2, K.5 Vol 1.71, 08/20

Compared to AFL patients, AF patients had a lower rate of

conversion. Of the AF patients who received ibutilide, only 31% (28/90) had their arrhythmia terminated; 19% (17/90) converted with the first infusion and 15% (11/90) converted with the second infusion.

Of the AF patients who converted with the second ibutilide infusion, 16% (5/31) converted with the low dose (0.5 mg) and 14% (6/42) converted with the high dose (1.0 mg). There was no statically significant difference between the success rates for the 2 dose groups.

Additional efficacy analysis

It was determined that the definition of success used by the sponsor for this protocol and report was inadequate. A revised definition of success--patients who converted from AFL or AF to sinus rhythm by hour 1.5 without emergency intervention and remained in sinus rhythm for at least 24 hours--was used to re-evaluate the efficacy of ibutilide. Note: the revised definition of success is used only in this section of the review, all other sections use the protocol's definition.

The following table shows that rates of successes and failure for all ibutilide patients using both the revised and the protocol's definitions of success. The rates for placebo patients remained unchanged and are omitted from the table.

	All ibutilide patients (n=180)	
	revised definition	protocol's definition
	n (%)	n (%)
success (converted)	63 (35)	78 (43)
failure (did not convert)	117 (65)	102 (57)

from table 4s, information amendment 024 received March 21, 1995

Using the revised definition, 35% (63/180) of all ibutilide patients converted compared to 43% (78/180) using the protocol's definition.

Patients with AFL and AF

The table below shows the success and failure rates for the two definitions categorized by strata. The placebo patients have been excluded.

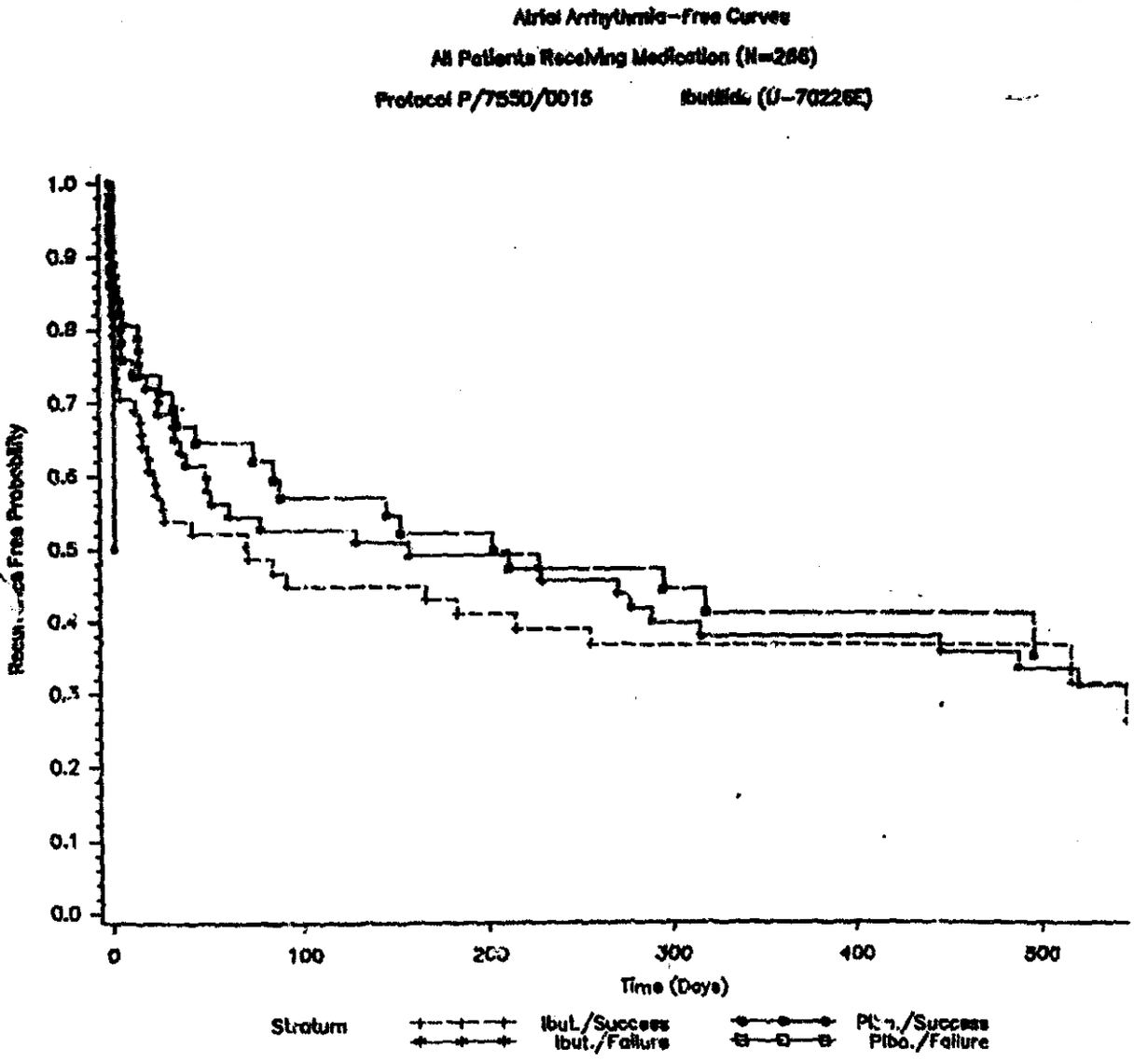
	Ibutilide patients with AFL n=90		Ibutilide patients with AF n=90	
	revised definition	protocol's definition	revised definition	protocol's definition
	n (%)	n (%)	n (%)	n (%)
success (converted)	46 (51)	50 (56)	17 (19)	28 (31)
failure (did not convert)	44 (49)	40 (44)	73 (81)	62 (69)

from table 4s, information amendment 024 received March 21, 1995

When the revised definition is compared to the protocol's definition, the success rates decreased minimally for the AFL patients (from 56% to 51%), but decreased strikingly for AF patients (from 31% to 19%). Overall, AF patients who received ibutilide were less likely to convert to sinus rhythm (& stay converted for at least 24 hours) compared to patients with AFL.

Recurrence of arrhythmia

The sponsor was asked to retrospectively collect data pertaining to the time (in days) the study patients who were converted to sinus rhythm reverted back to their arrhythmias. This was an attempt to try to answer the following question: is there a relationship between the time it took for study patients to revert to atrial fibrillation/flutter from sinus rhythm and the method used for conversion? The figure below shows the number of days after the study was completed and the recurrence rate for patients who were successes on ibutilide, successes on placebo, failures on ibutilide and subsequent successes with electroversion, and failures on placebo and subsequent successes with electroversion.



Note: When the day of the month was unknown the first day of the month was used (Patients 2153 and 2211

from informational amendment 022, vol 3 page 73, received March 15, 1995

According to this retrospective analysis, the time to recurrence of atrial fibrillation/flutter appears to be independent of the method used for conversion. By 100 days, approximately 45-55% of all patients who converted

during the study, regardless of method, had reverted back to their arrhythmias.

Dose comparison

All study patients either received placebo or ibutilide 1 mg for the first infusion. Patients who did not convert with the first dose of placebo (n=86) received a second dose of placebo. Patients who did not convert with the first dose of ibutilide (n=144) received a second dose of ibutilide, either 0.5 mg (n=66) or 1 mg (n=78). The table below shows the number and percent of patients who did not convert with the first dose of study drug and received a second dose, and the outcome of the second attempt at conversion. The placebo group has been omitted.

		Patients who converted with the second dose of study drug		Patients who did not convert with the second dose of study drug	
		n	%	n	%
all ibutilide patients	1mg/0.5mg (n=66)	17	26	49	74
	1mg/1mg (n=78)	25	32	53	68

from table K.4, vol 1.71, 08/20/15

Of the 66 patients (AFL and AF) who received 0.5 mg ibutilide for the second dose, 26% converted. Of the 78 patients who received 1 mg ibutilide for the second dose, 32% converted. It is not unexpected that there is a somewhat higher rate of conversion with the higher dose of study drug. However, the majority of patients who received the second infusion of ibutilide did not convert, regardless of dose received.

The table below shows the conversion rate with the second dose for each stratum. Note: placebo has been omitted.

		Patients who converted with the second dose of study drug		Patients who did not convert with the second dose of study drug	
stratum	dose	n	%	n	%
AFL only (n=71)	1mg/0.5mg (n=35)	12	34	23	66
	1mg/1mg (n=36)	19	53	17	47
AF only (n=73)	1mg/0.5mg (n=31)	5	16	26	84
	1mg/1mg (n=42)	6	14	36	86

from table K.4, vol 1.71, 08/20/15

There were 71 AFL patients and 73 AF patients who received a second dose of ibutilide. For the AFL patients, 34% of patients who received 0.5 mg as the second dose converted compared to 54.3% of patients who received 1 mg as the second dose. Patients with AFL, therefore, are more likely to convert if they receive 1 mg than if they receive 0.5 mg. In contrast, there was little difference in the conversion rate for the AF patients rate regardless of whether 0.5 mg or 1 mg was given as the second dose (16% and 14%, respectively).

Mean time to termination

The mean times to conversion from start of first infusion for ibutilide patients are shown below.

	dose	mean time (min.) to termination of arrhythmia
all ibutilide patients who converted n=78	1mg/0.5mg (n=37)	25.0
	1mg/1mg (n=41)	28.0
AFL only who converted n=50	1mg/0.5mg (n=21)	28.5
	1mg/1mg (n=29)	29.7
AF only who converted n=28	1mg/0.5mg (n=16)	20.4
	1mg/1mg (n=12)	24.0

from table K.6, vol. 1.71, 08/20/17

The mean time to termination of arrhythmia for all successful ibutilide patients was approximately 26 minutes. The patients with AFL had a slightly longer mean time to conversion (29-30 min) compared to patients with AF (20-21-min).

Study Drug Failures

The following table shows the study drug failures (for placebo and ibutilide) and the eventual outcome for these failures according to whether they underwent emergency termination of the arrhythmia prior to hr 1.5, had the arrhythmia terminated between hr 1.5 and 24, or did not have their arrhythmia terminated.

		Study Drug Failures					
		emergency termination prior to hr 1.5		arrhythmia terminated between hr 1.5 and 24		arrhythmia not terminated	
		n	%	n	%	n	%
all failure patients	placebo (n=84)	0	0	52	61	32	37
	1mg/0.5mg (n=49)	2	2	36	42	11	13
	1mg/1mg (n=53)	0	0	30	32	23	25
	total (n=186)	2	1	118	63	66	36

from table K.8, vol 1.71, 08/20/31

Of the 186 patients who failed study drug (either ibutilide or placebo), 63% (118) went on to have their arrhythmia terminated between hr 1.5 and 24 by other methods. For the 1mg/0.5mg ibutilide failures, 2 required emergency conversion prior to 1.5 hr. Both of the patients (#1001 and #1191) developed polymorphic ventricular tachycardia (patient #1191 had degenerated into ventricular fibrillation) during or shortly after the first infusion with ibutilide (1 mg). The arrhythmias were successfully terminated with electroversion.

The remaining 66 patients who failed study drug did not have their arrhythmia terminated either because they were unable to be converted by other methods or no attempt was made to convert them at that time.

Methods of converting the 118 study drug failure patients included non-emergency electroversion, pacing, or medication, or patients converted spontaneously. The table below displays the number and percent of the failure patients who were converted by one of these other methods.

Dose (mg)	Method of conversion for study drug failures							
	Electrocardioversion		Pacing		Medication		Spontaneously	
	n	%	n	%	n	%	n	%
pl/pl (n=52)	44	85	4	8	1	2	3	6
1/0.5 (n=36)	30	83	2	6	0	0	4	11
1/1 (n=30)	19	63	2	7	6	20	3	10
Total (n=118)	93	79	8	7	7	6	10	9

from table K.9.2, vol 1.17, 08/20/23

Electroversion was the treatment of choice for most patients who failed to convert with study drug. The majority of study drug failures (79%) underwent successful electroversion, while the rest were successfully converted by pacing (7%), other medication (6%), or converted spontaneously (9%).

There were 15 patients (5 with AFL and 10 with AF) who failed conversion with non-emergency DC shock. The failure rate with electroversion in this select population, therefore, was 14% (15/108, *data obtained from table K.9.3, vol 1.71, 08/20/24*).

Number of attempts with non-emergency electroversion

The data were examined for any difference between placebo and ibutilide regarding the number of attempts needed to successfully electrovert patients who failed study drug. The table below shows the mean and range of the number of attempts.

	study drug failure patients who were successfully electroverted between 1.5 and 24 hours- number of attempts at electroversion					
	placebo			ibutilide		
stratum	n	mean	range	n	mean	range
AFL	25	1.44		18	1.17	
AF	19	1.84		30	1.57	

from table L.13.1, vol. 1.71, 08/20/344

Overall, fewer attempts with electroversion were required for the ibutilide patients compared to placebo patients and this finding was true regardless of baseline arrhythmia.

The table below shows the number of joules needed to terminate the arrhythmia in the above mentioned patients.

	study drug failure patients who were sucoessfully electroverted between 1.5 and 24 hours- number of joules required					
	placebo			ibutilide		
stratum	n	mean	range	n	mean	range
AFL	25	240.4		18	177.8	
AF	19	453.7		30	320.7	

from table L.15.1, vol. 1.71, 08/20/344

Fewer joules were required to convert the ibutilide patients compared to placebo patients.

Study drug failures who were not converted by other means

There were 66 patients who failed to be converted with study drug and either failed to be converted by electroversion, other medication, or atrial flutter ablation, or no attempt was made to convert them. The table below outlines the number and percent of patients in each category.
It is of some interest to note that there was no attempt to terminate the arrhythmia in 19 patients who failed study drug. These patients, however, may have gone on to be converted after the study had ended.

Study drug failures who are not converted by other means

There were 66 patients who failed to be converted with study drug and either failed to be converted by electroversion, other medication, or atrial flutter ablation, or no attempt was made to convert them. The table below outlines the number and percent of patients in each category.

	Patients who failed study drug and could not be converted by other means							
	Electrocardioversion		Medication		Atrial Flutter Ablation		None	
	n	%	n	%	n	%	n	%
pl/pl (n=32)	10	31.3	17	53.1	0	0	5	15.6
1/0.5 mg (n=11)	3	27.3	3	27.3	1	9.1	4	36.4
1/1 mg (n=23)	2	8.7	11	47.8	0	0	10	43.5
Total (n=66)	15	22.7	31	47.0	1	1.5	19	28.8

It is of some interest to note that there was no attempt to terminate the arrhythmia in 19 patients who failed study drug. These patients, however, may have gone on to be converted after the study had ended.

Subgroups

Duration of arrhythmia

The original protocol required the duration of AFL to be greater than 3 hours and the duration of AF to be greater than 3 hours but less than 90 days. The protocol was amended later to specify that the duration of the arrhythmia could not be more than 45 days. The table below shows the mean duration of the arrhythmia (in days) categorized by treatment success or failure.

	ibutilide 1mg/0.5mg		ibutilide 1mg/1mg	
	success (days)	failure (days)	success (days)	failure (days)
all patients	14.1	23.8	14.1	18.1
AFL	15.8	26.5	11.0	21.2
AF	11.9	21.4	21.5	16.7

Tables K.16 and K.17, vol 1.71, 08/20/50-1

In all but one category (AF with 1mg/1mg), the ibutilide successes had a lower mean number of days of duration of the baseline arrhythmia. As expected, those patients with a relatively recent onset of arrhythmia were more likely to be converted.

Other subgroups

The following subgroups were examined: enlarged vs. normal left atrium, normal vs. decreased ejection fraction, and valvular vs. no valvular heart disease. (*The data for the following paragraphs are found in Tables K.20 and K.21, vol 1.71, 08/20/61 and 64.)*

left atrium size

Left atrium size was determined in 167 ibutilide patients. Of these patients, 140 (83.8%) were classified as having an enlarged atrium. This group of patients with an enlarged atrium was more likely to fail to be converted with ibutilide than they were to succeed (57.9% vs. 42.1%).

ejection fraction

Ejection fractions were categorized according to normal and abnormal criteria as determined by the individual investigators. Of the 142 ibutilide patients who were classified, more than half (77 patients, 54.2%) had decreased ejection fraction. There was nearly equal tendency for these patients to fail study drug as it was for them to succeed.

valvular heart disease

There were 168 ibutilide patients who were listed as either having a history (123 patients) or having no history (45 patients) of valvular disease. Those 123 patients with a history of valvular disease were more likely to fail to be converted with ibutilide (73 patients, 59.3%) than to succeed.

In summary, there is a tendency for patients to fail to be converted with ibutilide if they had an enlarged left atrium and/or a history of valvular heart disease. Decreased ejection fraction seemed to have little effect on outcome.

Concomitant medication

Patients receiving class I or other class III antiarrhythmic medications were not eligible for this study unless the medication had been discontinued for at least five half-lives prior to the infusion. The use of beta adrenergic blocking agents, calcium antagonists and digoxin was permitted. The following table, obtained from CANDA, displays the number of ibutilide patients who were receiving one or more of the permitted medications and whether they were successes or failures.

concomitant medication	success		failure	
	n	%	n	%
ca blockers (n=79)	36	46	43	54
no ca blockers (n=101)	42	42	59	58
beta blockers (n=33)	13	39	20	61
no beta blockers (n=147)	65	44	82	56
digoxin (n=104)	44	42	60	57
no digoxin (n=76)	34	45	42	55

The differences between the success rates for patients receiving and not receiving one or more the 3 specified concomitant medications are marginal.

Gender

Success and failure rates by gender for the ibutilide patients were obtained by CANDA and are shown below.

gender	success		failure	
	n	%	n	%
female (n=39)	16	41	23	59
male (n=141)	62	44	79	56

The incidence of success is independent of whether the patient was male or female.

QTc interval

treatment successes

As expected, ibutilide had a profound effect on the length of the QTc. For the 78 success patients who had received ibutilide, the mean values and ranges at baseline and time of arrhythmia termination are listed below.

Dose group+	mean at baseline (range)	mean at time of termination (range)	change from baseline
1mg/0.5 mg	405.24 (	459.08	54.75
1mg/1mg	415.68	472.51	56.83

+these were the dose groups to which the patients were randomized. Patients who converted with the first infusion did not receive the second.
Table K.29, vol 1.71, 08/20/128

The mean change from baseline at the time of arrhythmia termination was similar for the 2 dose groups.

treatment failures

Since most patients who converted did so between 21-30 minutes from start of drug infusion, the QTc intervals for the failure patients were examined at baseline as well as 30 minutes after start of infusion. For the 101 failure patients who received ibutilide, the mean values at baseline and at minute 30 are listed below (ranges were not given).

Dose group	mean at baseline (range)	mean at minute 30 (range)	change from baseline
1mg/0.5 mg	420.53 (	481.69	61.16
1mg/1mg	414.69 (	477.40	63.38

Tables K.31, K.33,, vol 1.71, 08/20/128 and 132

The changes from baseline are marginally larger for the failure group compared to the success group which may just be a reflection of failure patients receiving more ibutilide. Again, there was little difference in the change from baseline for the 2 dose groups.

IV. Safety

Medical Events

Medical events reported were those events starting or increasing in severity after the beginning of the first infusion, also known as TESS (treatment emergent signs and symptoms).

by body system

The following table shows the frequency of medical events by body system and dose group for all 266 randomized patients. Note: the patients are classified according to the dose group to which they were randomized, not according to actual dose received. The safety review has analyzed events by actual dose received.

Body System	Placebo (N=86)		1 mg/0.5 mg (N=86)		1 mg/1mg (N=94)	
	n	%	n	%	n	%
General Body	17	19.8	10	11.6	15	16.0
Cardiovascular	8	9.3	28	32.6	22	23.4
Digestive	7	8.1	8	9.3	6	6.4
Hemic/Lymphatic	0	0	1	1.2	1	1.1
Metabolic/Nutritional	3	3.5	4	4.7	5	5.3
Musculo-Skeletal	0	0	1	1.2	1	1.1
Nervous	3	3.5	5	5.8	5	5.3
Respiratory	7	8.1	7	8.1	5	5.3
Skin	1	1.2	2	2.3	3	3.2
Special Senses	0	0	0	0	1	1.1
Urogenital	2	2.3	3	3.5	4	4.3

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As expected from this class III antiarrhythmic agent, there was a significantly (p=0.001) higher incidence of cardiovascular medical events reported for the ibutilide patients compared to the placebo patients. The rates for ibutilide 1 mg/0.5mg, ibutilide 1 mg/1mg, and placebo were 32.6%, 23.4%, and 9.3%, respectively. The incidence rates for patients randomized to ibutilide for the other body systems are comparable to placebo.

within body systems

The table below is a frequency table of all treatment-emergent medical events by dose group and within body system. The following table lists all events which occurred in eight or more patients.

Medical Event	Placebo (N=86)		1 mg/0.5 mg (N=86)		1 mg/1 mg (N=94)	
	n	%	n	%	n	%
Headache	3	3.5	2	2.3	10	10.6
Nonsustained polymorphic VT	0	0	5	5.8	8	8.5
Back pain	6	7.0	3	3.5	2	2.1
Dyspnea	3	3.5	3	3.5	4	4.3
Ventricular extrasystoles	1	1.2	4	4.7	5	5.3
Nausea	0	0	6	7.0	3	3.2
Diarrhea	3	3.5	2	2.3	3	3.2
Fever	4	4.7	2	2.3	2	2.1
Nonsustained monomorphic VT	1	1.2	3	3.5	4	4.3

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There was a total of 13 reports of nonsustained polymorphic VT, all in patients who received ibutilide (p=0.027 for difference between ibutilide and placebo). Other events which were statistically significant (p<0.05) differences across dose groups include headache and nausea.

Poststudy Follow-Up Reports

Two patients had medical events that were not resolved when the 72 hour follow-up had ended. Patient #1054 reported a prolonged PR interval which began at Hour 1.5. The investigator reported the quinidine was discontinued, flecainide started, and the patient was discharged with first degree AV block. Patient #2088 had a cerebrovascular accident which had stabilized, but was not considered resolved, when follow-up ended.

<u>Serious medical events</u>

Deaths

One death (#1217, Stambler) in the placebo group occurred during the study. No deaths occurred in patients who received ibutilide.

Other serious medical events

The following table lists the serious treatment-emergent medical events by dose group.

Medical Event	Placebo (N=60)	1 mg/0.5 mg (N=55)	1 mg/1 mg (N=54)
total number of serious events	1	6	9
AV block complete	0	3	1
Cerebrovascular accident	0	1	0
Congestive heart failure	0	1	0
Diaphoresis	0	0	1
Hypotension	0	0	1
Kidney failure acute	0	1	1
Nausea	0	0	1
Nonsustained polymorphic VT	0	0	2
Respiratory failure	1	0	0
Sustained monomorphic VT	0	1	0
Sustained polymorphic VT	0	2	1
Ventricular extrasystoles	0	0	1

vol 1.68, 08/17/83

The placebo group had one serious event (respiratory failure resulting in death) compared to a total of 15 serious events for the 2 ibutilide groups combined. Of these 15 events, 8 were cardiac arrhythmias and are discussed below.

Proarrhythmia

The sponsor defined monomorphic and polymorphic ventricular tachycardia as three or more ectopic beats occurring at the rate of more than

100 per minute. Sustained VT was defined as VT with a duration of greater than 30 seconds or requiring intervention and nonsustained VT was defined as VT with a duration of less than 30 seconds and not requiring intervention.

The following table lists the number of patients with proarrhythmic events in this study.

Arrhythmia	Placebo (N=86)	1 mg/0.5 mg (N=86)	1 mg/1 mg (N=94)
Sustained polymorphic VT	0	2	1
Nonsustained polymorphic VT	0	5	8
Sustained monomorphic VT	0	1	0
Nonsustained monomorphic VT	1	3	4
Total	1	11	13

vol 1.68, 08/17/88

The incidence rates for placebo and both ibutilide doses combined were 1.2% (1/86) and 13.3% (24/180), respectively. Events were somewhat more frequent in the higher dose group (13.8%, 13/94) compared to the lower dose group (12.8%, 11/86). The one event in the placebo group was nonsustained monomorphic VT.

Overall, the change from baseline for the QTc intervals at 30 minutes after start of ibutilide for the 3 patients who developed sustained polymorphic VT ranged from a decrease of 31 msec to an increase of 321 msec. The baseline QTc interval for all study patients was limited to 440 msec. One patient developed the arrhythmia prior to completion of the first infusion (total dose 0.8 mg) and the other 2 developed their arrhythmia immediately after the first infusion (total dose 1 mg). One patient experienced a repeat episode 2.5 hours after infusion had been discontinued. All patients were successfully treated with electroversion.

Gender differences in proarrhythmic events

A gender difference in the incidence rate for torsade de pointes may exist for patients who take antiarrhythmics.[1]

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[1]Makkar, Raj R, et. al. Female gender as a risk factor for torsade de pointes associated with cardiovascular drugs, *JAMA*. 1993;270:2590-97

There were 39 females and 141 males who received ibutilide in study 0015. The table below shows the number of patients by gender who experienced each proarrhythmic event.

Arrhythmia	male n=141		female n=39	
	n	%	n	%
Sustained polymorphic VT	1	0.7	2	5.1
Nonsustained polymorphic VT	7	5.0	6	15.4
Sustained monomorphic VT	1	0.7	0	0
Nonsustained monomorphic VT	6	4.3	2	5.1

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In this trial, females had a much greater propensity to experience all types of proarrhythmic events with the exception of sustained monomorphic VT. The rates for sustained polymorphic VT for females and males were 5.1% and 0.01%, respectively, and for nonsustained polymorphic VT, the rates were 15.4% and 5.0%, respectively. However, the number of females studied is small compared to the number of males and this could account for the discrepancy in these incidence rates.

Medical Events Causing Discontinuation of Study Drug Infusion

All medical events causing discontinuation of the infusion occurred only in the ibutilide groups and were limited to the cardiovascular system. This evaluation is a bit misleading because patients only received one or two doses of study medication and events occurred after completion of dosing. The following table lists the number of patients who had an event that led to study discontinuation.

Medical Event	1 mg/0.5 mg (N=86)	1 mg/1 mg (N=94)	Total (N=180)
Total number of events	9	14	23
AV block complete	0	1	1
Heart block	1	0	1
Nonsustained monomorphic VT	1	1	2
Nonsustained polymorphic VT	2	7	9
QT segment prolonged	2	0	2
Supraventricular tachycardia	1	0	1
Sustained polymorphic VT	1	0	1
Tachycardia	0	1	1
Ventricular arrhythmia	1	0	1
Ventricular extrasystoles	0	4	4

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All of the medical events resulting in discontinuation of ibutilide were arrhythmias. The discontinuation rate for the 1mg/1mg dose was 14.9% (14/94) which is somewhat higher than the rate for the 1mg/0.5mg dose (10.5%, 9/86). The overall rate for the 2 groups combined was 12.8%. There were no study drug discontinuations in the placebo group.

Safety Laboratory Assays

Laboratory assays were obtained prior to as well as after study drug administration.

The only consistent abnormal values were for creatine kinase with some values reaching over 5000 U/L. In all cases, patients had undergone electroversion and only in a few cases were there elevated MB isoenzymes. In summary, there is no indication that short term infusion with ibutilide influences laboratory values.

abnormal laboratory values

Low WBC:
Decrease in WBC was minor and limited to one patient.

Patient #1056
WBC count at hour 24 was 2.8 $x10^3/mm^3$ (screen value was 3.0 $x10^3/mm^3$). This 73-year-old black female with a history of dilated cardiomyopathy, mitral valve repair, CHF, AFl/AF, alcohol abuse, COPD, gout and anorexia.

Liver function

Elevations in liver function tests were minor and limited to two patients.

Patient #1234
ALT and AST at Hour 24 were 73 U/L (normal range 3-36) and 108 U/L (normal range 16-41), respectively. Screen values were ALT: 21 U/L. and AST: 37 U/L. This patient was being treated for pneumonia.

Patient #1195
ALT, AST and Alk phos. at hour 24 were 58 U/L (normal range 7-56), 57 U/L (normal range 5-40), and 201 (normal range 38-126), respectively. Screen values were ALT: 41 U/L , AST: 36 U/L, Alk Phos. 179 U/L. No obvious reason was found for the mild elevations. The patient's laboratory values returned to normal after the study.

Kidney function

Elevations in both BUN and serum creatinine occurred in 3 patients and can be explained by other factors in two of the patients.

Patient #1058
BUN and serum creatinine at hour 24 were 30 mg/dl (normal range 10-25) and 1.3 mg/dl (normal range 1.1-1.3), respectively. Screen values were 15 mg/dL and 1.1 mg/dL. There was no obvious reason for these increases.

Patient #1061,
BUN and serum creatinine were 43 mg/dL (normal range 9-21) and 3.7 mg/dL (normal range 0.8-1.5) at hour 24. Screen values were 28 mg/dL and 1.6 mg/dL. This patient had experience hypotension (90/60 mmHg) the day before these elevated values were reported and is a likely cause.

Patient #1160,
BUN and serum creatinine were 58 mg/dL (normal range 9-21) at hour 24 and 2.6 mg/dL (normal range 0.8-1.5) 3 days after study drug. Screen values were 42 mg/dL and 2.2 mg/dl. This patient was concurrently receiving cyclosporin for previous heart transplant which is a likely reason for the elevations.

9-8-95
Maryann Gordon, MD

Appendix A Protocol review
Appendix B List of investigators

NDA 20-491

APPENDIX A: protocol 0015

Study objectives

The primary objectives of this study were:

- to demonstrate the effectiveness of 1 mg (or 0.01 mg/kg in patients weighing less than 60 kg) of ibutilide in the termination of atrial flutter (Afl) and atrial fibrillation (AF). Treatment was considered successful if the atrial arrhythmia terminated, for any length of time, by Hour 1.5.

- to investigate whether a second dose of 1 mg (or 0.01 mg/kg in patients weighing less than 60 kg) or 0.5 mg (or 0.005 mg/kg in patients weighing less than 60 kg) would increase the termination rate.

The secondary objective was:

- to assess the safety of ibutilide in this patient population.

Other objectives were:

- to determine the pharmacokinetics in this population.

- to analyze the cost-effectiveness of ibutilide treatment vs standard therapy.

There were 2 protocol amendments containing mostly minor changes. The major changes were a.) adjusting the dosing to mg/kg for patients weighing less than 60 kg and b.) shorting the duration of sustained atrial flutter/fibrillation from 90 to 45 days.

Study design

This multicenter study was a double-blind, placebo-controlled, randomized, dose-response trial in which patients were stratified based on baseline arrhythmia (AFl or AF). Patients in each stratum (AFl and AF) were randomized to receive two 10-minute infusions: placebo/placebo, 1 mg/0.5 mg ibutilide, or 1 mg/1 mg ibutilide. Those patients weighing less than 60 kg were dosed based on weight. If the arrhythmia did not terminate during or within 10 minutes after the end of the first infusion, the second infusion was administered. The infusion was discontinued at the time of arrhythmia termination.

A total of 240 evaluable cases (120 AFl and 120 AF) were required, with 80 patients (40 AFl and 40 AF) randomized to each dose group (placebo/placebo, 1 mg/0.5 mg ibutilide, 1 mg/1 mg ibutilide).

Treatment was considered successful if the atrial arrhythmia terminated, for any length of time, by Hour 1.5. (Time 0 = start of first infusion.) At Hour 24 both successes and failures were evaluated as to rhythm and treatment subsequent to Hour 1.5. All medical events through Hour 72 were recorded.

Study population

Eligibility Criteria

- Rhythm of sustained AFl or AF (duration greater than 8 hours and less than 45 days) [minor amendment].
- If AF had been present longer than 3 days, the patient should have received anticoagulant therapy (coumadin) for at least 2 weeks prior to enrollment as per standard clinical practice. The use of heparin was acceptable for patients who presented with AF of less than 3 days duration but could not be enrolled in the trial until after 3 days.
- No history of torsade de pointes.
- No prior exposure to ibutilide.
- Corrected QT interval (QTc) no greater than 440 msec on 12-lead ECG.
- Hemodynamically stable (systolic blood pressure greater than 80 mmHg and diastolic blood pressure less than 105 mmHg) and without symptoms of angina or congestive heart failure (CHF). Heart rate should have been no less than 60 beats per minute.
- Ability to comprehend and willingness to sign the informed consent.
- Age greater than 18 years.
- Body weight less than 300 lbs (136 kg).
- If female, must have been surgically sterile or postmenopausal (at least 12 months without a menstrual period).
- No myocardial infarction or cardiac surgery within the previous 30 days.
- No clinical evidence of hyperthyroidism.
- No serious pulmonary, hepatic, hematologic, metabolic, renal, gastrointestinal, CNS, or psychiatric disease, or any other disorders that could interfere with the conduct or validity of the study or compromise

patient safety. (Liver enzymes must have been less than two times maximum normal values.)

- Normal serum electrolytes. (Potassium of less than 4.0 mEq/L must have been corrected prior to enrollment.)

- No concurrent participation in another drug study or receipt of an investigational drug within 30 days prior to enrollment.

- No treatment with class I or class III antiarrhythmic medications (unless discontinued greater than five half-lives prior to enrollment).

- If the patient was being treated with digoxin, a careful clinical assessment was made to ensure that toxic levels were not present and a digoxin level (preferably trough) was obtained prior the infusion of study medication.

Noninvestigational medication/procedures

Patients receiving class I or other class III antiarrhythmic medications were not eligible for this study unless the medication had been discontinued for at least five half-lives prior to the infusion. The use of beta adrenergic blocking agents and calcium antagonists was permitted for heart rate control. If patients were being treated with digoxin, a careful clinical assessment was made to ensure that toxic levels were not present.

Administration of additional antiarrhythmic medication was delayed until 4 hours after the end of the infusions unless the investigator felt it was necessary to restore normal sinus rhythm (NSR) more quickly. In that case, drugs to facilitate conversion to NSR were given 1 hour or more after the end of the infusion.

If AFl or AF persisted past Hour 1.5, pacing or electrocardioversion was permitted at the discretion of the investigator.

Observations and evaluations

Each patient was scheduled to receive two 10-minute infusions. If the arrhythmia terminated prior to completion of the infusions, treatment was stopped. The infusion was also to be stopped if:

- Systolic blood pressure decreased to less than 90 mmHg.

- Any change in rhythm or atrioventricular conduction occurred which was a threat to patient safety.

- New bundle branch block occurred.
- QRS duration increased more than 50%.
- QTc interval increased to greater than 600 msec.
- New or repetitive forms of ventricular premature depolarizations were noted on the monitor.
- Any other threatening or potentially threatening adverse effects occurred.

If AFl/AF terminated, an electrocardiogram (ECG) was done at that time and the Hour 1.5 ECG was omitted. An additional 12-lead ECG was obtained if a significant change in rhythm occurred prior to Hour 1.5, or a significant adverse rhythm change occurred prior to Hour 24.

Population Characteristics

Patients were stratified by arrhythmia (AFl and AF) at the time of randomization. However, for the analyses, the rhythm recorded on the Minute -10 12-lead ECG was used to separate patients into the AFl or AF categories.

Baseline Period

The baseline period was the 10 minutes prior to the beginning of the first infusion (Minute -10 to Time 0).

Patients in a rhythm of AFl or AF at the end of the baseline period (Time 0) proceeded to the treatment phase of the protocol.

Treatment Period

Infusion Period

The infusion period lasted from the beginning of the first infusion (Time 0) until the end of the second infusion (Minute 30). During the infusion period, blood pressure and heart rate were recorded every 5 minutes, 12-lead ECGs were obtained at Minute 30 and if the arrhythmia terminated or if a significant rhythm change was observed, blood was drawn for an ibutilide plasma concentration (Minute 20), and the patients' ECGs were continuously monitored. Drug or placebo was infused according to schedule (first 10-minute infusion, a 10-minute wait, second 10-minute infusion) unless AFl or AF was terminated or a medical event occurred necessitating termination of

treatment.

Postinfusion Period

The postinfusion period lasted from the end of the infusion period (Minute 30) until Hour 24. A 12-lead ECG was done if the arrhythmia terminated or if a significant rhythm change occurred during the 1-hour period following the infusions (until Hour 1.5). A 12-lead ECG was also required at Hour 1.5 for patients whose arrhythmia did not terminate prior to that time, or if a significant adverse rhythm changed occurred through Hour 24. In addition, patients' ECGs were continuously monitored through Hour 24.

Blood samples for determination of ibutilide plasma concentration were drawn at Minute 40, Hour 1.5, and if AFl/AF terminated or proarrhythmia occurred prior to Hour 1.5. Blood and urine specimens for safety laboratory assays were obtained at Hour 24.

If AFl or AF persisted past Hour 1.5, pacing or electrocardioversion was permitted at the discretion of the investigator. Use of additional antiarrhythmic drugs, however, was discouraged until 4 hours following the end of the infusions. If the investigator felt it was necessary to restore sinus rhythm prior to that time, drugs to facilitate conversion were permitted 1 hour after the end of the infusions.

Study Endpoints

Primary

The primary efficacy endpoint of this study was the treatment-induced termination of AFl and AF. If termination occurred, the dose at which it occurred and the ibutilide plasma concentration at the time of termination were determined.

Secondary

Secondary endpoints included the effects of ibutilide on heart rate, blood pressure, safety laboratory assays, and ECG parameters.

Pharmacokinetics

Blood Sample Collection for Determination of Ibutilide Plasma Concentrations

Venous blood samples (7 mL) were collected into heparinized vacuum

tubes prior to dosing (Minute -10), and at Minutes 20, 40, and 90. If termination of AFl/AF or a significant change in rhythm occurred by Hour 1.5, a blood sample was also drawn at that time.

Safety

Vital Signs

Supine systolic blood pressure, diastolic blood pressure, and pulse were recorded at screen and at 5-minute intervals beginning at Minute -10 and ending at Minute 40, then at Hours 1, 1.5, 2, 4, 6, 8, 16, and 24.

Twelve-Lead Electrocardiograms

Twelve-lead ECGs were done at screen, Minute -10, Minute 30, and either at the time of termination (for successes) or at Hour 1.5 (for failures). In addition, an ECG was done if a significant rhythm change was observed prior to Hour 1.5, or if a significant adverse rhythm change occurred from Hour 1.5 through Hour 24. The Minute -10 ECG was used as baseline in the change from baseline calculations.

Medical Events

All medical events were followed until they resolved or the patient's participation in the study ended (Hour 72). In addition, all medical events which were serious and/or possibly related to the study medication were followed after Hour 72 until they resolved or stabilized. Abnormalities in safety laboratory values which were considered by the investigator to be clinically significant were also to be reported as medical events.

Statistical methods

Assumptions

Flutter and fibrillation indication can be pooled for analysis

Termination with placebo treatment is about 5%

Termination with active treatment is at least 30%

Primary variable

The primary efficacy variable is the variable termination/no_termination. The primary analysis will be with a linear model including treatment and

9-8-95

Maryann Gordon, MD

APPENDIX B: Investigators and Study Sites

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12.1

NDA 20-491

NDA REVIEW
Supporting Efficacy Studies

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

SEP 22 1995

NDA:	20-491
Name of Drug:	Ibutilide fumarate, injection
Sponsor:	Upjohn
Indications:	Acute conversion of atrial fibrillation/flutter
Submitted:	08/03/95
Received:	08/04/95
Assigned:	08/09/95
Reviewed:	09/19/95
Reviewer:	Shaw T. Chen, M.D.,Ph.D.

Addendum to NDA Review (Supporting Efficacy Studies)

The sponsor has submitted in this major NDA amendment the final report of a non-IND study, an international study comparing the safety and efficacy of intravenous ibutilide fumarate with that of iv dl-sotalol in terminating atrial flutter and atrial fibrillation. While dl-sotalol has not been approved for the same indication and there was no additional placebo control in this study, the sponsor and its expert consultants considered the data important for regulatory deliberation and requested that the study be presented to the Advisory Committee. The protocol, which has been briefly described in the main review for supporting trials (6/5/95), and results are reviewed as follows. Verification of statistical analyses by Dr. James Hung of Biometrics is also attached.

Study 19 (P/7550/0019)
A Multinational Comparative Study of the Safety and Efficacy of Intravenous Ibutilide with Intravenous dl-Sotalol to Terminate the Recent Onset of Atrial Flutter or Atrial Fibrillation in Patients who are Hemodynamically Stable.

PROTOCOL

This is a double-blind, parallel group controlled study comparing two single doses of ibutilide (1 and 2 mg) with one dose of i.v. dl-sotalol (1.5 mg/kg) in 300 patients (100 per group) with recent onset (3 hrs to 45 days) of atrial flutter/fibrillation. The objectives are to compare the safety and efficacy of the two drugs in converting the above atrial arrhythmias. Unlike that in Study 14, dosage of ibutilide were fixed, not by body weight.

Patients must be hemodynamically stable (SBP > 90 mmHg, DBP < 105 mmHg, ventricular rate 60 bpm or greater), weighed between 45 and 125 kg and had no recent (within 30 days) history of unstable angina, myocardial infarction, heart failure (revised later, see below) or other conduction disturbances (see protocol for details). Concurrent treatment with other antiarrhythmic agents was not permitted and prior exposure to study drugs or other agents that change cardiac conduction

(calcium and beta blockers) must be washed out adequately (off for at least 5 half lives). Serum potassium levels of less than 4.0 mEq/L were corrected prior to study treatment and QTc must be 440 ms or less at baseline. Anti-coagulation was provided before treatment with ibutilide if atrial fibrillation was longer than 3 days.

Patients with atrial flutter or fibrillation were randomized separately to receive **dosages of 1 mg ibutilide, 2 mg ibutilide or 1.5 mg/kg dl-sotalol infused for 10 minutes.** The infusion was stopped if atrial fibrillation was terminated before the completion of above dosing. Infusion of study drug was also terminated for safety endpoints of i) SBP less 90 mmHg, ii) hemodynamically intolerable changes in rhythm or AV conduction, iii) new bundle-branch block, iv) QRS increase by 50% or more, v) QTc increase to 600 ms, vi) repetitive forms of ventricular depolarization, vii) any other serious arrhythmias or adverse events. If atrial fibrillation persisted for one hour after the start of infusion, pacing or electrocardioversion was permitted at discretion of investigators. Additional antiarrhythmic agents for conversion failure were not used within the first hour, they were discouraged but permitted if necessary between hours 1 and 4. Maintenance antiarrhythmic therapy was not started until at least 4 hrs after the end of infusion (revised to 24 hrs, see below). Total monitoring was 24 hours, with a telephone follow-up on Day 3.

Primary **efficacy endpoint** was defined as termination of atrial flutter/fibrillation for any length of time within 60 minutes of start of first infusion. Comparison was made between individual treatment groups and between sotalol and combined ibutilide groups. Secondary endpoints included time to conversion, duration of conversion (to normal rhythm) and changes in ECG intervals. Per-protocol analyses (evaluable patients) were presented as the primary results in the sponsor's report, but intent-to-treat (all patients) analyses were also available. Only the latter will be described below in this memo.

Efficacy and safety **evaluations** were performed according to the following schedule:

		Minute				Hour		
Activity	Screen	-15	0-10	30	60	7	7-30	72
Informed Consent	X							
History/Physical	X							
12-Lead ECG	X			X	X	X		
Safety Labs	X					X		
BP/Heart rate	X		every 5-10 min			hourly		
Infusion			X					
ECG Monitor	X		continuous					
Holter Monitor			continuous			(success only)		
Medical Events			X	X	X	X	X	X
Telephone followup								X

Diagnosis and conversion of arrhythmia were verified by both ECG reading and Holtor monitoring, the latter was usually started 30 minutes before infusion, but not on all patients. Patients successfully treated were discharged at hour 7 with Holter monitoring continued for another 24 hours (hour 7 through hour 31). Although it was performed only in responded patients, Holter monitoring was not done in other ibutilide trials and is a unique feature of this study, which may be the reason why the sponsor considered the study important.

The protocol was revised in two amendments, which included; i) deleting provision of trans-esophageal echocardiogram to monitor need of anticoagulation, ii) inclusion of NYHA Class I-II heart failure patients, and iii) withholding prophylactic therapy for atrial flutter/fibrillation for 24 hrs after successful ibutilide therapy.

RESULTS

Patient Profile

Total of 319 patients entered the study at 40 centers. They were equally distributed in the three treatment groups. Patient demographics were comparable among treatment groups. Mean age of the patients was 60 (range 21-89) years and mean weight 81 kg (range 45-120). Approximately 30 % of patients were female and 96% were white.

In general, there was no significant difference among groups in prior medical history. Nearly half of patients in this study had various signs and symptoms of hypertension, myocardial infarction, coronary bypass surgery and congestive heart failure. Although the sponsor has noted that prior history of heart disease in *atrial flutter* patients was not evenly distributed between groups (marginal p of 0.0445), the total number of atrial flutter patients (about 20 per group) is small.

Of the total, approximately 20% had atrial flutter and 80% atrial fibrillation. Duration of atrial arrhythmias ranged from 0.3 to 91 days (mean 16.7, median 8.6 days). In patients with both Holter monitoring and ECG data, diagnosis of baseline atrial arrhythmia by the two techniques agreed in approximately 84% of the cases. While the Holter device described the prevalent arrhythmia more accurately, it was not done on all patients and data analyses were performed on the basis of ECG findings. Overall, more than half of the patients had prior history of atrial flutter/fibrillation and 44% (of total) were treated with digoxin. Number of patients with symptoms attributable to atrial arrhythmias was not reported. All these variables were well-matched among groups.

The number of patients who did not complete the 72 hour study was small and difference in patient disposition among groups could not account for the drug effect. Nine patients (3 in ibutilide 1 mg, 5 in ibutilide 2 mg and 1 in sotalol) had no data at hours 31 or 72, but all were followed for at least 7 hours and thus included in the per-protocol analyses (except one patient with 91 day duration of arrhythmia prior to entry). Eleven patients (3 each from the two ibutilide groups and 5 from sotalol) were excluded from the evaluable patient analyses, 9 had arrhythmias longer than 45 days and 2 did not receive full dose of the study drugs. Most of other protocol deviations were minor; infusion was longer than 10 minutes (up to 18 minutes in one, but total volume remained the same) in 26 patients, and ECG at hour 7 was performed in 57 patients whose arrhythmias were not terminated in one hour (contrary to what specified in the original protocol). Many patients were admitted in violations of certain entry criteria, which included serum potassium below 4 mEq/L (5 patients, all above 3.5 mEq/L), pulse below 60 bpm (1 patient, 8 bpm), systolic BP below 90 mmHg (2 patients, 85-87 mmHg), diastolic BP above 110 mmHg (7 patients, all 115 mmHg or below), QTc above 440 ms (16 patients[1]), and use of beta blockers (2 patients). Except for one patient with long QTc who also had atrial arrhythmia for more than 45 days, these patients were included in all analyses.

1. Range 444-527 ms, 5 in ibutilide 1 mg, 3 in ibutilide 2 mg and 8 in sotalol groups.

Ninety-three percent of all patients received full doses of study drugs infused over 10 minutes or longer (93% in 1mg ibutilide, 89% in 2mg ibutilide, 98% in sotalol, see Table[2] J.1, page 1023 of the study report). There were no statistically significant differences among groups in duration of **drug exposure**.

Efficacy Data

As shown in the table below, atrial arrhythmias were terminated in more patients treated with ibutilide (27% of 1 mg group, and 48% of 2 mg) than those who received sotalol (12%). The treatment differences in **response rate**, both overall and pair-wise[3], were highly significant (Tables K.1, K.1A, Pages 1051-1068). Not surprisingly, ibutilide was more effective in atrial flutter than in fibrillation, but the number of flutter patients in this study was small. The evaluable patient analysis generated essentially the same numbers (see Table K.1, page 370 of Study Report). Data of this primary endpoint also support a dose-response relationship, albeit only two doses of ibutilide were studied.

Arrhythmia	ibutilide 1 mg	ibutilide 2 mg	sotalol	chi-square p
All (n=319)	28 (27%)	52 (48%)	13 (12%)	<0.0001
atrial flutter (59)	9 (53%)	14 (70%)	4 (18%)	0.0027
atrial fib (260)	19 (22%)	38 (43%)	9 (10%)	<0.0001

Of all patients treated, 272 had both **ECG** and **Holter** data reported. Correlation of the two diagnostic methods was around 94% ((75+180)/272, as shown below, from Table K.9, Page 1118).

Holter	ECG		
	success	failure	Total
success	75	8	83
failure	9	180	189
Total	84	188	272

For patients successfully treated, arrhythmia termination occurred within mean of 21 and 13 minutes after infusion for the two ibutilide groups, 1 and 2 mg, respectively, as compared with 25 minutes for sotalol. The difference was statistically significant (without adjustment for multiple analyses). There were little variation between fibrillation and flutter in **time to termination** (Tables K.2.2 and 3, Page 1072, 1073). These responded patients **remained out of atrial arrhythmias** for at least 9 hours, with group means close to that of entire duration with Holter monitoring (27-34 hrs). However, there were no differences between treatments in this variable, both with Holter (Table K.12.1, Page 1127), and at 72 hrs telephone follow-up (with about half of the patients remained in sinus rhythm for at least 72 hrs, Table K.10.1, Page 1119). In the first 31 hrs, 11 responded patients **reverted to atrial arrhythmias**. Of these, patients treated with

2. In the study report, tables were designated by identical numbers for both evaluable-patient and intent-to-treat analyses, they are therefore located by page number in this memo to avoid confusion.
3. Both arrhythmias combined. For atrial flutter, the two ibutilide groups were indistinguishable, and ibutilide 1 mg was not better than sotalol in atrial fibrillation.

ibutilide 2 mg remained in sinus rhythm slightly longer than those of other groups (5 hrs vs 1-2 hrs, not significant, Table K.11.1, Page 1123).

Duration of pre-existing atrial flutter/fibrillation may have some predictive value for treatment effect, as suggested by the sponsor that ibutilide started within 15 days (an arbitrary cutoff) of atrial fibrillation/flutter was more effective (Figure 3, Page 35). But there was no between-group difference in this interaction (see also comments in Statistical Review) and higher dose was not more effective in patients of longer duration. The mean duration (in hrs) of atrial arrhythmias for success and failure are shown below (from Tables K.5.1 and K.6.1, Page 1099, 1101):

	Success	Failure
ibutilide 1 mg	13.5	21.2
ibutilde 2 mg	12.7	18.8
sotalol	6.8	16.4

While dose-related QTc prolongation was noted at the time of termination for the ibutilide groups, there were no significant differences in changes of QTc at 30 and 60 minutes and at Hour 7 between responders and non-responders (approaching statistical significance for the ibutilide 2 mg group, p-0.08). Use of digitalis or calcium channel blockers with 24 hrs of infusion did not affect treatment effect of ibutilide or sotalol, but the numbers of patients were small.

ECG parameters

Although the between-group differences in QRS interval were significant at baseline (85 ms for ibutilide 1 mg, 87 ms for ibutilide 2 mg and 81 ms for sotalol), mean QRS changes from baseline were small (1-4 ms) and essentially the same clinically for the three groups. While patients in all three treatment groups had significant increases in QT and QTc from baseline, differences among groups were noticeable only in the first hour (e.g. mean increase in QTc at 60 minute were 80 ms for ibutilide 2 mg, 49 ms for ibutilide 1 mg and 40 ms for sotalol, see Tables on Page 40). The sponsor also reported effect of ibutilide and sotalol on atrial cycle length for a small number of patients whose atrial flutter was not terminated. The results were neither conclusive (sample sizes of 10 or less), nor clinical relevant.

Safety Experiences

As noted in the Sponsor's Study Report, comparison of adverse experiences between ibutilide and sotalol was based on 319 total treated patients. No patients were excluded from the safety analyses. In the following discussion, one must bear in mind that relative risk assessment is meaningless until clinical benefit can be determined.

Medical Events

Approximately the same number of patients in the treatment groups reported a **new or worsening adverse event** (35% for ibutilide and 32% for sotalol), but there was a trend suggesting dose relations for ibutilide (27% for 1 mg and 41% for 2 mg, Table P.4, Page 2527). Most commonly reported were in the cardiovascular system (22-33% cardiovascular, 5-7% whole body, 1-6% respiratory, 1-5% nervous, and 1-3% metabolic systems, see Table on Page 47 of Study Report). Within the body systems, the patterns of distribution were also similar among

treatment groups (Table on Page 48). Notable reactions of 1% or more are summarized as follows (calculated from Table P.5 and ranked by incidence in total ibutilide patients).

Medical Events in 1% or more patients (% of patients)				
	Ibutilide 1 mg	Ibutilide 2 mg	Total Ibutilide	Sotalol
N=	102	109	211	108
extrasystoles ventri	5.9	9.2	7.6	1.9
nonsustained mono VT	4.9	8.3	6.6	3.7
bundel branch block	4.9	5.5	5.2	6.5
SVT	1.0	4.6	2.8	0.0
palpitation	2.9	0.9	1.9	0.9
QT prolongation	1.0	2.8	1.9	0.9
extrasystoles suprav	1.0	2.8	1.9	0.0
bradycardia	1.0	1.8	1.4	6.5
T-wave decreased	0.0	2.8	1.4	0.0
headache	1.0	1.8	1.4	2.8
chest pain	2.0	0.9	1.4	1.9
tingling	1.0	1.8	1.4	0.9
hypertension	0.0	1.8	0.9	0.9
hyperglycemia	1.0	0.9	0.9	0.9
hypotension	0.0	0.9	0.5	4.6
dizziness	0.0	0.9	0.5	4.6
dyspnea	0.0	0.9	0.5	3.7
nausea	0.0	0.9	0.5	1.9

About 71-78% of all medical events were reported as **"treatment related"** (Table P.11, Page 2617). Distribution pattern over body system was similar to that of all events (Table on Page 49).

Total of 20 patients reported a **serious event**, with the same frequencies for ibutilide and sotalol (both 5%). However, patients received ibutilide 2 mg appeared to have higher risk than those of the lower 1 mg dose (7% vs 2%, from Table P.15, see table below).

Ibutilide 1mg	Ibutilide 2mg	sotalol
sepsis/death	angina	abdominal pain
ECG abnormal	arrhythmia nodal	AV block
	endocarditis	left heart failure
	nonsust mono VT*	VF
	nonsust poly VT	cerebral infarct
	sust poly VT	
	vasovagal reaction	
	dyspnea	

* other 16 monomorphic NSVT were not considered serious, VT identified solely by Holter not included, see below.

While one can speculate that ibutilide treatment may affect the subsequent development and management of apparently unrelated adverse events (see case descriptions on Pages 51-53), it is

impossible to establish the temporal or causal relationship without sufficiently large number of observations and a significant differential between ibutilide and control (with the possible exception of ventricular arrhythmias, see below). Three deaths were reported, one (ibutilide 1 mg) due to sepsis occurred 20 days after infusion and two in the sotalol groups died, one of pulmonary embolism on Day 22 and the other of myocardial infarction 3 days following the infusion.

Not many patients were withdrawn from the study because of adverse experiences (2 in ibutilide 1 mg, 2 in ibutilide 2 mg and 1 in sotalol). Of these, three were not considered serious but were discontinued for bundle branch block and QT prolongation (all ibutilide). The other two were counted as serious reactions (AV nodal conduction, ibutilide, and complete AV block, sotalol).

Proarrhythmias

Even in this single study, risk of proarrhythmia from ibutilide treatment was evident and probably more serious and frequent than sotalol. Although the numbers of VT reported as medical events were small and differences did not reach statistical significance, more cases were reported in the higher dose of ibutilide (calculated from Tables P.5 and 2 of Page 3114):

% of patients	Ibutilide 1 mg	Ibutilide 2 mg	Total Ibutilide	Sotalol
N=	102	109	211	108
sustained poly VT	0.0	0.9	0.5	0.0
nonsustained poly VT	0.0	0.9	0.5	0.0
nonsustained mono VT	4.9	8.3	6.6	3.7
VT by Holter*	6.9	8.3	7.6	3.7
Total VT	11.8	18.3	15.2	7.4

* not reported as medical events, % based on total patients, not patients with Holter, see below

In 19 of the 20 reported as medical events, Holter recordings were available and identified 18 episodes of VT. While the diagnosis in only three (all in ibutilide 2 mg group) of the 16 reviewed were agreed upon by the majority of a panel of sponsor's consultants, all these cases should be conservatively considered as drug-related adverse effects on ventricular conduction, either tachycardia or "aberrancy". These VT's occurred mostly in non-responsive patients, but can also develop in patients converted to sinus rhythm by ibutilide (see case description on Pages 56-61). There were 80 additional cases of VTs identified by analysis of Holter tapes from 261 patients, but were not reported as medical events (see Appendix T of Study Report). The recordings were also reviewed by the same expert panel and reported as follows (Table 2 on Page 3114):

Interpretation	ibutilide 1 mg	ibutilide 2 mg	sotalol
VT	7	9	4
aberrant conduction	12	16	17
mixed*/others**	11	9	6

* "mixed": no majority opinion as to VT or aberrancy

** "other": not interpretable or idioventricular rhythm

Presumably these Holter-identified VT were all non-sustained. Of these, three (all ibutilide, one in 1 mg, two in 2 mg) were noted as polymorphic by all consultants, which may be an underestimate

as 11 VTs (all groups) were counted in at least one panel member's reading. Clinical meaning of the Holter-identified VTs is not clear, and without baseline reading (although recordings were available), it is difficult to attribute these arrhythmias to study drugs.

There may be an interaction between prior use of calcium antagonists within 24 hrs of infusion and risk of proarrhythmias (29% with use vs 6% without), but the total number of patients received calcium channel blockers was small (17). Increases in QTc of 50-100 ms or greater were observed at Minutes 30 and 60 in 14 of 20 patients. Development of ventricular arrhythmias could not be predicted by or attributed to entry arrhythmias, gender, digitalis use, serum potassium, magnesium or calcium concentration. Management of ibutilide-related ventricular arrhythmias did not appear to unusually difficult, only one case of polymorphic VT was sustained and required DC cardioversion.

Hemodynamics

As expected from it's beta-blockade activities, sotalol decreased systolic and diastolic blood pressures (10-15 mmHg and 5-10 mmHg, respectively), significantly from baseline and the effects were sustained for 6-7 hours. Ibutilide also reduced blood pressures, but to a lesser degree (about 5 mmHg for SBP and DBP) and varied little with dose (Figures 1 and 2). Heart rates were also decreased significantly from baseline in all three treatment groups (Figure 3), by about 15-30 bpm (from means of 106-107 bpm ventricular rates at baseline, Table M.1.3, Page 1542). The changes were dose-related for ibutilide and with similar extent for ibutilide 2 mg and sotalol. However, the heart rate changes of these degree reflected in part the intended termination of rapid ventricular rates in atrial arrhythmias and should not considered as adverse events. In patient failed to convert, there were no excessive slowing of heart rate for ibutilide (less than 20 bpm vs 20-25 bpm for sotalol, Figure 11 of Study Report on Page 44, not shown here).

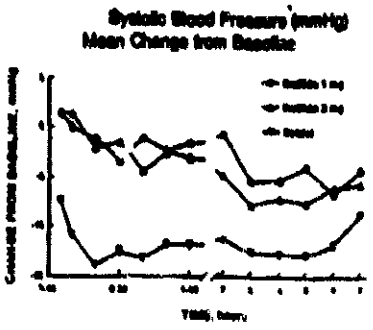

Figure1

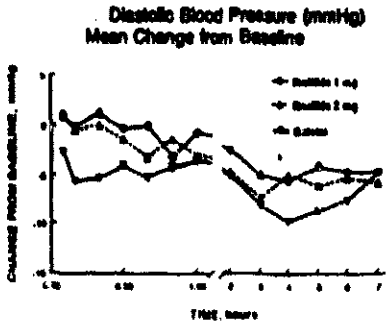

Figure 2

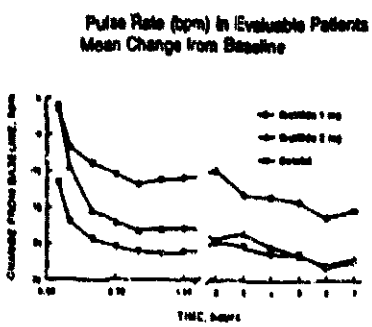

Figure 3

Hemodynamic changes described above (hypotension or bradycardia) were rarely reported as a clinical event in ibutilide groups (about 2%) but slightly more frequent for sotalol (10%). Postural hypotension reported in one ibutilide patient (2 mg) the day after infusion may also be attributed to oral sotalol (as maintain therapy). Five sotalol patients developed hypotension.

Adverse ECG Changes

Except for palpitation (see below), the ECG changes were asymptomatic in most patients. Overall

in all patient treated, there were no significant variations in the percentages of abnormal ECG (Q-wave, QRS complex, T-wave, ST-segment, ischemia or infarct) during the course of the study (up to Hour 7) (Table on Page 45 of Study Report). Between-group comparisons also suggest similar trend (Tables N.7-23).

Post Treatment Medication

There were no clear trends in post study medications that suggested patients were more difficult to manage clinically after receiving ibutilide therapy (Table on Page 46 of Study Report).

Laboratory Events

Although *within-group* changes from baseline in many laboratory parameters were statistically significant, the degrees of mean changes were of no clinical importance (see Tables on Pages 66, 68 and 72 of Study Report). In between-group comparisons, changes from baseline in monocytes and prothrombin time were statistically different but also not clinically meaningful (Table on Page 66).

Potentially important changes in laboratory values for individual patients[4] were described on Pages 67, 69-71. Of these changes suggesting temporal association with treatment, decreases in platelet counts in ibutilide Patients 2633 and 2637 cannot be ignored and ibutilide may increase ALT and AST moderately (Patients 2821, 2634 and 2238). Increases in creatinine kinase were prominent in one patient (2111), but clinical significance was unclear. While changes in sotalol patients were variable, ibutilide seemed to raise magnesium concentration modestly, probably without much clinical significance (in 4 patients) Decreases in serum calcium and potassium were noted in two respective ibutilide patients. Two patients reported drops in serum sodium concentration, but two sotalol patients also had similar changes.

COMMENTS

It is still not clear why the sponsor considers this study of importance in gaining regulatory approval. Superiority of intravenous ibutilide to placebo in acute termination of atrial flutter/fibrillation has been demonstrated in Studies 14 and 15 and is not a regulatory issue. The questions are whether acute pharmacological conversion of atrial arrhythmias confers any clinical benefit, justifies the risk of proarrhythmias and does not compromises long-term medical management of such patients. Current study did not provide any useful information to resolve these issues.

The sponsor's rationale in choosing sotalol as the active control in this study may be acceptable in foreign countries where sotalol has been approved for termination of atrial flutter/fibrillation. Such indication, although suggested by published literatures, has not been approved in the U.S. Thus even if the benefit/risk of ibutilide is more favorable than sotalol, it is relative to a reference not considered established yet. One may argue that sotalol is considered standard therapy by clinical community and ibutilide offers advantage over current practice, but there is no reason to advocate a unproven treatment in the first place.

4 Whether to include the rare changes described above in the labeling should be considered in the broader context of overall safety experiences of ibutilide, not just this single study.

One common difficulty in interpretation of active control study data is due to the uncertainty in optimal dosage for the control agent. Comparing with only one dose is unconvincing and full dose range for both study drugs are usually impractical. For this study, dose of sotalol was selected on the basis of pre-clinical assay ("equivalent to ibutilide") and the rate of arrhythmia termination by sotalol in this study is lower than that using lower doses (References 25 and 26 as cited in Study Report). Therefore, it is not sure whether the study found anything, relative to sotalol, on the efficacy of ibutilide.

One unique feature of this study is the use of Holter monitoring, which has not been performed in other ibutilide studies. While it is comforting that concordance between Holter and ECG in diagnosis of atrial flutter/fibrillation was quite decent (94%), substantially more ventricular arrhythmias were identified by the device than that reported as medical events. Nevertheless, without a clear clinical meaning and baseline reading (although recordings were available) for Holter-identified VT, not much else can be made of this additional information.

No new safety information about ibutilide was reported in this study. While ibutilide had less hemodynamic effects attributable to sotalol's beta-blocking activities, the data suggested that ibutilide caused more proarrhythmia than sotalol (although the small numbers were not statistically significant). Thus it is also debatable whether ibutilide is as safe as sotalol.

Since comparative studies are not required for approval and it has not been demonstrated convincingly in this study that the benefit/risk ratio of ibutilide is more favorable than a therapy not yet firmly established, data of this study are probably not useful in the regulatory deliberation of this application.

Shaw T. Chen, M.D.,Ph.D.

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ORIG: NDA- 20-491
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HFD-110/SChen/09/19/95

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SEP 22 1995

NDA REVIEW
Supporting Efficacy Studies

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

SEP 22 1995

NDA:	20-451
Name of Drug:	Ibutilide fumarate, injection
Sponsor:	Upjohn
Indications:	Acute conversion of atrial fibrillation/flutter
Submitted:	10/27/94
Received:	10/28/94
Assigned:	11/02/94
Reviewed:	03/30/95 **Review Completed:** 06/05/95
Reviewer:	Shaw T. Chen, M.D.,Ph.D.

Overview of NDA (Supporting Efficacy Studies)

Ibutilide is a new Class III antiarrhythmic agent being developed for acute termination of atrial fibrillation and flutter. In addition to clinical pharmacology studies, the NDA presented results of the following 10 clinical studies to support its claim (Tables 8.D-1, 2, 3, and 8.E):

Phase II	
Study 7	blinded and placebo controlled, dose-ranging, invasive electrophysiology
Study 13	open label, invasive electrophysiology in stable VT
Study 4	open label, dose-ranging, electrophysiology study, terminated after 3 patients
Phase III	
Studies 14, 15	randomized, double-blind, placebo controlled, major efficacy studies
Studies 3, 5	open label, pilot dose-finding
Studies 17, 19	on-going, post CABG in Study 17 and vs dl-sotalol in Study 19
Study 18	open label pilot for Study 19, terminated after 2 patients

In addition, two other Phase III studies have been submitted to IND- id are in progress:

Study 20	similar to Study 18, but is double-blind and parallel placebo controlled.
Study 21	double blind, active control with procainamide in AF termination.

As a part of parallel, team approach to primary medical review, this report covers **eight** of the above 12 clinical studies (**Studies 3, 4, 5, 17, 18, 19, 20, 21**) which are considered supportive but not definite evidence of effectiveness. The two major efficacy trials, Studies 14 and 15, were reviewed by Dr Raczkowski and Dr. Gordon, respectively. Overall safety experiences were summarized by Dr. Gordon and clinical pharmacology of ibutilide (which includes Studies 3, 5, 7 and 13)[1] was described by Dr. Raczkowski.

1 While Studies 7 and 13 were listed as supportive efficacy trials, they were actually electrophysiologic studies in patients unrelated to the indicated diseases (atrial flutter/fibrillation) and did not contain any efficacy data. Studies 3 and 5, with respect to antiarrhythmic drug effects, are described in this report, but pharmaco-kinetic and dynamic results are not included and instead referred to Dr. Raczkowski's Review.

As of the date of NDA writing, total of 358 patients were admitted to the five completed or terminated studies reviewed here (Studies 3, 4, 5, 18, 19). Of these, efficacy data have not been submitted for 319 patients in Study 19. For the latter and three on-going studies (17, 20, 21), protocols will be briefly described to provide an expectation of information to come, which may be helpful in regulatory deliberation.

Full reports of the completed or terminated studies are identified as References Numbers 8.15 (Study 3), 8.16 (Study 5), 8.25 (Study 4), and 8.26 (Study 18) in Volumes 1.75 and 1.76 of NDA. Protocols for the remaining studies can be located in IND- idies 17, 20, 21) and in Amendment of 4/6/95 (Study 19).

I. Completed/Terminated Studies

Study 3 (P/7550/0003)
Open-label, Dose-finding Study of Intravenous Ibutilide in Patients with Atrial Flutter.

Protocol

This is an open-label, dose finding study to assess the effects of intravenous ibutilide on cardiac rhythm in patients with atrial flutter. Patients with sustained atrial flutter for 3 hours or greater who were candidates for pharmacologic therapy, pacing or electro-cardioversion were eligible. Patients must be hemodynamically stable, without symptoms of angina or congestive heart failure and have no recent history of myocardial infarction. Concurrent treatment with other anti-arrhythmic agents was not permitted and serum potassium levels of < 3.5 mEq/L must be corrected prior to treatment with study drug.

After placement of a temporary pacing wire in the right ventricle, placebo was infused for 10 minutes followed by infusion of ibutilide in three sequentially ascending dose over 10 minutes each (0.005, 0.01 and 0.02 mg/kg, separated by 5 minutes washout). The infusion was stopped if atrial flutter was terminated before the completion of above dosing. Infusion of ibutilide was also terminated for safety endpoints of i) systolic BP less than 90 mmHg, ii) changes in rhythm or AV conduction, iii) new bundle branch block, iv) QRS increase by 50% or more, v) QTc increase to 600 ms, vi) any other serious adverse events. Heart rate and rhythm were monitored continuously and blood pressure every two minutes for 10 minutes after infusion and at specified time thereafter. After two patients developed polymorphic VT (and 15 patients enrolled), the two higher doses were eliminated in a protocol amendment. Patients were followed for 24 hours.

The primary efficacy endpoint was termination of atrial flutter. Effect of ibutilide on heart rate, blood pressure and electrophysiology, as well as measurements of pharmacokinetic parameters, are secondary endpoints.

There were three protocol amendments submitted. Except for the one deleting the high dose infusion, none of the other changes affected interpretability of the data.

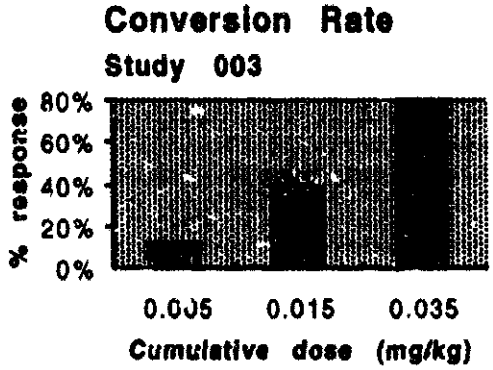
Results

Total of 17 patients (13 male, 4 female, 13 whites and 4 blacks) entered the study. Mean age of

the patients was 65.4 (range 25-81) years. Atrial flutter was symptomatic (dyspnea and exhaustion) in 12 (71%) of patients. Patients in this study had various histories of hypertension, myocardial infarction, coronary bypass surgery and congestive heart failure. Their atrial flutters were of different lengths of time, ranged from 0 to 413 days (median 4 days), with evidence suggesting more effective conversion in patients with shorter duration of atrial flutter.

Sixteen of the 17 patients completed the study. Most of protocol violations were minor (over age or weight limits, low plasma sodium and chloride concentration), but one patient may have atrial fibrillation in addition to atrial flutter. This patient was included in the analysis, but two patients treated under the low dose amendment (0.005 mg/kg only) were excluded. One patient did not complete the study due to onset of polymorphic VT seven minutes into the 0.02 mg/kg infusion. All 17 patients were followed for 24 hours.

Of the 17 patients, atrial flutter was terminated in 12. The conversion rate increased with accumulative dose (see chart below), thus related to duration of infusion with a mean of 33 minutes. Arrhythmia termination occurred within 22 minutes after infusion for the four patients who received the highest dose. In the chart, two patients who were not titrated above 0.005 mg/kg are included in the response rate for the lowest dose (2/17 or 12 %). Sinus rhythm was restored in 10 patients, the remaining 2 were converted to junctional rhythm and sinus bradycardia, respectively.



Atrial flutter was terminated in all nine patients with documented left atrial dilation, but in only one of the three with normal left atrial diameter. The numbers are, however, just too small to suggest any relationship between atrial size and antiarrhythmic effect of ibutilide. There were no such correlation with left ventricular ejection fraction either.

At the time of atrial flutter conversion, serum ibutilide concentration ranged from 1.5 to 12 ng/ml, without a clear trend in serum concentration-response relationship. For the two patients who developed polymorphic VT, drug levels were not excessive (2.1 and 6.4 ng/ml).

Changes in QTc were variable among individual patients, with 7 of 12 patients with increases of 6-87 msec). While the mean was not changed from baseline in patients whose atrial flutter was converted by ibutilide, mean QTc increased from 449 to 473 ms for the three who were not converted. Other electrophysiologic and pharmacokinetic measurements, as well as possible

interaction with digoxin, are referred to Dr. Raczkowski's review.

Comments

Despite a sequential dosing regimen and without formal statistical analysis, the results of this open label pilot study suggested that ibutilide is effective in termination of atrial flutter and the response rate increased with cumulative dose. However, lack of clear dose- and serum drug concentration-response relationships in this small group of patients indicated that treatment in clinical setting must be titrated and individualized. QTc and structural (atrial size) changes were not correlated with antiarrhythmic effect of ibutilide.

This study can be considered as a positive study supporting the short-term effectiveness of ibutilide in termination of atrial flutter.

Study 5 (P/7550/0005)
Open-label, Dose-finding Study of Intravenous Ibutilide in Patients with Atrial Fibrillation.

The study design of this protocol was almost identical to Study 3 as described above, except for the patient population to be studied (patients with atrial fibrillation instead of atrial flutter).

Protocol

This is an open-label, dose finding study to assess the effects of intravenous ibutilide on cardiac rhythm in patients with atrial fibrillation. Patients with sustained atrial fibrillation for at least 12 hours but less than 30 days were eligible. Atrial fibrillation of longer duration (up to one year) were also admitted in an amendment which was abandoned later for lack of efficacy in more chronic patients. Patients must be hemodynamically stable, and have no recent history of myocardial infarction. Concurrent treatment with other antiarrhythmic agents was not permitted and serum potassium levels of less than 3.5 mEq/L must be corrected prior to treatment with study drug. Anti-coagulation for two weeks was provided before treatment with ibutilide if atrial fibrillation is longer than 3 days.

For each patient, placebo was infused for 10 minutes followed by infusion of ibutilide in three sequentially ascending dose over 10 minutes each (0.005, 0.01 and 0.02 mg/kg, separated by 5 minutes washout). The infusion was stopped if atrial fibrillation was terminated before the completion of above dosing. Infusion of study drug was also terminated for safety endpoints of i) systolic BP less than 90 mmHg, ii) changes in rhythm or AV conduction, iii) new bundle branch block, iv) QRS increase by 50% or more, v) QTc increase to 600 ms, vi) any other serious adverse events. If atrial fibrillation persisted for 4 hours after end of infusion (later changed to one hour), electrocardioversion was permitted at discretion of investigators. Heart rate and rhythm were monitored continuously and blood pressure every two minutes for 10 minutes after infusion and at specified time thereafter. After two patients in the concurrent atrial flutter study developed polymorphic VT, the two higher doses were eliminated in a protocol amendment. Total follow up was 24 hours.

The primary efficacy endpoint was termination of atrial fibrillation. Effect of ibutilide on heart rate and blood pressure and electrophysiology, as well as measurements of pharmacokinetic

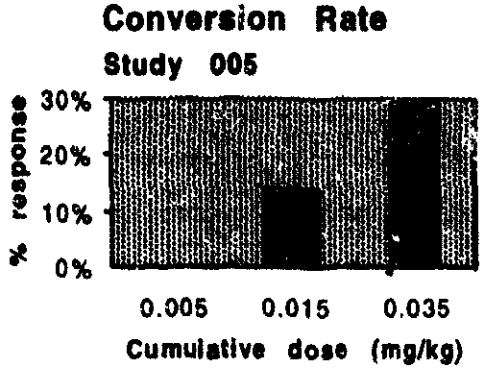
parameters, are secondary endpoints.

There were four protocol amendments submitted. The first one informed investigators the risk of proarrhythmia and added ECG and kinetic studies. As noted above, the protocol was amended to allow electrocardioversion earlier (in one hour) after infusion in patients failed to respond and to increase the chronicity of atrial fibrillation to be studied from 30 days to one year. The latter protocol was revised back to original protocol for lack of efficacy in chronic patients. Another amendment deleted the two higher dose infusions, as described above.

Results

Total of 19 patients (16 male, 3 female, 15 whites, 2 Hispanic, 1 blacks and 1 Filipino) entered the study. Mean age of the patients was 63.7 (range 39-78) years. Atrial fibrillation was symptomatic (palpitation and shortness of breath) in 8 (42%) of patients. Eleven of the 19 patients in this study had various histories of hypertension, coronary artery disease, congestive heart failure, cardiomyopathy, myocardial infarction, coronary bypass surgery, stable angina and mitral valve stenosis. Their atrial fibrillations were of different lengths of time, ranged from 0 to 325 days (median 71, mean 102 days), with a shorter duration (median 2 days, mean 42 days) for those responded to ibutilide treatment.
Eighteen of the 19 patients completed the study as specified by the protocol. Most of protocol violations were minor, which included less than 2 weeks of anticoagulation in 3 patients, one patient transferred from Study 3 with a duration of atrial fibrillation less than 12 hours, over age or weight limits, low plasma chloride and magnesium concentrations, and less frequent monitoring of vital signs (every 5 vs every 2 minutes). One patient did not complete the study due to onset of non-sustained VT after the 0.01 mg/kg infusion, but was included in the analysis. Dosing error was suspected for this patient because serum ibutilide was not detected. All 19 patients were followed for 24 hours.

Of the 19 patients, atrial fibrillation was terminated in 4, three converted to sinus rhythm and one to a non-sinus atrial rhythm. Of those not responded, 5 were not titrated above 0.005 mg/kg (per protocol amendment), thus were not included in the calculations for the higher doses. The conversion rate increased with accumulative dose (see chart below). Arrhythmia termination occurred 28 minutes after completion of infusion for the patient who received the highest dose.



For termination of atrial fibrillation, ibutilide was equally effective in patients with or without documented left atrial dilation. There numbers were too small for drawing any conclusion on the relationship between left ventricular ejection fraction and response.

At the time of atrial fibrillation conversion, serum ibutilide concentration ranged from 2.1 to 49.2 ng/ml, without a clear trend in serum concentration-response relationship. For the two patients who developed non-sustained VT, drug levels were not excessive compared with those of responded patients (13.6 and 2.0 ng/ml, the latter one had onset 215 minutes after start of dosing and had completed the ibutilide infusion).

Increases in QTc at the end of ibutilide infusions were dose-related (33-66 ms) and statistically significant, with the effect lasted for 4 hours. At the time of conversion, while the change in mean QTc was not significant (+11 ms), three had increases of 39-71 ms and one had a decrease of 110 ms. Other electrophysiologic and pharmacokinetic measurements, as well as possible interaction with digoxin, are referred to Dr. Raczkowski's review.

Comments

Similar to the atrial flutter study, despite a sequential dosing regimen and without formal statistical analysis, the results of this open label pilot study suggested that ibutilide is effective in termination of atrial fibrillation and the response rate increased with cumulative dose. Again, lack of clear dose- and serum drug concentration-response relationships in this small group of patients indicated that treatment in clinical setting must be titrated and individualized. QTc and structural (atrial size) changes, and left ventricular function were not correlated with antiarrhythmic effect of ibutilide.

Although the response in this study was less prominent than that for atrial flutter, this study can be considered as a positive study supporting the short-term effectiveness of ibutilide in termination of atrial fibrillation. Better defined dosage and patient selections may improve treatment outcome in atrial fibrillation.

Study 4 (P/7550/0004)

This was an open-label, dose-ranging electrophysiologic study of ibutilide in patients undergoing invasive studies for any indications. Patients should be in sinus rhythm, without Class I or III antiarrhythmic treatment. and hemodynamic stable with adequate LVEF (> 35%). After placement of a temporary pacing wire in the right ventricle, placebo will be infused for 10 minutes followed by infusion of ibutilide in three sequentially ascending dose over 10 minutes each (0.005, 0.01 and 0.02 mg/kg, separated by 5 minutes washout). The parameters to be determined include sinus node recovery time, AV conduction intervals, atrial and ventricular refractoriness, atrial and ventricular monophasic action potentials. Serum concentrations of the study drug were to be measured for determination of pharmacokinetic parameters. The protocol planned to study sufficient number of patients to give 10 evaluable cases. However, only one patient was admitted and the objective of the protocol was replaced by other early phase studies.

Electrophysiologic activities of ibutilide are referred to Dr. Raczkowski's clinical pharmacology review. Measurements on the single patient in this study added little to the understanding of pharmacology of ibutilide, revealed few surprising safety problem, and provided no efficacy data in the patients to be treated.

Study 18 (P/7550/0018)

This was an open label pilot study to evaluate the study procedure of terminating paroxysmal atrial fib/flutter using iv ibutilide in preparation for a larger trial comparing ibutilide and sotalol. Patients with paroxysmal atrial fib/flutter (> 1 hr but ≤ 24 hrs) were to receive 1 mg fixed single dose of iv ibutilide over 10 minutes and to be followed with ECG and Holter monitoring. Study of 10-15 patients were originally planned but the protocol was terminated after two patients were enrolled (the investigators/sponsor decided to proceed to the definite study). In one of the two patients, the atrial arrhythmia was not converted by ibutilide infusion of 1 mg over 10 minutes, despite a 13% increase (30 min after infusion) in QTc from 420 ms at baseline. ECG change and the effect on the arrhythmia were not reported for the other patient. This study contributed very little to the drug development of ibutilide.

II. Ongoing Studies

Study 17 (P/7550/0017)
A Study of the Conversion Efficacy and Safety of Repeated Intravenous Doses of Ibutilide in Patients with Atrial Flutter or Atrial Fibrillation Following Valvular or Coronary Artery Bypass Surgery

Protocol

This is a randomized, double-blind, parallel placebo controlled, dose-response study to assess the efficacy and safety of i.v. ibutilide in termination of atrial fibrillation/flutter for patients post valvular or coronary artery bypass surgery.

Total of 300 patients with sustained atrial flutter/fibrillation (≥ 1 hrs but less than 3 days) occurring between one and seven days following valvular or coronary artery bypass surgery will be randomized to receive one of the following four regimens:

N	Infusion 1	Infusion 2
75	1.0mg (0.01mg/kg)	1.0mg (0.01mg/kg
75	0.5mg (0.005mg/kg)	0.5mg (0.005mg/kg)
75	0.25mg (0.0025mg/kg)	0.25mg (0.0025mg/kg)
75	placebo	placebo

Patients with body weight less than 60 kg will received the per-kg dosage. The second infusion will be given if atrial flutter/fibrillation does not terminate within 10 minutes after the end of first dose. Ibutilide infusion will be discontinued anytime during the two infusions if atrial flutter/fibrillation is converted. Patients will be treated for 30 minutes and monitored for 3 days. The sponsor thought the study could be completed in 12-18 months, but as of 4/95, only 152 patient were admitted.

Efficacy success is defined as termination of atrial flutter or atrial fibrillation for any length of time in the first 90 minutes. Subsequent rhythm and further treatments in the first 24 hrs will be monitored. All medical events in the 3 days of study will be documented. Patients with persisted

arrhythmia may be paced or electrocardioverted after 90 minutes but additional antiarrhythmic therapy will not be started in 4 hrs unless medically indicated.

The protocol is essentially identical to P/7550/0015, one of the two major efficacy trials in non-surgical patients which was reviewed by Dr. Gordon. Definition of atrial arrhythmias (paroxysmal vs chronic in non-surgical patients) is less complicated here but whether termination of atrial arrhythmia with the study drug in the first 90 minutes leads to real clinical benefit in these patients has not been not addressed in this protocol. Although clinical course will be monitored for 3 days following drug administration, secondary endpoints such as recurrent rate of arrhythmias and subsequent morbidity/mortality were not specified prospectively in details.

Since the original study design, the sponsor has requested to relax entry criteria for the study due to great difficulty in recruiting patients. The reasons were basically reluctance of surgeons to observe post operative patients in atrial arrhythmia for 3 hours (original protocol) before treatment and high percentage of patients had to be excluded for concomitant valvular procedure, pre-op atrial fib/flutter and recent MI in the original protocol. The sponsor thus revised the protocol to extend enrollment of patients post valvular surgery and the above pre-existing conditions, and to shorten the observation period to one hour. The change appeared to be necessary from a practical perspective. As the sponsor pointed out, while the extended enrollment introduced more confounding clinical conditions, the gain in safety experiences probably offset the loss.

Comments

Since this study enrolls post-operative patients whose acute onset of atrial arrhythmias may adversely affect outcome of high-risk cardiac surgery, the need to treat is more evident and risk/benefit assessment is less difficult than that in non-surgical patients with more chronic atrial arrhythmias. If clinical benefit of terminating atrial flutter/fibrillation can not be ascertained from the completed efficacy studies, data from this study may be worth waiting for before final approval of atrial flutter/fibrillation indication.

It is not clear that any dose response information can be obtained from the dosage design of this study, but the dose-range is probably acceptable for safety considerations (4.5% pro-arrhythmia).

Study 19 (P/7550/0019)
A Multinational Comparative Study of the Safety and Efficacy of Intravenous Ibutilide with Intravenous dl-Sotalol to Terminate the Recent Onset of Atrial Flutter or Atrial Fibrillation in Patients who are Hemodynamically Stable.

This is a large European international study which was not filed to IND. At the Agency's request, the protocol was submitted in the 4/6/95 Amendment (No. 029). While dl-sotalol has not been approved for atrial flutter/fibrillation, at the advice of its consultants, the sponsor has asked that no regulatory action regarding this NDA be taken before the final report (to be submitted in August 1995) of this study is reviewed.

Protocol

This is a double-blind, parallel group controlled study comparing two single doses of ibutilide (1 and 2 mg) with one dose of i.v. dl-sotalol (1.5 mg/kg) in 300 patients with recent onset (3 hrs to

45 days) of atrial flutter/fibrillation. The objectives are to compare the safety and efficacy of the two drugs in converting the above atrial arrhythmias. Unlike that in Study 14, dosage of ibutilide will be fixed, not by body weight.

Patients must be hemodynamically stable (SBP > 90 mmHg, DBP < 105 mmHg, ventricular rate 60 bpm or greater), weigh between 45 and 125 kg and have no recent (within 30 days) history of unstable angina, myocardial infarction, heart failure or other conduction disturbances. Concurrent treatment with other antiarrhythmic agents or prior exposure to study drugs was not permitted. Serum potassium levels of less than 4.0 mEq/L must be corrected prior to study treatment and QTc must be 440 ms or less at baseline. Anti-coagulation was provided before treatment with ibutilide if atrial fibrillation is longer than 3 days.

Patients with atrial flutter or fibrillation will be randomized separately to receive 1 mg ibutilide, 2 mg ibutilide or 1.5 mg/kg dl-sotalol infused for 10 minutes. The infusion will be stopped if atrial fibrillation was terminated before the completion of above dosing. Infusion of study drug will also be terminated for safety endpoints of i) SBP less 90 mmHg, ii) hemodynamically intolerable changes in rhythm or AV conduction, iii) new bundle branch block, iv) QRS increase by 50% or more, v) QTc increase to 600 ms, vi) repetitive forms of ventricular depolarization, vii) any other serious arrhythmias or adverse events. If atrial fibrillation persists for one hour after the start of infusion, pacing or electrocardioversion will be permitted at discretion of investigators. Additional antiarrhythmic agents for conversion failure should not be used within the first hour, they are discouraged but permitted within 4 hrs of after the end of infusion. Total patient monitoring is 24 hours, with a telephone follow-up on Day 3.

Primary efficacy endpoint was defined as termination of atrial flutter/fibrillation for any length of time within 60 minutes of start of first infusion. Comparison will be made between individual treatment groups and between sotalol and combined ibutilide groups. Secondary endpoints include time to conversion, duration of conversion (to normal rhythm) and changes in ECG intervals.

The protocol was revised in two amendments, which included; i) deleting provision of trans-esophageal echocardiogram to monitor need of anticoagulation, ii) inclusion of NYHA Class I-II heart failure patients, and iii) withholding prophylactic therapy for atrial flutter/fibrillation for 24 hrs after successful ibutilide therapy.

Comments

Since efficacy of dl-sotalol in converting atrial flutter/fibrillation has not been established, it is difficult to understand why the sponsor viewed the results of this study as an important piece of information to gain approval of the indication. Nevertheless, this is a large efficacy study about the same size of the two completed major trials (Studies 14 and 15), thus it will be hard to ignore the results. Safety experiences in this study are probably useful, but the data may not add anything for efficacy, because, again, patients in this study have no long-term follow-up beyond 3 days.

Study 20 (P/7550/0020)
A Study of the Conversion Efficacy and Safety of Ibutilide in Patients with Atrial Flutter or Atrial Fibrillation.

Protocol

This is a double-blind, parallel placebo controlled, repeated dose study with similar objectives as that of open-labeled, single-dose Study 0018. Unlike that in Study 14, dosage of ibutilide will be fixed, not by body weight.

Patients who weigh 60 kg or above and have atrial flutter or fibrillation of more than 3 hours but less than 90 days duration will be screened appropriately. Except for the duration of pre-existing atrial arrhythmias, patients selection was similar to that of Studies 3 and 5 (see above) but probably healthier than in Study 5 (no history of torsade, symptoms of heart failure or QTc >440 ms, potassium corrected to 4.0 mEq/L). Total of 240 patients (200 ibutilide, 40 placebo) will be randomized (at ratio of 5:1) to receive a ten-minute iv infusions of 1.0 mg ibutilide or placebo over a period of 30 minutes and if arrhythmias are not terminated in 10 minutes after the first 1 mg dose, followed with another fixed dose of 1.0 mg or placebo infused over 30 minutes. Ibutilide infusion will be discontinued anytime during the two infusions if atrial flutter/fibrillation is converted. Infusion of study drug will also be terminated for safety endpoints of i) symptomatic or serious hypotension, ii) changes in rhythm or AV conduction, iii) new bundle branch block, iv) QRS increase by 50% or more, v) QTc increase to 600 ms, vi) any other serious arrhythmias or adverse events. If atrial arrhythmias persist or recur after 90 minutes, patients may be treated with pacing or cardioversion. Additional antiarrhythmic agents will be delayed until 4 hours after the end of infusion. All patients will be followed for 3 days. The study is expected to complete in one year.

Primary efficacy endpoint was defined as termination of atrial flutter/fibrillation for any length of time within 90 minutes of start of first infusion. Secondary endpoints include time to conversion and changes in ECG intervals.

The protocol has been revised in three amendments, all changes were of minor importance in study design (changed size of vials, clarified infusion system and increased women patients to 40%). The sponsor indicated in a telephone communication that final report of this study is expected in October 1995.

Comments

This is a large efficacy study about the same size and with similar design as the two completed major trials (Studies 14 and 15). For regulatory deliberations, it will not be easy to ignore the results, if available near approval. However, patients in this study have no long-term follow-up beyond 3 days, thus it is not clear how useful the data will be in terms of providing additional support for ibutilide's efficacy.

In this study, low body weight patients (less than 60 kg) are excluded and ibutilide is given in fixed dose of 1 or 2 mg. It will be difficult to apply dosing information in this study to other patients with body weights outside of the specified range (60-136 kg).

Study 21 (P/7550/0021)
A Study of the Conversion Efficacy and Safety of Ibutilide I.V. Compared to Procainamide I.V.in Patients with Atrial Flutter or Atrial Fibrillation.

Protocol

This is a double blind, active control study very similar in design to Study 20, except that the ibutilide will be compared with procainamide, without a concurrent placebo group. In addition, the total sample size will be 120 with a randomization ratio of 1:1.

As in Study 20, patients with the same weight range (60-136 kg) and duration of atrial flutter or fibrillation (3 hours to 90 days) will be screened with almost identical inclusion/exclusion criteria as in Study 20 (in addition, patients with complete second or third degree history of heart block will be excluded). Ibutilide 1.0 mg will be given as a ten-minute iv infusion and followed by a second dose if arrhythmia persists 10 minutes after completion of the first dose. Procainamide will be given up to three ten-minute infusions of 400 mg each. Ibutilide and procainamide administrations will be discontinued anytime during the infusions if atrial flutter/fibrillation is converted. The treatment will completed over a period of 30 minutes and followed with ECG for 3 days. The study is expected to complete in one year.

Efficacy and safety endpoints are similar to those in Study 20, which include termination of arrhythmia in 90 minutes (primary efficacy), time to termination and proportion of patients converted during infusions and remain in sinus rhythm for 6 hours.

The protocol has been revised in an amendment, which increased enrollment of women patients to 40% and clarified the time to use other anti-arrhythmic agents (after 24 hrs if patients remained converted, after 6 hrs if no termination in 1.5 hrs, cardioverted within 1.5 hrs, or reverted after initial success).

Comments

Despite the limitations of an active control study, results of this study, especially regarding safety, will be useful as supportive evidence when viewed together with other major efficacy trials. However, it is not clear how the treatments will be blinded, since ibutilide will be given in two infusions and procainamide up to three.

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THIS SAFETY REVIEW INCLUDES A REVIEW OF THE FOUR MONTH SAFETY UPDATE SUBMITTED ON FEBRUARY 27, 1995.

12.1

CSO

OCT 12 1995

NDA-20-491

to 8/3/95

AM

Maryann Gordon, MD
Sept 8, 1995; NDA#20491

III. Safety Addendum

This safety addendum was prepared after the review of the Safety Update. It contains complete safety data from one study (0019), a combined safety analysis for all completed and terminated Phase II/III clinical trials, and limited safety data from 3 ongoing studies (0017, 0020, and 0021).

Summary: the most frequently reported medical events were the cardiac arrhythmias, ranging from the relatively benign nonsustained monomorphic VT and ventricular extrasystole to the life-threatening sustained polymorphic VT. Of the 679 ibutilide patients, 12 (1.8%) developed sustained polymorphic VT compared to 0 placebo patients. The patients who developed this arrhythmia did so either during ibutilide infusion or shortly thereafter. All of these events were successfully resolved, usually with electroversion. The Holter monitoring results obtained in recent study 0019 raises the question that there are additional VT occurrences that are asymptomatic and, therefore, not counted in the medical event reporting. This may be only of academic interest.

Medical events occur at roughly the same rate for doses between 0.75 mg and 2 mg infused over 10 minutes. It is unknown if prolonging the infusion rate could affect the rate of these events.

No deaths or serious medical events, other than the tachyarrhythmias, could be associated with the use of ibutilide. No laboratory values appear to be adversely affected by short term ibutilide use.

a. Completed Study 0019

This was a non-IND study conducted at 43 centers in Europe (37), Russia (3), and South Africa (3) that enrolled patients with atrial fibrillation (afib) or flutter (afl). The design of the study was double blind, randomized, active control (vs. sotalol), with 3 parallel groups (ibutilide 1 and 2 mg and sotalol 1.5 mg/kg). The objective, similar to the other Phase II/III protocols, was acute termination of the atrial arrhythmia, for any time period, within 60 minutes of the start of a 10 minute infusion. Patient selection was similar to that of the other protocols. The subjects were patients with sustained afib or afl of a duration of at least 3 hours but not more than 45 days, who were hemodynamically stable, had adequate serum potassium levels, and had QTc intervals ≤ 440 m sec on 12-lead ECG. Patients were stratified based on the baseline atrial arrhythmia.

There was a total of 319 patients randomized: 102 to ibutilide 1 mg, 109 to ibutilide 2 mg, and 108 to sotalol. The table below displays the number of

patients by baseline arrhythmia and treatment group.

	ibutilide		sotalol	
arrhythmia	1 mg	2 mg	1.5mg/kg	total
afl	17	20	22	59
afib	84	89	84	260
combined	108	109	106	319

from study report page 94

Demographics

Patients had a mean age of 60 years (range 21-89), a mean weight of 81 kg (range 45-130), and were mostly white (96%) and male (70%). Treatment groups were similar at baseline for demographic variables as well as for medical history *(from Vol. 4 of study report 0019, tables F and G)*

Treatment emergent medical events

The table below lists the adverse events and (percents) that occurred in at least 1% of the total study population. As expected, the largest number of events reported were related to the cardiovascular system.

Treatment Emergent Medical Events

		ibutilide		
	sotalol n=108	1 mg n=103	2 mg n=109	all ibut n=211
Any event	**25 (23.4)**	**28**	**45**	**73 (34.6)**
Cardiovascular-any	**24 (22.2)**	**24**	**36**	**60 (28.4)**
ventricular extrasystole^	2 (1.9)	8	10	18 (8.5)
non sustained monomorphic VT	4 (3.7)	5	9	14 (6.6)
bundle branch block	7 (6.5)	5	6	11 (5.2)
supraventricular VT	0	1	5	6 (2.8)
palpitation	1 (0.9)	3	1	4 (1.9)
QT segment prolongation	1 (0.9)	1	3	4 (1.9)
supraventricular extrasystole	0	1	3	4 (1.9)
decreased T wave amplitude	0	0	3	3 (1.4)
bradycardia#	7 (6.5)	1	2	3 (1.4)
hypertension	1 (1.0)	0	2	2 (1.0)
hypotension@	5 (4.6)	0	1	1 (0.5)
Body-any	**8 (7.4)**	**5**	**5**	**10 (4.7)**
headache	3 (2.8)	1	2	3 (1.4)
chest pain	2 (1.9)	2	1	3 (1.4)
Nervous-any	**5 (4.6)**	**2**	**1**	**3 (1.4)**
tingling	1 (1.0)	1	1	2(1.0)
dizziness	5 (4.6)	0	1	1 (0.5)
Respiratory-any	**7 (6.5)**	**1**	**2**	**3 (1.4)**
dyspnea	4 (3.7)	0	2	2 (1.0)
Digestive-any	**3 (2.8)**	**0**	**2**	**2 (1.0)**
nausea	2 (1.9)	0	1	1 (0.5)
Metab/Nutri-any	**2 (1.9)**	**1**	**3**	**4 (1.9)**
hyperglycemia	1 (1.0)	1	1	2 (1.0)

^ includes extrasystole ventricular bigeminy
#includes sinus bradycardia
@includes postural hypotension

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(from Vol. 8 of study report 0019, tables P.4 and 5.)

Overall, the occurrence of any medical event was similar for the sotalol and the all ibutilide groups (32.4% vs. 34.6%). As expected, the most frequent medical events for both drugs were in the cardiovascular system. Compared to sotalol, the all ibutilide group experienced more ventricular extrasystole (8.5% vs. 1.9%), non-sustained monomorphic VT (6.6% vs. 3.7%), and supraventricular VT (2.8% vs. 0%). There was a tendency for more events to occur with the higher dose of ibutilide. The sotalol group, on the other hand, experienced more bradycardia (6.5% vs. 1.4%) and hypotension (4.6% vs. 0.5%).

Regarding non-cardiovascular events, there was little difference between sotalol and ibutilide except for greater occurrences in the sotalol group of dizziness (4.6% and 0.5%) and dyspnea (3.7% and 0.5%).

Deaths, other serious safety, study drug discontinuations

Deaths

There were no deaths at the time of or immediately after infusion of either of the study drugs. The 3 reported deaths occurred 2, 3, and 22 days after the study period.

Deaths

patient #	days after study	cause of death
14294/1005 ibutilide 1 mg	20	septic shock resulting from pneumonia
14350/2402 sotalol	2	VF possibly resulting from MI
14871/2915 sotalol	3	Pulmonary embolism and stroke

(from Vol. 1 of study report 0019, pages 50,53)

No death could be associated with the use of study drug. A more detailed description of each death is found in appendix II.

other serious safety

The table below shows the number of patients who experienced one (or more) serious adverse event that was not subsequently reported as a death.

Serious medical events not reported as a death

Event	sotalol	ibutilide 1 mg	ibutilide 2 mg
tachycardia & hypotension		x	
angina & nonsustained PMVT			x
junctional bradycardia			x
endocarditis			x
hypotension (vasovagal reaction)			x
nonsustained MMVT@			x (2)
sustained PMVT#			x
nonsustained PMVT			x
dyspnea			x
abdominal pain/chest discomfort	x		
complete AV block	x		
left heart failure	x		

@ monomorphic ventricular tachycardia
# polymorphic ventricular tachycardia
(from Vol. 8 of study report 0019, tables P.15 and 16.)

There were 9 events recorded as serious for patients who received ibutilide 2 mg compared to 1 and 3 events for patients who received ibutilide 1 mg and sotalol, respectively. The majority of events involved the cardiovascular system, particularly arrhythmias. All patients recovered from their events. The most serious, sustained polymorphic VT, required emergency electroversion. A more detailed description of each event is found in appendix II.

study drug discontinuations (for medical events)

There were 5 patients who were prematurely withdrawn from study drug because of a medical event.

Study drug discontinuations for medical events

patient#	medical event	comments
14871/2906 ibutilide 1 mg	bundle branch block	ibutilide disc'd after 6 min.
14386/2105 ibutilide 1 mg	increased AV nodal conduction with tachycardia and hypotension	ibutilide disc'd after 9 min; serious medical event.
14386/2106 ibutilide 2 mg	QT-U interval prolongation (590-600 msec)	ibutilide disc'd after 5 min; patient remained asymptomatic
14386/2107 ibutilide 2 mg	QTc interval prolongation (>600 msec)	ibutilide disc'd after 7 min; patient remained asymptomatic
14386/2101 sotalol	complete AV block	sotalol disc'd after 3 min.

Of the 5 patients who were discontinued, 4 patients were receiving ibutilide and 1 was receiving sotalol. All reasons for discontinuations were for cardiac rate or rhythm disturbances or for an ECG abnormality. All patients recovered.

Ventricular tachycardia and QTc prolongation

Ventricular tachycardia reported as medical events

The table below displays the number and percent of patients who experienced one or more of the following ventricular tachycardias.

Ventricular tachycardia reported as a medical event

		ibutilide		
	sotalol n=108	1 mg n=102	2 mg n=109	all ibut n=211
non sustained monomorphic VT	4 (3.7)	5 (4.9)	9 (8.3)	14(6.6)
non sustained polymorphic VT	0	0	1 (1.0)	1 (0.5)
sustained polymorphic VT	0	0	1 (1.0)#	1 (0.5)
total	4 (3.7)	5 (4.9)	11 (10.1)	16 (7.6)

patient ##14352/2426 is discussed in appendix
(from Vol. 8 of study report 0019, table P.5.)

Overall, the rate of occurrence of VT (reported as a medical event) was twice as large for those patients who received ibutilide compared to those who

received sotalol (7.6% vs. 3.7%). The majority of these events were episodes of self limited monomorphic VT.

There is a dose response for the occurrence of VT; the 2 mg dose ibutilide caused more than twice the rate of occurrence of VT compared to the 1 mg dose (10.1% vs. 4.9%).

The durations of the QTc intervals for the 20 patients who experienced VT were as long as 612 msec at minute 30 and 747 msec at minute 60. On the other hand, for some of these patients, the intervals were as short as 175 msec at minute 30 and 166 msec at minute 30. The change from baseline for the QTc interval at minute 30 for patients with VT ranged from 4 msec up to 223 msec. Although the entry criteria limited the study to patients with baseline QTc intervals no longer than 440 msec, there is no evidence that excluding patients with longer QTc intervals diminishes the risk for VT.

Ventricular tachycardia reported by Holter monitoring

All study patients were to undergo Holter monitoring for the first 7 hours of the trial. An additional 24 hours of monitoring was to be obtained in those patients who had their atrial arrhythmia terminated. All available tapes underwent initial screening by Hertford Medical Holter technicians and selected tapes were reviewed by a panel of 4 cardiologists.

For those 20 patients who had VT reported as a medical event, 19 had Holter tapes. Upon review by the panel, all but 1 of the 19 patients had an abnormality on tape that coincided with the reporting of the event (the exception was patient # 2958 had a reported episode of nonsustained monomorphic VT epsiode). Although the reviewers agreed with the 2 medical events reported as polymorphic VT, there was disagreement with the identification of some of the monomorphic VT events which were termed aberrancy.

In addition, there were 80 episodes identified by the Hertford tchnicians as VT that were not reported as medical events, i.e. presumed asymptomatic events. These tapes were reviewed and the episodes were classified by the panel. The results of the review are shown in the following table:

Selected abnormalities on Holter monitor

interpretation	sotalol	ibutilide 1 mg	ibutilide 2 mg
monomorphic VT	4	6	7
polymorphic VT	0	1	2
aberrant conduction	7	12	16
mixed^/other^^	5	11	9
total	16	30	34

^ interpreted as either VT or aberrancy
^^interpreted as idioventricular rhythm or not interpretable.
from vol 9 study report 0019 page 3114

These episodes of VT occurred up to 18 hours after infusion of study drug (*from fax dated August 15, 1995*).

The implication of these "asymptomatic" episodes of VT and other abnormalities is unknown. However, as a result of these events occurring up to 18 hours after drug intake, the duration of the post ibutilide observation period for patients should be no less than 18 hours.

QTc interval prolongation

The table below displays the mean QTc intervals (msec) for all success patients by drug group at screen, time of the atrial arrhythmia termination, change from baseline at the time of the termination, and maximum change from baseline

QTC intervals for success patients

	QTc interval at screen	QTc interval at termination	change from baseline	maximum change from baseline
ibutilide 1 mg	410 (n=26)	446 (n=27)	33**	234
ibutilide 2 mg	403 (n=55)	477 (n=52)	76***	294
sotalol	418 (n=15)	461 (n=12)	8	59

**p=0.009 for change from baseline
***p=0.0001 for change from baseline
(from Vol. 4 of study report 0019, tables K. 13, 14) .

Clearly, in those patients who had their atrial arrhythmia successfully terminated, ibutilide had a much greater effect on lengthening of the QTc interval than did sotalol and there was a dose response.

For those patients who failed to be converted with study drug, their mean changes from baseline at Minute 30 were 62, 82, and 37 msec for ibutilide 1 mg, ibutilide 2 mg, and sotalol, respectively.

There were no significant differences for any of the drug groups for mean change from baseline for QTc interval at Minute 30, comparing patients who were study drug successes or failures (*from Vol. 4 of study report 0019, table P.19.1*). The lengthening of the QTc interval did not determine treatment success or failure.

Most of the 16 ibutilide subjects who experienced a proarrhythmic event had increases in QTc intervals. These increases averaged 84 msec at Minute 30 and ranged from -34 to 223 msec. For the 4 sotalol patients who had a proarrhythmic event, the average of the QTc interval at Minute 30 was 79 msec and the range was from 23 to 130 msec. *(from Vol.8 of study report 0019, table P.22)*

Laboratory Values

Hematology

There were no consistent changes from baseline at endpoint (Hour 7) that emerge as having clinical significance for any of the hematologic parameters.

There were 2 reports of decreased platelet count (both patients received ibutilide) and they are shown below. A decreased count was defined as less

than 100 x 10^3/mm^3.

Patients with abnormally low platelet counts

subject #	baseline value (10^3/ml)	endpoint value (10^3/ml)
14434/2633 ibutilide 1 mg	148	59
14434/2637 ibutilide 2 mg	111	79

normal range was 150-450 x 10^3/ml
(from vol.1 of study report 0010, page 67)

Neither abnormal value was reported to be clinically significant, there were no explanations for the abnormalities and there were no follow up values.

There were no reports of patients with hemoglobin < 8 mg/dl or WBC less than 3.0 x 10^3/mm^3. There was a report of one sotalol patient (#Wellens/2040) with increased WBC (defined as greater than 20.0 x 10^3/mm^3). The baseline count for this patient was elevated (18.3 x 10^3/mm^3) which rose to 21.1 x 10^3/mm^3 at endpoint. There was no explanation for the increase and it was viewed by the investigator as not clinically significant.

Blood chemistries

As with hematology, there were no consistent changes from baseline at endpoint (Hour 7) that emerge as having clinical significance for any of the blood chemistry paramcters.

Individual abnormalities in liver function tests included one patient with increased ALT and AST (ibutilide 2 mg), two patients with increased ALT but not AST (ibutilide 2 mg and sotalol) and two patients with increased AST but not ALT (ibutilide 1 and 2 mg). The table below discusses the ibutilide patients.

Patients with abnormally high ALT and/or AST

subject #	ALT (U/L)		AST (U/L)		
	baseline	endpoint	baseline	endpoint	comments
14434/2634@ ibutilide 2mg	14	97	9	58	none
2634@ ● ibutilide 2 mg	66	156	NG	NG	reported as a medical event and resolved 2 months after study
2638+ ibutilide 1mg	NG	NG	18	97	reported also being related to current status (prior stomach resection 28yrs) with increased gamma GT at baseline
14282/2383++ ibutilide 2 mg	NG	NG	95	98	considered to be result of underlying condition; baseline value elevated

NG: not given
@nl range ALT: 0-22 U/L, AST: 0-18 U/L)
@@ nl range 5-50 U/L
+nl range 0-18 U/L
++nl range 0-32
from vol 1 study report for 0019 page 69

Other abnormalities appear to be inconsequential.

Conclusion: there is no evidence that short term infusion (10 minutes) of ibutilide affects any hematologic or blood chemistry value.

Vital signs

Vital signs were measured at baseline and 5 minutes post drug, then every 10 min for the first 60 minutes then hourly for an additional 6 hours.

Both doses of ibutilide decreased systolic and diastolic blood pressure from baseline by about 1-7 mm Hg systolic and 3-7 mm Hg diastolic for most of the 7 hour time period. There was a tendency for the effects of the 2 mg to be greater than for the 1 mg dose. However, the effects of sotalol were significantly greater than either ibutilide dose (*(from Vol. 6 of study report 0019, tables M.3.)*

Ibutilide and sotalol caused significant decreases in pulse in the "all patient" category as well as in those patients who failed to be converted. The higher dose of ibutilide decreased heart rate to a significantly greater extent compared to the lower dose. Decreases from baseline were approximately 8-

20 bpm for 1 mg and about 11-27 bpm for 2 mg. The duration of effect on blood pressure went beyond the 7th hour of measurement. The effect of sotalol was similar to that of 2 mg ibutilide.

Appendix

Deaths in study 0019

Sotalol: this was a 72 year old white female (#14350/2402) with a history of mild congestive heart failure, blindness as a result of glaucoma, newly diagnosed breast cancer, and atrial fibrillation who was randomized to sotalol. The patient's arrhythmia was not cocuverted by the infusion so electroversion was used. Approximately 26 hours after the sotalol infusion, the patient was found unconscious and in ventricular fibrillation thought to be the result of a myocardial infarction. Although the VF was terminated, the patient became progressively hypotensive and died about 2 days later. No autopsy was performed. Relation to study drug: unlikely.

Sotalol: this was a 65 year old white female (#14871/2915) with a history of myocardial infarction and hypertension who was randomized to sotalol. At the end of the infusion, she developed aberrant QRS complexes and a right bundle branch block which continued for 10 minutes. She then became bradycardic (44 bpm) and hypotensive (74/56 mm Hg) with dizziness, weakness, nausea, and vomiting. The patient was treated with atropine and her blood pressure rose to 100/70 mm Hg. Conversion to sinus rhythm occurred about 40 minutes later with a heart rate around 60 bpm. About 2 days after study drug infusion, the patient experienced a cerebral infarction and died of a pulmonary artery embolism about 20 days later. Relation to study drug: unlikely.

Ibutilide: this was a 48 year old white male (#14294/1005) with a history of cardiac arrest, hypertension, renal transplantation, and atrial flutter who was taking prednisolone and antibiotics at the time of entry into the study. Patient was randomized to 1 mg ibutilide but conversion was unsuccessful. Approximately 2 days later he developed pneumonia (Klebsiella) and died of septic shock 18 days later. Relation to study drug: no

Serious safety not reported as death in Protocol 0019

Sotalol: patient #14386/2108 was a 57 year old white male who developed abdominal pain and chest discomfort after completing the study. Abdominal pain was attributed to oral sotalol. Symptoms resolved.

Sotalol: patient #14386/2101 was a 85 year old white female with a history of valve disease and replacement. About 3 minutes after the start of the study drug infusion, she developed complete AV block with ventricular rate below 50 bpm. Treatment was prematurely discontinued and the condition was resolved.

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Sotalol: patient #14351/2420 was a 56 year old white male with a history of hairy cell leukemia and heart failure. Two hours after study drug infusion he developed dyspnea and 9 hours later he developed left ventricular failure after verapamil was started. Patient recovered.

Ibutilide 1 mg: patient # 14386/2105 was a 52 year old white female was a history of paroxymal atrial fibrillation who developed increased AV nodal conduction with tachycardia (ventricular rate up to 200 bpm) and hypotension (95/48 mm Hg) about 9 minutes after the start of the study drug infusion. Concurrent complaints were palpitations, lightheadedness, and dyspnea. Study drug was discontinued. Patient was converted with DC shock and recovered fully.

Ibutilide 2 mg: patient # 14386/1101 was a 65 year old white male who had a history of hypertension. He received the entire 10 minute infusion of study drug and converted to sinus rhythm 1 minute later. This was followed 5 minutes later by episodes of nonsustained polymorphic VT, one episode lasting 7 minutes that was nearly continuous except for some sinus beats. He was treated with magnesium sulfate and sinus rhythm was restored although QTc interval remained prolonged (up to 647 msec compared to 558 msec at baseline) until hour 7. Two days after discharge, patient was readmitted for angina and a coronary angiogram showed significant stenosis.

Ibutilide 2 mg: patient #1433 /2301 was a 71 year old white male who had a history of valve replacement. About 2 hours after the end of study drug infusion, he developed junctional bradycardia. Several days later, the patient was electroverted and he again developed junctional bradycardia. Neither episodes required treatment.

Ibutilide 2 mg: patient #14402/1687 was a 55 year old white female with a history of rheumatic fever during childhood with subsequent aortic valve replacement. Two days following successful conversion to sinus rhythm during the study drug infusion, the patient became febrile and endocarditis was suspected. This event resolved about 2 months later.

Ibutilide 2 mg: patient #14294/2001 was a 79 year old white male with a history of COPD, paroxysmal atrial fibrillation and heart block with pacemaker insertion. He was successful converted to sinus rhythm 10 minutes after study drug infusion. About 10 minutes later he had a 10 minute episode of hypotension (61/38 mm Hg) described as vasovagal reaction with respiratory arrest. This resolved within 10 minutes.

Ibutilide 2 mg: patient #14674/2762 was a 46 year old white male who received the full dose of study drug without converting to sinus rhythm. Five

minutes after the end of the infusion, he began to have episodes of up to 8 beats of nonsustained monomorphic VT. QTC at baseline and minute 30 were 457 and 489 msec, respectively.

Ibutilide 2 mg: patient #14352/2426 was a 64 year old non white male who had a history of mitral incompetence and heart failure as well as evidence of COPD on physical examination. One minute after completion of study drug infusion, the patient experienced sustained polymorphic VT that required electoversion (3 attempts with 360 joules per attempt). QTc intervals at baseline and minute 30 were 405 and 480 msec, respectively.

Ibutilide 2 mg: patient #14292/2016 was a 68 year old white female with mital valvular disease. She received the full infusion of study drug and 2 minutes later converted to sinus tachycardia. Two days later she developed severe dyspnea and underwent a valve replacement about 6 weeks later and the condition resolved.

14b. All completed Phase II/III studies

This section discusses safety data for

- **586 patients who received ibutilide in one of the completed Phase II/III studies for patients with atrial fibrillation or flutter (protocols 0003, 0005, 0014, 0015, and 0019),**

- **679 patients who received ibutilide in one of the completed or terminated^ Phase II/III studies (protocols 0003, 0004^, 0005, 0007, 0013, 0014, 0015, 0018^, and 0019),**

- **limited safety data (deaths, discontinuations for medical events, the number of reports of ventricular tachycardia, and other serious medical events) from the 3 ongoing studies (protocols 0017, 0020, and 0021).**

In summary, the most frequently reported medical events were the cardiac arrhythmias, ranging from the relatively benign nonsustained monomorphic VT and ventricular extrasystole to the life-threatening sustained polymorphic VT. Of the 676 ibutilide patients, 12 (1.8%) developed sustained polymorphic VT compared to 0 placebo patients. The patients who developed this arrhythmia did so either during ibutilide infusion or shortly thereafter. All of these events were successfully resolved, usually with electroversion. None of the serious medical events that were associated with ibutilide use resulted in patient death.

<u>All completed Phase II/III studies (excluding EPS)</u>

There were 586 patients who received ibutilide in 1 of the 5 completed studies with 52% having received the highest doses (>1.25 mg), 35% having received mid doses (between 0.75 and 1.25 mg), and 13% having received the lowest doses (< 0.75 mg). The most recent safety update added 211 ibutilide patients from protocol 0019 to the data base. No additional placebo patients were added.

<u>Treatment emergent signs and symptoms</u>

frequency by body system

The table below displays the number and percent of medical events by body system and by dose group for all patients who received either placebo or ibutilide.

Treatment emergent medical events by body system

Body System+	Placebo		Ibut < 0.75 mg		Ibut ≥ 0.75 mg, ≤ 1.25 mg		Ibut > 1.25 mg		All Ibut	
	n=127		n=76		n=203@		n=307^		n=586	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	9	7.1	13	17.1	52	25.6	81	26.4	146	24.9
Whole Body	19	15.0	10	13.2	12	5.9	28	9.1	50	8.5
Digestive	9	7.1	-	-	2	1.0	16	5.2	18	3.1
Metabolic & Nutritional	3	2.4	1	1.3	5	2.5	11	3.4	17	2.9
Respiratory	7	5.5	2	2.6	2	1.0	12	3.9	16	2.7
Nervous	3	2.4	1	1.3	3	1.5	11	3.4	15	2.6
Urogenital	3	2.4	-	-	3	1.5	9	2.9	12	2.0
Skin	1	0.8	-	-	2	1.0	4	1.3	6	1.0
Hemic & Lymphatic	-	-	-	-	2	1.0	3	1.0	5	0.8
Special Senses	-	-	-	-	1	0.5	1	0.3	2	0.3

+musculo-skeletal system was omitted because it was absent from study 0019.
@ 102 patients from ibutilide 1 mg group, protocol 0019 were added
^ 109 patients from ibutilide 2 mg group, protocol 0019 were added
(from table A-12 information amendment 011 and vol 8 study report for protocol 0019 table P.4)

The greatest number of medical events occurred in the cardiovascular system, and the all ibutilide group had a 3.5 times greater rate of these events compared to placebo. The mid and high dose ibutilide groups had event rates that were higher than the low dose group but were similar to one another. The event rates for the other body systems were similar for the ibutilide and placebo patients with one exception (whole body).

frequency within body systems

The table below shows the medical events within body systems that occurred at least 1.2% in the all ibutilide group and occurred more frequently than in the placebo group.

Treatment emergent medical events within body system

	placebo n=127		ibut <0.75mg n=76		0.75≤ibut ≤1.25mg n=203		ibut>1.25 mg n=307		all ibutilide n=586	
Medical Event	n	%	n	%	n	%	n	%	n	%
extrasystole ventricular+	1	0.8	2	2.6	12	5.9	17	5.5	31	5.3
nonsustained monomorphic VT	1	0.8	1	1.3	10	4.9	18	5.9	29	4.9
headache	4	3.1	3	3.9	3	1.5	15	4.9	21	3.6
nonsustained polymorphic VT	0	0	3	3.9	6	3.0	7	2.3	16	2.7
tachycardia++	1	0.8	4	5.3	6	3.0	6	2.0	16	2.7
hypotension^	2	1.6	2	2.6	2	1.0	8	2.6	12	2.0
nausea	1	0.8	0	0	1	0.5	10	0.3	11	1.9
A-V block^^	1	0.8	1	1.3	2	1.0	8	2.6	11	1.9
bundle branch block	0	0	0	0	5	2.5	6	2.0	11	1.9
sustained polymorphic VT	0	0	1	1.3	4	2.0	5	1.6	10	1.7
hypertension	0	0	0	0	1	0.5	6	2.0	7	1.2
QT segment prolongation	0	0	0	0	3	1.5	4	1.3	7	1.2
bradycardia#	1	0.8	0	0	1	0.5	6	2.0	7	1.2

+ includes extrasystole ventricular and extrasystole ventricular bigeminy
++includes sinus tachycardia, supraventricular tachycardia, and tachycardia
^ includes hypotension and postural hypotension
^^includes complete, first and second degree, heart block, and P-R segment prolongation
includes sinus bradycardia and bradycardia NOS
from revised table A-13, information amendment 011 and vol 8 of study report 0019 table P.5

Not unexpectedly, the list of medical events is dominated by cardiac rhythm and rate disturbances. For ventricular extrasystole, the most common event seen with ibutilide use, the rate for ibutilide was 7 times the rate for placebo. The tachyarrhythmias also were much more common compared to placebo. When nonsustained monomorphic VT, sustained and nonsustained polymorphic VT, sinus tachycardia, supraventricular tachycardia, and tachycardia are combined, the rate for all ibutilide patients is 12.1% (71/586) which is 8 times the rate for placebo patients (1.6%, 2/127).

While there were fewer events with the lowest ibutilide doses, the mid

and high doses tended to produced similar event rates.
All completed/terminated Phase II/III studies

The table below displays the medical events that have a frequency of more than 1% in the all ibutilide group and occurred more often in the ibutilide than in the placebo group. This includes all completed (protocols 0003, 0005, 0007, 0013, 0014, 0015, and 0019) and all terminated (protocols 0004, n=3, and 0018, n=2) Phase II/III studies.

Treatment emergent medical events

	placebo n=139		all ibutilide n=679	
Medical Event	n	%	n	%
extrasystoles ventricular +	1	0.7	31	4.6
nonsustained monomorphic VT	1	0.7	31	4.6
headache	4	2.9	27	4.0
nonsustained polymorphic VT	0	0	18	2.7
hypotension++	2	1.4	16	2.4
tachycardia	1	0.7	14	2.1
chest pain	2	1.4	14	2.1
bundle branch block	0	0	13	1.9
nausea	2	1.4	13	1.9
sustained polymorphic VT	0	0	12	1.8
A-V block+++	1	0.7	12	1.8
localized pain	1	0.7	9	1.3
QT segment prolonged	0	0	8	1.2
atrial fibrillation#	–	–	7	1.0
hypertension	0	0	7	1.0
bradycardia	1	0.7	7	1.0
palpitations	1	0.7	7	1.0

+extrasystoles ventricular includes extrasystoles ventricular bigeminy
++hypotension includes postural hypotension
+++includes complete, first and second degree, heart block, and P-R segment prolongation
#atrial fibrillation was considered a medical event only in protocols 0007, 0013, and 0019.
from informational amendment 020 submitted March 13, 1995 and Vol. 8 of study report 0019, table P.5

Ventricular extrasystole, nonsustained monomorphic VT, nonsustained and sustained polymorphic VT were among the most frequently reported medical events for patients who received ibutilide. These events occurred rarely, if at all, in the placebo group.

Deaths, other serious medical events, ventricular tachycardia

Deaths

There was 1 death in the 679 patients randomized to ibutilide in a completed or terminated Phase II/III trial. This death (protocol 0019, #14294/1005), attributed to septic shock resulting from pneumonia, occurred 20 days after patient received ibutilide and it was not associated with ibutilide use. In addition, there was 1 death in the placebo group and 2 deaths in the sotalol group. No deaths have occurred in any of the 3 ongoing trials (protocols 0017, 0020, and 0021).

Other serious medical events

The table below displays the number and percent of medical events, reported as serious, that occurred in at least 2 study patients. Note: the serious events that occurred in only 1 ibutilide patient and no placebo patients include: infection, AV block, congestive heart failure, pulmonary embolism, extrasystole ventricular, sinus arrhythmia, nausea, dizziness, diaphoretic, angina, arrhythmia nodal, ECG abnormality not otherwise specified, endocarditis, vasovagal reaction, and dyspnea.

Serious medical events

	placebo n=139		all ibutilide n=679	
	n	%	n	%
any serious event	2	1.4	34	5.0
any cardiovas.	1	0.4	30	4.4
sustained polymorphic VT	0	0	12	1.8
nonsustained polymorphic VT	0	0	5	0.7
hypotension	0	0	3	0.4
sustained monomorphic VT	0	0	2	0.3
nonsustained monomorphic VT	0	0	2	0.3
CVA	1	0.8	1	0.1
acute kidney failure	0	0	2	0.3

from vol 8 information amendment 040 Table A.23 A. and vol 8 of information amendment 040 tables P.14-15.

There were 34 serious events reported for the ibutilide group (5.0%) compared to 2 events for the placebo group (1.4%). The majority of events were related to the cardiovascular system. There were 2 cases of acute renal failure in patients who received ibutilide. The 2 events reported for the placebo group were cerebral vascular accident and respiratory failure.

The most frequent serious medical events reported for ibutilide patients were sustained and non sustained polymorphic VT (1.8 and 0.7%, respectively). These events were not reported for any of the 139 placebo patients.

Regarding the 2 reports of acute renal failure for the ibutilide group, 1 patient (protocol 0015 patient #1031) had undergone heart catheterization and the renal failure was attributed to contrast dye. The other patient (protocol 0015 #1061) became hypotensive (90/50 mm Hg) after 4 hours after receiving ibutilide and remained hypotensive for about 24 hours. The increase in serum creatinine and BUN were attributed to a pre-renal cause. Other serious medical events were rare.

Ventricular tachycardia

The table below shows the number and percent of ibutilide patients who

developed ventricular tachycardia that was reported as a medical event

Ventricular tachycardias

	placebo n=139		all ibutilide n=679	
	n	%	n	%
polymorphic VT				
sustained	0	0	12	1.8
nonsustained	0	0	18	2.7
monomorphic VT				
sustained	0	0	5	0.7
nonsustained	1	0.7	31	4.6

+23 patients had 24 events (1 patient had both sustained and nonsustained polymorphic VT).
from revised table A-13, information amendment 011 and amendment 040 table A 13.B

Nonsustained monomorphic VT was the most frequently reported of these events for the ibutilide patients (31 patients, 4.6%) and this was 6.6 times greater than what was reported for placebo (1 patient, 0.7%).

Of the 679 ibutilide patients, 12 patients (1.8%) experienced sustained polymorphic VT and 18 (2.7%) experienced nonsustained polymorphic VT. No placebo patient experienced polymorphic VT.

The breakdown, by gender, of monomorphic and polymorphic, sustained and nonsustained VT for the 679 ibutilide patients is as follows:

Gender distribution of monomorphic and polymorphic VT
all ibutilide patients

	events all ibutilide patients											
	Polymorphic				Monomorphic				Total arrhythmias			
	sustained		non sustained		sustained		non sustained		sustained		non sustained	
	n	%	n	%	n	%	n	%	n	%	n	%
male (n=532)	8+	1.5	11	2.1	5+	0.9	20	3.8	12+	2.3	31	5.8
female (n=147)	4++	2.7	7++	4.8	0	0	11	7.5	4	2.7	18	12.2
Total (n=679)	11+	1.8	18	2.7	5+	0.7	31	4.6	16+	2.4	49	7.2

+one male patient with sustained polymorphic and monomorphic VT
++two female patients with sustained and nonsustained polymorphic VT
from fax sent 8-25-95

Although there was a trend for more of these events to occur in females, when a logistic regression analysis was performed with the model to include sex, total dose, and sex by total dose as predictive of the occurrence of proarrhythmia, the sex by total dose interaction was not significant (p=0.38) (*from fax sent 8-2195).*

c. Ongoing trials

There are 3 ongoing trials with ibutilide: protocols 0017, 0020, and 002. The following table displays discontinuations for medical events, episodes of serious and non serious VT, and other serious medical events for all patients enrolled as of March 31, 1995. No deaths have been reported in any of these trials.

Ongoing trials

protocol #	no. of patients: completed^/ planned	disc'd due to medical event	non serious VT	serious VT	other serious events
0017	150/300	1	1	0	3
0020	171/240	8	12	6	4
0021	61/120	1	0	0	2

^ as of March, 31-95
from information amendment 040 page 37

Protocol 0017 is a double blind, randomized, placebo controlled trial in patients who developed atrial fibrillation or atrial flutter after undergoing CABG or cardiac valve surgery. Doses of ibutilide are 1 mg, 0.5 mg, and 0.25 mg infused over 10 minutes. A second identical dose is given to nonresponders. There was one patient who discontinued for chest pain and dyspnea. The 3 patients with other serious medical events include a) asystole 24 hours after receiving study drug (diagnosed with sick sinus syndrome), b) recurrent atrial fibrillation requiring hospitalization, and c) cardiac arrest occurred about 16 hours after study drug infusion and while patient was receiving quinaglute.

Protocol 0020 is a double blind, randomized, placebo controlled trial in patients with atrial fibrillation or atrial flutter. Dose is 1 mg infused over 10 minutes with an identical dose given to nonresponders. There are 7 discontinuations for medical events: asymptomatic prolongation of QT interval (1), sustained polymorphic VT (3) with one that degenerated into ventricular fibrillation, nonsustained polymorphic VT (2), cardiac arrest following sustained polymorphic VT that occurred during study drug infusion(1). There are 6 patients who experienced serious ventricular tachycardia including sustained polymorphic VT (5) and sustained monomorphic VT (1). The 4 other serious medical events were pulmonary edema, AV block, stroke, and cardiac arrest (leading to study drug discontinuation).

Protocol 0021 is a double blind, randomized, procainamide controlled trial. Dose of ibutilide is 1 or 2 10-minute infusions of 1 mg. There is one study drug discontinuation for hypotension, and the 2 serious medical events are acute delirium (history of multiple infarct dementia) and an unwitnessed near-syncopal episode occurring 2 days after study drug infusion.

9-8-95
Maryann Gordon, MD

CSO

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NDA-20-491

Marjann Gordon, MD

Sept 8, 1995; NDA#20491

III. Safety Addendum

a. Completed Study 0019

- Demographics
- Treatment emergent medical events
- Deaths, other serious safety, study drug discontinuations
- Ventricular tachycardia and QTc prolongation
- Laboratory Values
- Vital signs

Appendix

b. All completed Phase II/III studies

- Treatment emergent signs and symptoms
- Deaths, other serious safety, ventricular tachycardia

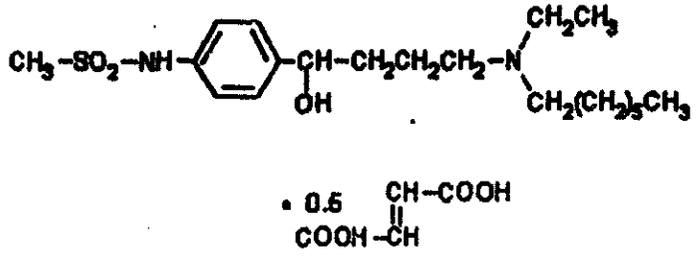
c. Ongoing trials

Maryann Gordon, MD

Summary of Safety Evaluation

Ibutilide, a class III antiarrhythmic, acts by increasing an inward depolarizing sodium current which, in turn, prolongs the duration of the action potential of the atrial and ventricular myocytes. Ibutilide is being developed for the acute termination of atrial flutter and atrial fibrillation. The drug is to be administered by short term infusion.

The structure of ibutilide fumarate is as follows:



The Phase I program consisted of 4 trials with a total of 83 ibutilide subjects. The Phase II/III program consisted of 4 completed trials (2 placebo controlled, 2 open label), 2 recently completed trials (1 placebo controlled, 1 open label), 4 ongoing trials (2 placebo controlled, 2 active control), and 2 terminated trials (both open label). The number of patients evaluated for complete safety (including laboratory analyses) is 375 for ibutilide and 127 for placebo. The total number of patients evaluated for medical events and serious safety is 465 for ibutilide and 139 for placebo. An additional 425 patients have been enrolled in 1 of the 4 ongoing (and blinded) studies and are discussed only in the "Ongoing Protocols" section. [The safety addendum added 211 patients for a total of 676 patients who received ibutilide in a completed Phase II/III study.]

The doses used in the dose-response trial 0014 ranged from 0.005 to 0.02 mg/kg infused over 10 minutes. All ibutilide patients in the other pivotal trial (0015) received 1 mg infused over 10 minutes and a second infusion, if necessary, of either 1 or 0.5 mg also infused over 10 minutes. Patients weighing less than 60 kg received doses of 0.01 or 0.005 mg/kg.

In normal volunteers and patients, ibutilide administered by infusion over 10 minutes was found to prolong the QTc interval. This prolongation was directly related to dose with lower doses (less than 0.003 mg/kg) increasing the QTc by about 20-30 msec and higher doses (up to 0.03 mg/kg) increasing it up to 172 msec. The maximum change from baseline occurred within 30 minutes after the start of dosing and lasted up to 3 hours for the lower doses and up to 6 hours for the higher doses.

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During the clinical trials, there was little difference between the number of patients reporting medical events in the placebo group compared to the ibutilide group for all body systems except cardiovascular. For this system, 22.9% of the ibutilide patients experienced a medical event (primarily an arrhythmic event) which was more than three times the rate experienced by the placebo group (7.1%). Lower ibutilide doses tended to result in fewer reported events.

The most common arrhythmia linked to ibutilide use included ventricular extrasystoles and nonsustained and sustained polymorphic and monomorphic ventricular tachycardia (VT). The overall rate of sustained VT in patients who received ibutilide was 3.2% (15/465) compared to 0 patients who received placebo. Three patients degenerated into ventricular fibrillation and electroversion was required in all 15 cases.

The majority of the VT events occurred either during or shortly after the ibutilide infusion. However, there were patients who had episodes of polymorphic VT up to 3 hours and episodes of monomorphic VT up to 11 hours after the infusion. There was one report of sustained monomorphic VT occurring 2 days after the study and at the time the patient was starting quinidine. The doses that provoked VT were as low as 0.464 mg.

While there was no difference in QTc interval prolongation between men and women, women experienced VT more frequently than men. The overall rates for the 77 women and 388 men who received ibutilide were 5.4% and 2.8% for sustained VT, respectively, and 16.9% and 5.2% for nonsustained VT, respectively.

The only death reported during the clinical development occurred in a placebo patient. Serious adverse events other than cardiac arrhythmias reported in the clinical trials do not seem to be related to ibutilide and there is no evidence that ibutilide alters laboratory values. A retrospective examination of safety data reviewed up to 3 months after treatment produced no convincing evidence that there are long term risks to patients who received short term infusion(s) of ibutilide.

The safety addendum added 211 patients (protocol 0019) for a total of 676 patients who received ibutilide in a completed Phase II/III clinical trial. Ventricular extrasystole (4.6%), nonsustained monomorphic VT (4.6%), nonsustained and sustained polymorphic VT (2.7% and 1.8%, respectively) were among the most frequently reported medical events for the all ibutilide patients. These events occurred rarely, if at all, in the 139 placebo patients.

In conclusion, the safety reported for ibutilide, in the patient population

numbering less than 680, is consistent from study to study and is limited to the cardiovascular system. While all cases of ibutilide-induced ventricular arrhythmia were successfully terminated with DC shock, this will not likely be the case with wider use. The drug has a narrow therapeutic window.

I. Phase I Trials

a. Descriptions of trials

The 4 Phase I protocols are referred to as 0001, 0008, 0016, and 0022. A brief description of each study, the dose(s) of ibutilide used, the length of infusion, number of subjects per group, the mean age and range, the number of subjects in each gender, and the number of subjects in the main ethnic groups are shown below. Protocol 0001 is listed twice because it incorporated 2 different infusion durations: 10-minute and 8-hour.

Protocol No.	Study Design and Description	Treatment/ length of infusion	No. of Dosed Subjects/ Group	Age (y): Mean (Range)	M/F W/B/O
0001	Single-dose, double-blind, placebo-controlled, parallel group, dose-escalating, tolerance, PK, PD study in healthy, male volunteers	Placebo 0.001 mg/kg 0.003 mg/kg 0.01 mg/kg 0.03 mg/kg (10-min infusion)	9 8 8 8 8	30 (19–45)	41/0 36/?/3
0001	Single-dose, double-blind, placebo-controlled, parallel group, dose-escalating, tolerance, PK, PD study in healthy, male volunteers	Placebo 0.01 mg/kg 0.03 mg/kg 0.06 mg/kg 0.10 mg/kg (8-hr infusion)	10 6 6 8 8	25 (18–50)	38/0 36/1/1
0008	Single-dose, 3-way crossover, PK, PD study of ibutilide and its enantiomers in healthy, male volunteers	0.01 mg/kg ibutilide, (+), (-) enantiomers (10-min infusion with 1-wk washout)	6	32 (22–50)	6/0 4/1/1
0016	Open-label metabolism/ excretion study of [^{14}C]ibutilide in healthy, male volunteers	About 0.8 mg containing 25 µCi (10-min infusion)	6	45 (37–49)	6/0 6/0/0
0022	Single-dose, open-label PK, PD study in healthy male and female volunteers	0.01 mg/kg (10-min infusion)	16	65 (53-72)	8/8 16/0/0

from vol 1.52, 08/01/432

All studies were single dose and infusions were given for 10 minutes (or 8 hours, protocol 0001). The doses ranged from 0.001 to 0.1 mg/kg. Total number of subjects in the Phase I program was 88 on ibutilide and 19 on placebo. The mean ages were 25-45 years except in protocol 0022 which evaluated older subjects. Protocol 0022 was also the only Phase I study to include females. The majority of subjects in all of the Phase I protocols were white.

b. Medical events

There were few reports of medical events in the Phase I studies. Only headache (7 subjects) and back pain (3 subjects) were reported by more than 2 ibutilide subjects in the dose tolerance trial 0001(10-minute infusion). The subjects in the 8-hour infusion phase of trial 0001 had more nausea compared to the subjects who received the 10-minute infusion (4 subjects compared to 1). There were no differences in the medical events reported by subjects who received either the (+) or the (-) enantiomer compared to ibutilide. *(Data from Table A-1, vol 1.53, 08/02/15-16)*

There were no deaths, dropouts for medical events, or other serious safety in Phase I studies with the infusion. However, with the discontinued oral tablet formulation, one normal volunteer experienced polymorphic ventricular tachycardia one hour after receiving 75 mg of ibutilide. The mean QTc interval was prolonged approximately 24% with 50 mg to 75 mg doses of the oral formulation.

c. QTc interval prolongation

QT interval prolongation was measured by averaging 25 QT intervals using a signal-averaged ECG device (Corazonics Predictor I). Rate- corrected QT intervals (QTc) were calculated from the QT interval divided by the square-root of the RR interval.

<u>10-minute infusions</u>

Protocol 0001 explored the effect on the QTc interval of doses 0.001, 0.003, 0.01 and 0.03 mg/kg infused over 10 minutes. While placebo had no consistent effect, ibutilide increased the interval from baseline in a dose-response manner. This increase was evident soon after the start of the infusion. The two lower doses (0.001 and 0.003 mg/kg) increased the interval by about 20-30 msec. For these doses, the greatest change from baseline was seen at 0.5 hours after start of dosing.

The table below shows the mean QTc interval and the mean change from baseline for the two <u>higher</u> doses of ibutilide.

Mean QTc interval and Mean Change from Baseline

Time, hr	Mean QTc ± SD (msec)		Mean QTc (msec) change from baseline@	
	0.01 mg/kg+	0.03 mg/kg++	0.01 mg/kg+	0.03 mg/kg++
0.5	477	570	74	172
1	450	515	46	117
2	442	491	39	93
3	424	451	21	53
4	415	435	11	37
6	416	446	12	48
8	428	420	24	22
10	421	408	17	6
12	411	421	6	23
24	413	401	10	3

@baseline for the purposes of this table is the hr -1 recording
+0.6 mg in 60 kg adult
++1.8 mg in 60 kg adult
data from Table A-3, vol 1.53, 08/02/20

For the two higher doses, the greatest mean changes from baseline for both doses occurred 0.5 hr after the start of the infusion and were 74 msec and 172 msec for the 0.01 and 0.03 mg/kg doses, respectively. The 0.03 mg/kg dose increased the QTc by about 43% above baseline. The QTc interval prolongations for 0.01 mg/kg and 0.03 mg/kg doses returned to near baseline levels by approximately 3 and 8 hours, respectively.

The figure below shows the mean change from baseline for all doses infused for 10 minutes.

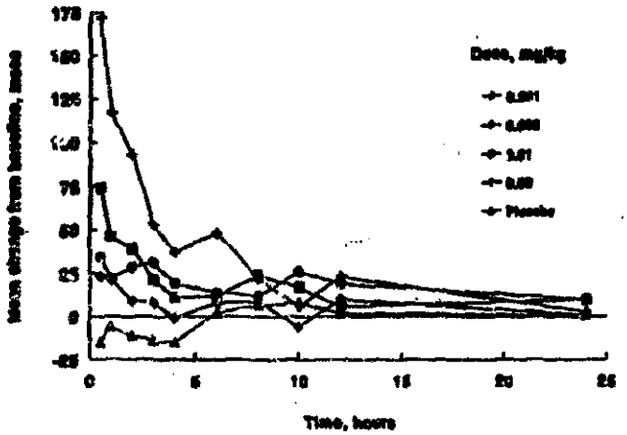


figure 8.G-1 from vol 1.52, 08/01/437

8-hour infusions

In protocol 0001, infusions of ibutilide were also given for 8 hours. [Apparently, the sponsor was evaluating ibutilide for the use in ventricular arrhythmias.] The figure below displays the mean QTc change from baseline for all dose groups infused for 8 hours.

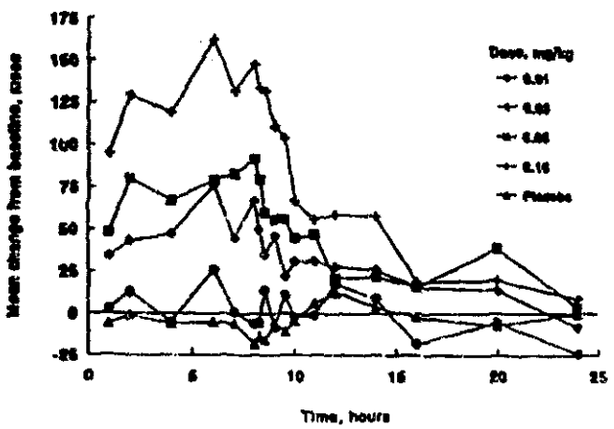


figure 8.G-2, vol 1.52, 08/01/438

As expected, there were large increases from baseline in the QTc

interval and these increases were dose related. Although the intervals started to return to baseline within 15 minutes after the infusion was terminated, there was still significant prolongation with the highest dose for an additional 6 hours *(data from Table A3, vol 1.53, 08/02/20-23).*

Enantiomers

The effects of ibutilide and its enantiomers (U-82208E and U-822009E) on the QTc interval were evaluated in protocol 0008, a cross-over study using 0.01 mg/kg doses infused for 10 minutes. The figure below displays the mean change from baseline for the parent compound and the enantiomers.

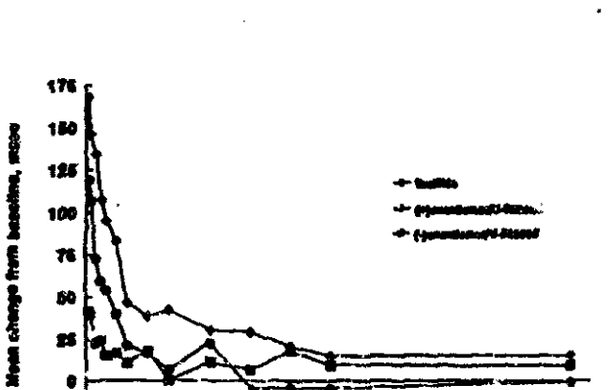


figure 8.G-3, Vol 1.52, 08/01/439

There were larger increases from baseline in the QTc intervals with the U-82208E [(+)enantiomer] compared to the U-82209E [(-) enantiomer]. Ibutilide was roughly additive for the 2 enantiomers *(data from Table A3, vol 1.53, 08/02/23-24).*

Gender

The mean changes from baseline in QTc intervals for older men and older women were evaluated in Protocol 0022 using a single dose of 0.01 mg/kg infused over 10 min. The average baseline QTc values for males and females were 409 and 422 msec, respectively.

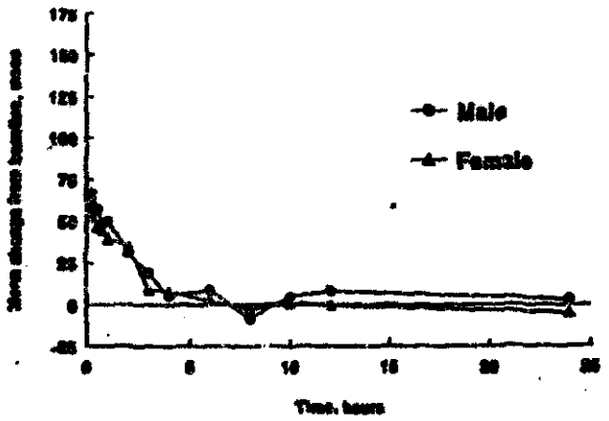


figure 8.G-4 vol 1.52, 08/01/440

The increases in the QTc intervals and the duration of the increases were similar for males and females. However, there was a much greater propensity for female patients to develop polymorphic ventricular tachycardia (VT) in the Phase II/III studies.

II. Phase II/III Trials

a. Description of trials

There are 10 Phase II/III protocols that are either completed prior to NDA submission (protocols 0014, 0015, 0003, 0005), recently completed (after NDA submission) and available for the Safety Update (protocols 0007, 0013), ongoing (protocols 0017, 0019, 020, and 021), or terminated (protocols 0004, and 0018). A brief description of each study, the dose(s) of ibutilide used, the length of infusion, number of subjects per group, the mean age and range, and the number of subjects in each gender and the number of subjects in the main ethnic groups are shown below.

Protocol No.	Study Design and Description	Treatment/ Regimen	No. of Patients	Age (y): Mean (Range)	M/F W/B/O
0014	Multicenter, double-blind, placebo-controlled, randomized, dose-response, pharmacodynamic, pharmacokinetic, safety, and efficacy study in patients with atrial flutter or atrial fibrillation	Placebo 0.005 mg/kg 0.010 mg/kg 0.015 mg/kg 0.025 mg/kg (10-min infusion)	41 41 40 38 40	64 (25–82)	180/20 142/55/3
0015	Multicenter, double-blind, placebo-controlled, randomized, repeat-dose, safety, efficacy, pharmacokinetic, and pharmacodynamic study in patients with atrial flutter or atrial fibrillation	Placebo – Placebo 1.0 mg – 0.5 mg 1.0 mg – 1.0 mg (two 10-min infusions over 30 min)	86 86 94	67 (29–90)	213/53 222/40/4
003	Multicenter, open-label, dose-finding study in patients with sustained atrial flutter	Placebo 0.005 mg/kg 0.01 mg/kg 0.02 mg/kg (10-min infusions, 5 min between infusions)	17 17 13 9 (17 total)	65 (25–81)	13/4 13/4/0
0005	Multicenter, open-label, dose-finding study in patients with sustained atrial fibrillation	Placebo 0.005 mg/kg 0.01 mg/kg 0.02 mg/kg (10-min infusions, 5 min between infusions)	19 19 14 11 (19 total)	64 (39–78)	16/3 15/1/3

from vol 1.52, 08/01/442

There are 4 completed Phase II/III studies evaluating ibutilide in the target patient population. Protocols 0014 and 0015, both placebo controlled, are the main efficacy studies. Protocol 0003 is an open label study in patients with atrial flutter and protocol 0005 is an open label study in patients with atrial fibrillation.

Protocol No.	Study Design and Description	Treatment/ Regimen	No. of Patients	Age (y): Mean (Range)	M/F W/B/O
[illegible]					
0007 (completed after NDA submission)	Multicenter, double-blind, randomized, placebo-controlled, dose-ranging study in patients undergoing invasive electrophysiologic study	Placebo – Placebo 0.01 – 0.002 mg/kg 0.02 – 0.004 mg/kg 0.03 – 0.006 mg/kg (10-min loading dose – 30-min maintenance dose)	11 12 12 8	57 (21-80)	37/6 36/6/1
0013 completed after NDA submission)	Multicenter, open-label, dose-ranging, efficacy study in patients with well-tolerated, hemodynamically stable ventricular tachycardia undergoing invasive electrophysiologic study	0.005 – 0.001 mg/kg 0.01 – 0.002 mg/kg 0.02 – 0.004 mg/kg (10-min loading dose – 30-min maintenance dose)	20 20 15	65 (40-83)	47/8 52/3/0
[illegible]					
0017	Multicenter, double-blind, placebo-controlled, parallel group, randomized, dose-response, safety, efficacy, pharmacokinetic, and pharmacodynamic study in postvalvular or coronary artery bypass graft patients	Placebo – Placebo 0.25 – 0.25 mg 0.5 – 0.5 mg 1.0 – 1.0 mg (two 10-min infusions over 30 min)	300/55	NA	NA
0019	Multicenter, double-blind, parallel group, randomized, comparative safety and efficacy study of ibutilide or d,l-sotalol in patients with atrial flutter or atrial fibrillation	Ibutilide: 10-min infusion of 1 or 2 mg OR d,l-Sotalol: 10-min infusion of 1.5 mg/kg	300/26	NA	NA
020	Double-blind, parallel group, randomized, safety and efficacy study of ibutilide	Placebo-Placebo 1-1 mg (up to two 10-minute infusions over 30 min)	240/97	NA	NA
021	Double-blind, parallel group, randomized, comparative safety and efficacy study of ibutilide or procainamide in patients with atrial flutter or atrial fibrillation	ibutilide (see protocol 020) OR procainamide up to 3 10-min infusions of 400 mg each over 30 min	120/20	NA	NA

0004	Open-label, dose-ranging study in patients undergoing electrophysiologic study	0.005 mg/kg 0.01 mg/kg 0.02 mg/kg (10-min infusions, 5 min between infusions)	1 1 1	56	1/0 1/0/0
0018	Open-label, single-dose, pilot study in patients with paroxysmal atrial flutter/fibrillation	1 mg (10-min infusion)	2	76 (70-81)	1/1 2/0/0

There are 4 ongoing Phase II/III studies: study 0017 involves patients who recently underwent CABG, studies 0019 and 021 are comparative trials and study 020 is a placebo controlled efficacy trial. There are 2 studies in the EPS lab: studies 0007 and 0013 (completed at the time of the 4-month safety update submission). There are 2 small terminated Phase II/III studies: study 0018 was evaluating patients with paroxysmal atrial flutter/fibrillation and study 0004 was evaluating patients undergoing electrophysiologic studies.

b. Total number of patients in NDA

There are a total of 375 patients who received ibutilide in 1 of 4 completed Phase II/III trials.

protocol number	number of patients on ibutilide	number of patients on comparator
0014	159	41 (placebo)
0015	180	86 (placebo)
0003	17	(no control)
0005	19	(no control)
Total	375	127

from vol. 52, 08/01/442-4

The following table displays the number of patients enrolled in the 2 recently completed studies.

protocol number	number of patients on ibutilide	number of patients on comparator
0007	35	11 (placebo)
0013	55	(no control)

from safety update, information amendment 016, page 5

There were few patients enrolled in the 2 terminated studies.

protocol number	number of patients on ibutilide	number of patients on comparator
0018	2	no control
0004	3	no control

from vol. 52, 08/01/449-4

The numbers of patients evaluated for complete safety (medical events and laboratory analyses) are 375 for ibutilide and 127 for placebo (from protocols 0014, 0015, 0003, 0005). The total number of patients in the NDA who received ibutilide is 462 (87 additional patients from protocol 0007, 0013, 0018 and 0004) and 138 placebo patients (11 additional patients from protocol 0007). Abnormal laboratory values were reported only as a serious medical event.

c. Total number of patients in Safety Update

The cut off date for the 4-month safety update was November 15, 1994. During this time, protocol 0007 and 0013 were completed and 4 patients (3 ibutilide and 1 placebo) were added to the safety database for a total of 465 ibutilide patients and 139 placebo patients.

Currently, there are 2 ongoing studies (0017 and 0019) and 2 newly initiated studies (0020 and 0021). Protocol 0020 is a placebo controlled trial evaluating rates of conversion of atrial arrhythmia using 1 mg ibutilide given up to 2 times (planned N= 240) and protocol 0021 is a trial comparing ibutilide 1 mg given up to 2 times to procainamide 400 mg given up to 3 times (planned N=120). At the time of the safety update submission, 117 patients had been enrolled but the blind remains unbroken.

d. Dose

In the 375 patient data base for the NDA, 76 patients (20.3%) received total doses less than 0.075 mg, 101 patients (26.9%) received total doses between 0.075 and 1.25 mg, and 198 patients (52.8%) received total doses greater than 1.25 mg.

e. Completed phase II/III studies
(available for NDA and includes protocols 0003, 0005, 0014 and 0015)

Demographics

The table below displays the demographic characteristics for the 502 patients studied in the 4 completed trials.

Variable		Placebo N=127	All Ibutilide N=375	Total N=502
Age (yr)	Mean	65	66	66
	Range	28 - 90	25 - 89	25 - 90
Weight (lb)	Mean	182	183	183
	Range	96 - 280	94 - 310	94 - 310
Race n (%)	White	109 (86)	283 (76)	392 (78)
	Black	18 (14)	82 (22)	100 (20)
	Hispanic	0 (0)	9 (2)	9 (2)
	Other	0 (0)	1 (0.3)	1 (0.2)
Sex n (%)	Female	17 (13)	63 (17)	80 (16)
	Male	110 (87)	312 (83)	422 (84)

from vol. 52, 08/01/446

Mean age for all patients was 66 years and the range was from 25 to 90 years. Of the 375 ibutilide patients, 217 (58%) were older than 65 years (*data obtained from table X of the information amendment 011 received Feb 14, 1995.*). Mean weight was 183 pounds (83.2 kg). The majority of patients were white (78%) and male (84%).

<u>atment emergent medical events</u> (N=502)

equency by body system

The table below shows, by body system, the number of placebo patients (N=127) and the number of ibutilide patients by dose groups (and then for all ibutilide patients combined, N=375)) who reported at least one medical event.

Medical events by body system and dose group

Body System	Placebo		Ibut < 0.75 mg		Ibut ≥ 0.75 mg, ≤ 1.25 mg		Ibut > 1.25 mg		All Ibut	
	n=127		n=76		n=101		n=198		n=375	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	9	7.1	13	17.1	28	27.7	45	22.7	86	22.9
Whole Body	19	15.0	10	13.2	7	6.9	23	11.6	40	10.7
Digestive	9	7.1	-	-	2	2.0	14	7.1	16	4.3
Metabolic & Nutritional	3	2.4	1	1.3	4	4.0	8	4.0	13	3.5
Respiratory	7	5.5	2	2.6	1	1.0	10	5.1	13	3.5
Nervous	3	2.4	1	1.3	1	1.0	10	5.1	12	3.2
Urogenital	3	2.4	-	-	3	3.0	5	2.5	8	2.1
Skin	1	0.8	-	-	2	2.0	3	1.5	5	1.3
Hemic & Lymphatic	-	-	-	-	1	1.0	2	1.0	3	0.8
Musculo-Skeletal	-	-	-	-	1	1.0	2	1.0	3	0.8
Special Senses	-	-	-	-	1	1.0	-	-	1	0.3

from revised table A-12, information amendment 011 received Feb 14, 1995

There is little difference between the number of patients reporting medical events in the placebo group compared to the all ibutilide group for all body systems except the cardiovascular system. For cardiovascular, the percent of patients who reported a medical event in the ibutilide group (22.9%) was over three times as high compared to the placebo group (7.1%). There were more events reported with ibutilide doses at or above 0.75 mg compared to the lower dose.

frequency within body system

The table below shows all treatment emergent medical events that were reported by at least 1% of the all ibutilide group (N=375) and occurred at least 1% more frequently than in the placebo group (N=127). The dose category is by actual dose received.

Medical events within body system and by dose group

	placebo n=127		ibut <0.75mg n=76		0.75≤ibut ≤1.25mg n=101		ibut>1.25 mg n=198		all ibutilide n=375	
Medical Event	n	%	n	%	n	%	n	%	n	%
headache	4	3.1	3	3.9	2	2.0	13	6.6	18	4.8
nonsustained monomorphic VT	1	0.8	1	1.3	5	5.0	9	4.5	15	4.0
nonsustained polymorphic VT	0	0	3	3.9	6	5.9	6	3.0	15	4.0
extrasystole ventricular+	1	0.8	2	2.6	4	4.0	7	3.5	13	3.5
hypotension++	2	1.6	2	2.6	2	2.0	7	3.5	11	2.9
nausea	1	0.8	0	0	1	1.0	9	4.5	10	2.7
A-V block+++	1	0.8	1	1.3	2	2.0	7	3.5	10	2.7
sustained polymorphic VT	0	0	1	1.3	4	4.0	4	2.0	9	2.4
hypertension	0	0	0	0	1	1.0	4	2.0	5	1.3

+extrasystoles ventricular includes extrasystoles ventricular bigeminy
++hypotension includes postural hypotension
+++includes complete, first and second degree, heart block, and P-R segment prolongation
from revised table A-13, information amendment 011 received Feb 14, 1995

As expected, the ventricular arrhythmias predominate (these are discussed at length in a later section). Other medical events that were reported more frequently by the ibutilide patients compared to the placebo patients include headache (4.8%), hypotension (2.6%), nausea (2.7%), and hypertension (1.3%). These events tended to be reported more frequent with the high dose (>1.25 mg) than the low dose (< 0.75 mg).

Safety Update

The previous table was revised to include all patients who received ibutilide in the Phase II/III clinical trials (N=765). The table below shows all treatment emergent medical events that were reported by at least 1% of the all ibutilide group and occurred at least 1% more frequently than in the placebo group.

Medical events for all patients

	placebo n=139		all ibutilide n=465	
Medical Event	n	%	n	%
headache	4	2.9	23	4.9
nonsustained monomorphic VT	1	0.7	17	3.7
nonsustained polymorphic VT	0	0	17	3.7
hypotension+	2	1.4	15	3.2
extrasystoles ventricular ++	1	0.7	13	2.8
nausea	2	1.4	12	2.6
sustained polymorphic VT	0	0	11	2.4
chest pain	2	1.4	11	2.4
A-V block+++	1	0.7	10	2.2
atrial fibrillation#	0	0	5	1.1
hypertension	0	0	5	1.1

+hypotension includes postural hypotension
++extrasystoles ventricular includes extrasystoles ventricular bigeminy
+++includes complete, first and second degree, heart block, and P-R segment prolongation
from revised version of Table A-13
#atrial fibrillation was considered a medical event only in protocols 0007 and 0013
from informational amendment 080 submitted March 13, 1995

The changes to the safety review with the additional 90 ibutilide and 12 placebo patients were minor and limited to the addition of atrial fibrillation (reported as a medical event only in studies 0007 and 0013) and chest pain (reported by 2.4% of the ibutilide group compared to 1.4% of the placebo group).

Ventricular tachycardia (VT) (N=502)

The table below displays the number and percent of patients by dose group who experienced any arrhythmia and, then, those who experienced VT.

Number and percent of arrhythmias by dose group

	placebo n=127		ibut < 0.75 mg n=76		≤0.75 ibut ≤1.25 mg n=101		ibut > 1.25 mg n=198		all ibutilide n=375	
	n	%	n	%	n	%	n	%	n	%
any arrhythmia#	6	4.7	15	19.7	29	28.7	42	21.2	86	22.9
polymorphic VT	0	0	4	5.3	10	9.9	10	5.1	24+	6.4
sustained	0	0	1	1.3	4	4.0	4	2.0	9	2.4
nonsustained	0	0	3	3.9	6	5.9	6	3.0	15	4.0
monomorphic VT	1	0.8	1	1.3	6	5.9	9	4.5	16	4.3
sustained	0	0	0	0	1	1.0++	0	0	1	0.3
nonsustained	1	0.8	1	1.3	5	5.0	9	4.5	15	4.0

includes: arrhythmia nodal, arrhythmia ventricular, atrial fibrillation, AV block (complete, first degree, second degree), bradycardia, extrasystole ventricular bigeminy, extrasystole ventricular, idioventricular rhythm, sustained and nonsustained monomorphic and polymorphic VT, palpitations, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia.
+23 patients had 24 events (1 patient had both sustained and nonsustained polymorphic VT).
++this patient also had sustained polymorphic VT
from revised table A-13, information amendment 011 received Feb 14, 1995

There is a clear imbalance between the percent of ibutilide patients who developed an arrhythmia and the placebo patients (22.9% and 4.7%, respectively). When episodes of polymorphic VT (sustained as well as nonsustained) are culled out, 24 ibutilide patients (6.4%) experienced this arrhythmia compared to 0 placebo patients. A description of the 9 ibutilide patients who experienced sustained polymorphic VT is presented below.

The 9 patients who experienced sustained polymorphic VT

pt and protocol#	age, sex, race	QTc msec baseline/ maximum+ /change	pre/post K+ and Mg++ (meq)	Dose (mg) received	Concomi-tant cardiac meds	Baseline arrhythmia/ Medical history
207/0003	70/M/ W	430/540 (30)/110	4.5/3.9 2.2/1.8	0.996	digoxin diltiazem isordil furosemide	atria. fibrillation/ CAD, pulmonary edema, with dyspnea and chest pain for 2 weeks; 17 months prior had CABG and valve replacements
208/0003	68/M/ W	440/555 (30)115	4.8/3.9 1.7/1.7	1.885	none	atrial flutter/ 1 month dyspnea and tachycardia; 4 months prior had CABG, ASD repair. Reduced LVF
1106/0014	65/M/ B	417/660 (7)/243	4.4/4.3 2.1/3.3	0.660	lasix	atrial flutter/ CHF; 2 months prior had AV replacement
1513/0014	45/M/ B	448/469 (60)/21	4.8/4.6 1.6/1.9	1.838	lasix clonidine lisinopril digoxin	atrial flutter/ CHF, HTN, cardiomyopathy; MV replacement
2214/0014	67/M/ W	385/360 (60)/-25	4/4.1 2/2.1	1.374	lisinopril verapamil digoxin thiazide	atrial fibrillation/ HTN
2216/0014	40/M/ W	384/551/ 167	4.2/3.6 2/1.8	1.865	nitropaste lasix digoxin diazide	atrial fibrillation/ recent admission for CHF; HTN and obesity
1001/0015	72/M/ W	405/428 (30)/23	5.1/4.3 2.2/2.0	1.0	lanoxilin nitropaste lisinopril lasix	atrial flutter/ MI, atherectomy, angioplasty, CHF, EF=34%. 2 days later had sustained monomorphic VT while on quinidine
1191/0015	47/F/ B	402/723 (30)/321	4/4.5 2/2.9	0.8	digoxin lasix zaroxolyn captopril	atrial flutter/ IDDM, CHF, PVD, EF 20%, mild mr, moderate tr, renal insufficiency
2019/0015	69/F/ W	438/407 (30)/-31	4/4.2 2/1.7	1.0	lanoxin lasix	atrial fibrillation/ CAD, 5 years prior surgery for WPW.

+ maximum QTC recorded; time recorded in minutes after start of infusion is given in parentheses.
data obtained from case record forms and narratives in Vol 1.52, 08/01/507

The average change from baseline at the maximum recorded QTc

interval for these 9 patients was approximately 100 msec and the range was from -31 to +243 msec. Mean baseline QTc interval was 417 msec and ranged from 384 to 448 msec. The sponsor attempted to exclude patients from entering the later trials who had baseline QTc intervals above 440 msec and it is unknown if this exclusion influenced the overall occurrence of proarrhythmia. Of the 9 patients, 3 (#1106 and #2216 protocol 0014, #1191 protocol 0015) degenerated into ventricular fibrillation. While all 9 patients required DC shock, there was no indication that any of these episodes of VT were particularly difficult to abolish.

Overall, the majority of patients who developed polymorphic VT did so either during the infusion or within 20 minutes following the infusion. However, there were 2 patients (#2019 and 2097, protocol 0015) who developed repeated episodes of polymorphic VT up to 3 hours later.

Regarding monomorphic VT, episodes were reported up to 11 hours after the ibutilide infusion and one patient (#1001, protocol 0015) experienced an episode of monomorphic VT 2 days after receiving ibutilide and while being started on quinidine.

The doses that provoked polymorphic VT ranged from as low as 0.464 mg. Two patients were administered slightly higher doses by mistake and developed VT: one patient received 2.5 mg rather than 1 mg and the other received 1.8 mg rather than 0.7 mg.

Safety Update

The entire safety database as of November 15, 1994 consists of 465 patients who received ibutilide during one of the Phase II/III clinical trials. The number and percent of this patient population who experienced a proarrhythmic event are shown below.

Number and percent of ibutilide patients who developed a proarrhythmia

polymorphic VT				monomorphic VT				total VT			
sustained		nonsustained		sustained		nonsustained		sustained		nonsustained	
n	%	n	%	n	%	n	%	n	%	n	%
11[#@]	2.4	17[@]	3.7	5[#]	1.1	17	3.7	15[#@]	3.2	34[@]	7.3

 # patient 1001 protocol 15 is contained in both sustained polymorphic and sustained monomorphic subpopulations. This patient is counted only once in the "total" column.
@ patients 2019 protocol 15 and 224 protocol 13 are contained in both sustained and nonsustained polymorphic subpopulations. These patients are counted only once in the "total" column.
from informational amendment 022 received March 15, 1995, page 37

Overall, 15 patients had at least one episode of sustained VT and 34 patients had at least one episode of nonsustained VT. The incidence rate of VT, therefore, is 10.1% (47/465).

Submission of the Safety Update included 2 new patients with sustained polymorphic VT. Both patients were enrolled into protocol 0013 and both had a history of VT. These 2 patients are discussed below.

Safety Update patients who experienced sustained polymorphic VT

pt and protocol#	age, sex, race	QTc msec baseline/ maximum+ /change	pre/post K+ and Mg++ (meq)	Approx. Dose (mg) received	Concomi-tant cardiac meds	Medical history
216/0013	71/F/ W	441/546 (25)/105	4.0/4.4 2.0/2.2	0.83	quinidine, digoxin, enalapril	intermittent AF, CABG, MI CHF, HTN, documented monomorphic VT
224/0013	59/F/ W	454/669 (10)/215	5.5/4.8	1.75	hydralazine lasix, capoten, isordil, digoxin, lidocaine, dobutamine	CABG x 5, CHF, MI, HTN, PVD, VF

+ maximum QTC recorded; time recorded in minutes post start of infusion is given in parentheses.
data obtained from case record forms and information amendment 016 appendix B

Both of the patients were female. The baseline QTc interval for both patients was above 440 msec which was increased by an average of 160 msec either during or shortly after the ibutilide infusion. DC shock was required in

both cases to abolish the ventricular arrhythmia. The approximate dosages received by these 2 patients were 0.83 and 1.75 mg.

QTc Prolongation

Changes in QTc interval from baseline to Hour 1 (Protocols 0003, 0005, and 0014) or Minute 30 (Protocol 0015) are shown below categorized by low dose, mid dose, and high dose of ibutilide. Changes in QTc interval from baseline to the time of AFl/AF termination, if it occurred, are also included.

Mean QTc interval and change from baseline by dose group

Dose Group	Study Period	N	Mean QTc Interval (msec)	Change from Baseline (msec)	
				n	mean
Low	Before first infusion	47	428.5	-	-
	Hour 1	48	450.2	47	21.1
	Termination of AFl/AF	5	457.0	5	46.0
Mid	Before first infusion	169	424.1	-	-
	Minute 30	79	475.0	79	59.9
	Hour 1	80	466.1	79	31.4
	Termination of AFl/AF	70	455.7	70	36.3
High	Before first infusion	153	422.2	-	-
	Minute 30	89	477.7	88	61.1
	Hour 1	59	481.3	59	47.5
	Termination of AFl/AF	68	471.3	67	49.7
All	Before first infusion	369	423.9	-	-
	Minute 30	168	476.4	167	60.6
	Hour 1	187	467.7	185	33.9
	Termination of AFl/AF	143	462.2	142	43.0

from table 8.G.17 vol. 52, 08/01/463

The mean QTc interval at baseline for ibutilide patients (N=369) was 424 msec. There was a 60 msec increase from baseline for the mid and high doses of ibutilide at 30 minutes after start of the 10-minute infusion. At hour 1, the QTc prolongation was about half of the increase seen at minute 30. For those patients in the mid and high ibutilide groups who were study drug successes, the increases from baseline at the time of the atrial arrhythmia termination were 36 and 50 msec, respectively.

Deaths

The one reported death occurred in a placebo patient. Patient# 1217 in protocol 0015 had a history that included severe chronic obstructive pulmonary disease, asbestosis, a lung mass, and congestive heart failure. After failing to be converted to sinus rhythm with placebo, he was electrically converted. The patient's respiration became progressively more compromised, he refused intubation, and died 3.5 hours later.

Serious medical events

Serious medical events by body system experienced by the placebo (N=127) and ibutilide patients (N=375) are shown below.

Serious Adverse Events

	placebo n=127		ibut < 0.75 mg n=76		≤ 0.75 ibut ≤ 1.25 mg n=101		ibut > 1.25 mg n=198		all ibutilide n=375	
	n	%	n	%	n	%	n	%	n	%
any serious event	2	1.6	5	6.6	5	5.0	10	5.1	20	5.3
any cardiovas.	1	0.8	5	6.6	5	5.0	8	4.0	18	4.8
sustained polymorphic VT	0	0	1	1.3	4	4.0	4	2.0	9	2.4
nonsustained polymorphic VT	0	0	2	2.6	1	1.0	1	0.5	4	1.1
hypotension	0	0	1	1.3	0	0	1	0.5	2	0.5
AV block complete	0	0	0	0	0	0	1	0.5	1	0.3
CVA	1	0.8	0	0	1	1.0	0	0	1	0.3
CHF	0	0	0	0	0	0	1	0.5	1	0.3
extrasystole ven. bigeminy	0	0	1	1.3	0	0	0	0	1	0.3
extrasystole ventricular	0	0	0	0	0	0	1	0.5	1	0.3
sinus arrhythmia	0	0	1	1.3	0	0	0	0	1	0.3
sustained monomorphic VT	0	0	0	0	1	1.0	0	0	1	0.3
acute kidney failure	0	0	0	0	0	0	2	1.0	2	0.5
nausea	0	0	0	0	0	0	1	0.5	1	0.3
dizziness	0	0	1	1.3	0	0	0	0	1	0.3
respiratory failure	1	0.8	0	0	0	0	0	0	0	0
diaphoretic	0	0	0	0	0	0	1	0.5	1	0.3

from revised tables A-22 and A-23, information amendment 011 received Feb 14, 1995, page 153

There were 20 ibutilide patients (5.3%) who experienced a total of 23 serious events compared to 2 placebo patients (1.6%). The following section discusses the serious medical events (excluding the ventricular

tachyarrhythmias which are discussed in an earlier section) by individual patient. *Data obtained from vol 1.52, appendix B.*

1. AV block complete and nonsustained polymorphic VT (ibutilide patient #2127 protocol 0013)

This was a 68 year old white male with a history of cardiomyopathy secondary to CAD, MI, intermittent heart block, an embolic arterial event, HTN, infra HIS block, and atrial fibrillation. He mistakenly received 2.5 mg ibutilide rather than 1 mg. His QTc at Minute -10 was 372 msec. One minute following the infusion he had complete heart block (preexisting intermittent block). He became bradycardic and developed nonsustained polymorphic VT. Pacing was instituted and the VT did not recur. The patient's QTc interval at minute 30 was 643 msec. The second infusion was withheld. The patient spontaneously converted to normal sinus rhythm 1.5 hours after the start of ibutilide and a permanent pacer was inserted.

2. Cerebrovascular accidents (ibutilide patient #2088 protocol 0015, placebo patient #2225 protocol 0014)

Patient #2008 was a 76 year old white female with a history of head and neck cancer and atrial fibrillation. She successfully converted to sinus rhythm after the first infusion of 1.0 mg ibutilide. The next day she developed dysphasia, right facial droop, and paralysis of the right upper extremity. A CT scan showed a new subacute infarction in the right MCA/PCA watershed distribution area.

Patient #2225 was 52 year old white male who was admitted with new-onset atrial fibrillation. He was anticoagulated with heparin and the next day received a 10-minute infusion of placebo. One hour after the infusion he was DC cardioverted to sinus rhythm. The next morning he was noted to be ambulatory and oriented by the nursing staff. However, he suddenly developed expressive aphasia with right-sided weakness. His initial CT scan revealed no evidence of a hemorrhage and no acute infarct. His symptoms of right hemiplegia and expressive aphasia eventually improved.

3. Congestive heart failure (ibutilide patient #1069 protocol 0015)

This was a 66 white male with atrial flutter had a extensive medical history that included MI, CABG, diabetes, and CVA. Prior to start of study drug he had evidence of heart failure with rales in the right base, decreased breath sounds in both bases, shortness of breath and ankle and pedal edema on physical exam. The patient received 1.5 mg of ibutilide without terminating his arrhythmia. He spontaneously converted approximately 2 hours later.

Sotalol was started at Hour 2.5 to maintain sinus rhythm. The patient became restless, developed mental confusion (thought to be related to hypoxia) and had elevated creatinine. Sotalol was discontinued, treatment with diuretics was instituted, and the CHF improved.

4. Extrasystole ventricular bigeminy and sinus arrhythmia (ibutilide patient # 1104 protocol 0014)

This patient was a 65 year old white male with atrial flutter. He had a history of CAD, chronic CHF, HTN, chronic AFl, and a possible anterior MI. Symptoms upon admission were palpitations and dizziness with exercise. He received 0.430 mg of ibutilide (0.005 mg/kg) without termination of his atrial flutter. At approximately 1 hour after the end of the infusion, the patient was paced out of atrial flutter. He developed sinus bradycardia (approximately 44 bpm) and had a 5-second pause (sinus arrest) following conversion, followed by junctional rhythm with ventricular bigeminy. The post-termination junctional bradycardia lasted approximately 30 minutes. Temporary pacing was utilized as the drug effect on rhythm wore off. Temporary pacing was continued for approximately 24 hours while the patient was given procainamide. The pacemaker was removed and the patient recovered.

5.Extrasystole ventricular and nonsustained monomorphic VT (ibutilide patient #2128 from protocol 0015)

This patient was a 69 year old white male with a history of MI, CABG, PTCA and atrial flutter. He had an internal cardioverter device implanted 2 weeks prior to the study for induced VT. The patient was randomized to receive 1 mg/1 mg ibutilide and his QTc at minute -10 was 426 msec. He mistakenly received 2.5 mg rather than 1 mg for the first 10-minute infusion. The second infusion was not administered because of increased ectopy. He remained in atrial flutter. His QTc at minute 30 was 366 msec which increased to 612 msec 1 hour later. The patient developed monomorphic VT 6.5 hours after receiving ibutilide which was terminated by the internal defibrillator.

6. Hypotension and dizziness (ibutilide patient #2347 protocol 0014)

This patient was a 72 year old black male with a history of CAD, CABG, and atrial fibrillation. He experienced mild dizziness during the screening phase of the study. Prior to drug administration, his blood pressures were 120/77, 128/70, and 120/74 mmHg. He was randomized to 0.005 mg/kg ibutilide fumarate and received the entire 10-minute infusion. The study drug was unsuccessful at terminating the arrhythmia and he was electrically cardioverted. The patient's blood pressure remained in the same range as pretreatment values through hour 16. The day following the infusion the

patient was too dizzy to walk and his blood pressure was 62/30 mmHg at hour 24. He was given normal saline fluid challenge IV and his blood pressure increased to 110/70 mmHg within 30 minutes. Digoxin, procainamide, and diltiazem were discontinued.

7. Hypotension, diaphoresis, nausea (ibutilide patient #1117 protocol 0015)

This patient was a 54 year old white male who had a history of MI, 3-vessel CAD, and previous atrial flutter. At baseline his blood pressure was 119/91 mmHg. The patient received 1.5 mg and did not convert. Approximately 7.5 hours after the end of the infusion the patient experienced nausea, hypotension (84/64 mmHg), and diaphoresis. The patient was electrically cardioverted to sinus rhythm during this episode and the symptoms resolved. It was concluded that the hypotension was the result of baseline volume depletion and the interaction of procainamide and atenolol.

8. Acute kidney failure (ibutilide patients #1031 protocol 0015 and #1061 protocol 0015)

Patient #1031 was a 77 year old white male with a history of MI, CABG, and atrial flutter. His screen creatinine was 1.7 mg/dL (normal range up to 1.3), BUN was 32 mg/dL (upper normal range 20), and sodium was 132 mEq/L (normal range 135-145). He received both infusions of ibutilide converted to sinus bradycardia. The patient underwent a heart catheterization the following day. His serum creatinine at 24 hours was 2.3 mg/dL, BUN was 38 mg/dL, and sodium was 124 mEq/L. His creatinine peaked at 6.1 mg/dL on the fourth day following the infusion, and then returned to baseline one week later. The transient acute renal failure was attributed to the contrast dye.

Patient #1061 was a 73 year old white male with a history of CAD, CABG, HTN, TIAs, stroke and atrial flutter. He received two 1 mg ibutilide infusions over a total of 20 minutes and converted to sinus bradycardia. At screen his serum creatinine was 1.6 mg/dL (normal range up to 1.5). BUN was 28 mg/dL (upper normal range 21) and blood pressure was 136/83 mmHg. Four hours following the infusion his blood pressure was 90/50 mmHg, and it remained decreased until Hour 24. His serum creatinine peaked at 5.1 mg/dL with a BUN of 62 mg/dL on the second day following the infusion. Urine electrolytes and urinalysis were most consistent with a prerenal cause. Six days following the infusion the creatinine was 1.7 mg/dL. The patient was on concomitant captopril for CHF and diltiazem for HTN which were discontinued.

Conclusions

The one patient who received 2.5 mg rather than 1 mg immediately developed complete heart block and polymorphic VT upon start of the 10

minute infusion, resulting in the conclusion that minor dosing errors can result in serious consequences. The cases of cerebrovascular accident, congestive heart failure and kidney failure are only remotely if at all linked to ibutilide use. The patient who developed hypotension, diaphoresis, and nausea 7.5 hours after receiving 1.5 mg of ibutilide recovered with electroversion. The other patient developed hypotension and dizziness about 24 hours after receiving ibutilide so the causality is unlikely.

Regarding the cases of acute kidney failure, patient #1031 received contrast dye prior to cardiac catheterization which is probably the cause of his elevated serum creatinine. Patient #1061 became hypotensive 4 hours after the infusion and remained hypotensive with elevated serum creatinine and BUN. This patient was also receiving captopril and diltiazem. His kidney failure is probably related to the hypotension.

The episode of congestive heart failure in patient #1069 was probably linked to the use of sotalol. He had a history of CHF and was symptomatic at baseline (rales, pedal edema, shortness of breath).

Safety Update

The following table contains the serious safety events for the 465 ibutilide (all dose groups combined) and 139 placebo patients.

Serious Medical Events

	placebo n=139		all ibut n=465	
	n	%	n	%
any serious event	2	1.4	24	5.2
any cardiovas.	1	0.4	22	4.7
sustained polymorphic vT	0	0	10	2.2
nonsustained polymorphic VT	0	0	4	0.9
hypotension	0	0	3	0.6
sustained monomorphic VT	0	0	2	0.4
AV block complete	0	0	1	0.2
CVA	1	0.7	1	0.2
CHF	0	0	1	0.2
pulmonary embolism	0	0	1	0.2
extrasystole ven. bigeminy	1	1.4	1	0.2
extrasystole ventricular	0	0	1	0.2
sinus arrhythmia	0	0	1	0.2
acute kidney failure	0	0	2	0.4
nausea	0	0	1	0.2
dizziness	0	0	1	0.2
diaphoretic	0	0	1	0.2
respiratory failure	1	0.7	0	0

from Table A 22, information amendment 084 received March 21, 1995

There were 4 serious medical events added in the Safety Update: 1 pulmonary embolism, 1 hypotension, 1 sustained monomorphic and 1 sustained polymorphic VT. The VT events are discussed in the ventricular tachycardia, safety update section. *Data from Safety Update, information amendment 016, appendix B.*

1. Pulmonary embolism (ibutilide patient #2109 protocol 0007)

This patient was a 69 year old white male who had a history of three myocardial infarctions, valvular disease, abnormal cardiac wall function with ejection fraction 32%. On admission he had rare premature ventricular contractions and couplets which progressed to asymptomatic non-sustained ventricular tachycardia. The patient was being treated prophylactically with lidocaine. He received ibutilide loading dose of 0.01 mg/kg and maintenance infusion of 0.002 mg/kg. One day later, the patient was diagnosed with pulmonary emboli. The symptoms subsided three days later.

2. Hypotension (ibutilide patient #220 protocol 0013)

This patient was a 65 year old white male with a history of coronary artery disease, diabetes mellitus, peripheral vascular disease, and sustained monomorphic VT. He had symptoms of increasing shortness of breath, chest tightness, and palpitations and his ejection fraction was 70%. The patient received 0.020 mg/kg ibutilide infused over 10 minutes. He complained of chest tightness at the midpoint of the infusion and was given sublingual nitroglycerin. At the end of the loading infusion and beginning of programmed stimulation, the patient complained of worsening chest tightness and pain radiating to his neck with associated shortness of breath. His blood pressure decreased from 131/76 mmHg at baseline to 72/43 mmHg at minute 10 and 80/58 mmHg at minute 15. The maintenance infusion (0.004 mg/kg) was discontinued after 9 minutes. He was placed in Trendelenburg and an IV bolus of normal saline was given. His blood pressure returned to 105/63 mmHg. The patient was found to have heme positive stools and a hemoglobin/hematocrit of 8.5 g/dL and 28%, respectively (baseline values were 9.1 g/dL and 30%).

In conclusion, while the pulmonary embolism appeared to be unrelated to ibutilide use, the hypotension could be related. Currently, the total reported cases of serious hypotension with ibutilide is 3 (0.6%, 3/465).

Study drug discontinuations

This classification is difficult to evaluate and may be misleading because most of the study patients received only a single dose (or at the most two) infused over 10 minutes. The table below displays the number and percent of patients in whom the study drug was discontinued.

Number and percent of patients who discontinued study drug

	placebo n=127		ibut < .75 mg n=76		≤0.75 ibut ≤1.25 mg n=101		ibut > 1.25 mg n=198		all ibutilide n=375	
	n	%	n	%	n	%	n	%	n	%
patients who discontinued study medication	0	0	5	6.6	9	8.9	8	4.0	22	5.9

from revised tabled A-95, information amendment 011 received Feb 14, 1995, page 165

A total of 22 ibutilide patients and 0 placebo patients were discontinued from study drug. As expected, all of the ibutilide discontinuations were for cardiovascular reasons. The table below shows, by event, the number and percent of patients in each dose group who discontinued ibutilide.

Ibutilide discontinuations

	ibut < 0.75 mg n=78		≤0.75 ibut ≤1.25 mg n=101		ibut > 1.25 mg n=198		all ibutilide n=375	
	n	%	n	%	n	%	n	%
nonsustained polymorphic VT	2	2.6	4	4.0	4	2.0	10	2.7
extrasystoles ventricular	1	1.3	2	2.0	1	0.5	4	1.1
sustained polymorphic VT	1	1.3	1	1.0	2	1.0	4	1.1
QT segment prolonged	0	0	2	2.0	1	0.5	3	0.8
nonsustained monomorphic VT	1	1.3	2	2.0	0	0	3	0.8
heart block	0	0	1	1.0	0	0	1	0.3
arrhythmia ventricular	0	0	1	1.0	0	0	1	0.3
AV block complete	0	0	0	0	1	0.5	1	0.3
supraventricular VT	0	0	1	1.0	0	0	1	0.3
tachycardia	1	1.3	0	0	0	0	1	0.3

from revised tabled A-26, information amendment 011 received Feb 14, 1995, page 166

Note: patients could discontinue for more than 1 reason.

Safety Update

The table below shows the number and percent of patients who discontinued ibutilide for the entire ibutilide database (N=465) by low (0.005 mg/kg), mid (0.010 mg/kg, 0.015 mg/kg, 1.5 mg), and high (0.025 mg/kg, 0.035 mg/kg, 2 mg) dose categories. There were no discontinuations in the placebo group. Note: these were the doses to which the patients were randomized but did not necessarily receive.

	low dose ibut n=69		mid dose ibut n=303		high dose ibut n=193		all ibutilide n=465	
	n	%	n	%	n	%	n	%
any reason+	2	2.9	8	3.9	18	9.3	28	6.0
cardiovascular								
nonsustained polymorphic VT	0	0	2	1.0	10	5.2	12	2.6
sustained polymorphic VT	0	0	5	1.5	3	1.6	6	1.3
extrasystoles ventricular	0	0	0	0	4	2.1	4	0.9
QT segment prolonged	0	0	2	1.0	2	1.0	4	0.9
nonsustained monomorphic VT	1	1.4	1	0.5	1	0.5	3	0.6
arrhythmia ventricular	0	0	1	0.5	0	0	1	0.2
AV block complete	0	0	0	0	1	0.5	1	0.2
heart block	0	0	1	0.5	0	0	1	0.2
hypotension	0	0	0	0	1	0.5	1	0.2
supraventricular VT	0	0	1	0.5	0	0	1	0.2
sustained monomorphic VT	1	1.4	0	0	0	0	1	0.2
tachycardia	0	0	0	0	1	0.5	1	0.2
angina pectoris	0	0	0	0	1	0.5	1	0.2
noncardiovascular								
dyspnea	0	0	0	0	1	0.5	1	0.2

Information amendment 024 received March 21, 1995, Table A-25, page 5

Other than the one ibutilide patient who dropped out because of

dyspnea, all discontinuations were for cardiovascular events. Nonsustained and sustained polymorphic VT were the most common reasons for drop out (2.6% and 1.3%, respectively), followed by QT segment prolongation and ventricular extrasystoles (0.9%).

Ongoing studies

No deaths have been reported for any of the 4 ongoing blinded studies. The medical events that have been reported for these trials are listed below. These events are not included in any of the tables in this review. (*Data obtained from Safety Update, information amendment 016, page 16*).

Protocol 0017 (placebo controlled trial in patients who recently underwent coronary artery by-pass grafting; N=114): 1 non serious proarrhythmia (4-beat VT), 1 discontinued treatment for chest pain and dyspnea and increased ventricular ectopy, 1 heart arrest approximately 16 hours after the end of the study drug infusion.

Protocol 0019 (comparative trial with sotalol, N=194). 6 non serious proarrhythmias (non sustained VT), QT prolongation, 2 serious proarrhythmias (sustained and nonsustained polymorphic VT), 3 treatment discontinuations including AV block and QT segment prolongation, 6 other serious medical events including angina, nodal arrhythmia, AV block, endocarditis, hypotension, dyspnea.

Protocol 0020 (placebo controlled trial, N=97). 4 non serious proarrhythmias (non sustained polymorphic VT), 2 serious events including proarrhythmias (1 torsade de pointes, 1 sustained monomorphic VT), AV block and cerebrovascular accident, 3 treatment discontinuations including non sustained VT and torsade de pointes.

Protocol 0021 (comparative trial with procainamide, N=20). None.

f. Special populations

Gender differences

There is evidence[1] that females who are taking antiarrhythmic drugs are more susceptible than their male counterparts to developing drug-induced ventricular tachycardia. The table below displays the number of sustained and nonsustained polymorphic and monomorphic VT episodes reported for the

[1]Makkar Raj R, et al, Female Gender as a Risk Factor for Torsade de Pointes Associated with Cardiovascular Drugs. *JAMA* 1993;270:2590-97

465 ibutilide study patients grouped by sex. There was 1 placebo patient who had an episode of non sustained monomorphic VT and is omitted from the table.

	Proarrhythmia events Ibutilide patients only (protocols 0003, 0005, 0007, 0013, 0014, 0015)											
	Polymorphic				Monomorphic				Total arrhythmias			
	sustained		non sustained		sustained		non sustained		sustained		non sustained	
	n	%	n	%	n	%	n	%	n	%	n	%
male (n=388)	7+	1.8	10	2.6	5+	1.3	11	2.8	11+	2.8	21	5.4
female (n=77)	4++	5.2	7++	9.1	0	0	6	7.8	4	5.2	13	16.9
Total (n=465)	11+	2.4	17	3.7	5+	1.1	17	3.7	15+	3.2	34	7.3

+one male patient with sustained polymorphic and monomorphic VT
++two female patients with sustained and nonsustained polymorphic VT
from informational amendment 022 received March 15, 1995, page 1.37

There were 11 males (2.8%) and 4 females (5.2%) who experienced either an episode of sustained polymorphic and/or monomorphic ventricular tachycardia. There was even a larger discrepancy in the rates seen with nonsustained VT: 16.9% of females compared to 5.4% of males. Women appear to be more susceptible than men to the development of a proarrhythmic event with ibutilide.

Age

The table below shows the mean age as well as the standard deviation, and the minimum and maximum ages in the ibutilide groups separated into those who developed either polymorphic VT, monomorphic VT, or developed neither.

		Years of age				
		n	mean	S.D.	min	max
Polymorphic VT	All ibutilide	23	64.5	10.2	40.0	77.0
Monomorphic VT	All ibutilide	16	67.1	9.6	52.0	85.0
None	All ibutilide	337	65.9	9.9	25.0	89.0

from table A-215, vol 1.54, 06/05/391

There is no obvious relationship between the age of patients who developed monomorphic or polymorphic VT (64.5 and 67 years of age, respectively) and those who did not (mean age 65.9 years).

Kidney/liver impaired patients

According to the ^{14}C ibutilide study, about 82% of ibutilide is excreted in the urine (with about 7% as unchanged ibutilide), and 19% is eliminated in the feces. The sponsor makes the arguments that because 1.) the duration of infusion is limited to under 30 minutes, 2.) less than 10% of unchanged ibutilide is excreted in the urine, 3.) the hepatic clearance is perfusion rate limited, and 4.) the drug distribution may be one of the primary mechanisms for termination of drug effect, there was no need to evaluate the safety of ibutilide in these subpopulations and no need for dose adjustment. The entry criteria for the 2 pivotal trials (0014 and 0015) had the following stipulations: liver enzymes must be less than 2 times maximum normal values and (for protocol 0014 only) serum creatinine must be less than 2.0 mg/dL.

Of the 465 ibutilide patients, 3 had SGPT $\geq$ 130 U/L and SGOT $\geq$ 80 U/L (#0013/13025/221, 0014/10175/2105 and 0015/13808/1196). One of the three patients had a medical event (wide complex tachycardia).

There were 32 patients who had serum creatinine $\geq$ 2.0 mg/dL at any time during the study. Three of these patients had serious adverse events (0013/13025/224–sustained polymorphic VT, 0015/13811/1031 and 0015/13808/1061–acute kidney failure).

Drug-drug interactions

No Phase I drug-drug interaction studies were conducted by the sponsor. Instead, the effects of digoxin, calcium channel blockers, and beta blockers were evaluated in Phase II/II studies 0014 and 0015. The table below shows the clearance and the volume of distribution for ibutilide in patients receiving (and not receiving) the concomitant medication.

Ibutilide pharmacokinetic parameter estimates* relative to concomitant therapy with digoxin, calcium channel blockers or β-blockers (Protocol 0014)

Concomitant Medication	Number of Patients	Used within 24 hours prior to dosing?	CL, mL min^{-1}/kg	V_{ss}, L/kg
Digoxin	55	Yes	38 ± 16 (42%)	3.3 ± 3.4 (54%)
	38	No	35 ± 16 (46%)	7.0 ± 4.8 (69%)
Calcium Channel Blockers	35	Yes	36 ± 18 (50%)	6.3 ± 3.6 (57%)
	58	No	38 ± 15 (39%)	6.7 ± 4.3 (64%)
Beta Adrenergic Blockers	17	Yes	43 ± 15 (35%)	8.0 ± 3.8 (48%)
	76	No	36 ± 16 (44%)	6.2 ± 4.0 (65%)

* Data expressed as the mean ± standard deviation (% coefficient of variation).
from vol. 1.42, 06/01/39.

Based on the above information, drug-drug interactions with one of these 3 medications would not be expected. The table below shows the number of patients receiving (and not receiving) at least one of the following concomitant drugs and the number and percent of proarrhythmic events. Note: the total number of ibutilide patients evaluated is 375.

concomitant med	proarrhythmic events	
	n	%
digoxin?		
yes (n=214)	23	10.7
no (n=161)	15	9.3
ca blocker?		
yes (n=158)	20	12.7
no (n=217)	18	8.3
beta blocker?		
yes (n=68)	4	5.9
no (n=307)	34	11.1

table derived from CANDA

There is some indication that patients receiving a beta blocker may be less likely to develop a proarrhythmia.

g. Laboratory values

Of the 462 patients treated with ibutilide, 375 had laboratory assessments. Apart from the random variation, only creatine kinase showed dramatic changes from baseline, but these changes occurred in patients who had been electroverted. The sponsor had investigated patients whose hematology and/ chemistry values met one or more of the sponsor's designated criteria. These patients and others are briefly discussed below. (*data obtained from vol 1.52, Appendix B*)

Hematology

Hemoglobin <8.0 g/dL
Platelet count <100 or >600 (x 10^3/mm^3)
White blood cell count <3.0 or >20.0 (x 10^3/mm^3).

There were 2 patients from protocol 0014 (#1350 and #2211) with low hemoglobin (7.6 and 7.9, g/dl) post treatment. Both patients had low values at screen. There was one patient (#2323 protocol 0014) with abnormally high WBC (23.6 x 10^3/mm^3) who was found to have a urinary tract infection and another patient (#1086 protocol 0015) who had an abnormally low WBC (2.8 x

$10^3/mm^3$) after ibutilide use but the screen value was also low ($3.0 \times 10^3/mm^3$).

Blood chemistries

Liver function tests

ALT >3 times the upper limit of normal
AST >3 times the upper limit of normal

Three patients all from protocol 0014 (#2115, #1347, # 2317) met the above criteria; all had undergone electroversion and one was a placebo patient.

Patient #1234 protocol 0015 had elevated values post treatment (ALT 73 U/L, screen 21 U/L and AST 108 U/l, screen 37 U/L). He was receiving concomitant antibiotic therapy for pneumonia.

BUN and creatinine

BUN >2 times the upper limit of normal
Creatinine >3.0 mg/dl.

Of the 8 patients selected for abnormal BUN and/or creatinine, 7 received ibutilide and 1 received placebo. All had elevated levels at screen and only 1 had a corresponding rise in creatinine. This patient (#1061 protocol 0014) had become hypotensive (90/60 mm Hg) during the ibutilide infusion. His BUN rose from 28 mg/dl to 62 mg/dl and serum creatine rose from 1.6 mg/dl to 5.1 mg/dl two days after the study drug was infused. Serum creatinine return to baseline approximately 4 days later.

There were 2 additional patients with increases in BUN and serum creatinine that were reported as medical events but were less than the cut off points cited above. Patient #1103, protocol 0014 had BUN and serum creatinine increases from 21 to 40 mg/dl and from 1.8 to 3.1 mg/dl, respectively. Patient #1304 protocol 0014 had increases in BUN from 17 to 33 mg/dl and serum creatinine 1.4 to 2.3 mg/dl. Both events were unexplained.

Creatine kinase

Creatine kinase >5 times the upper limit of normal

All of the 17 patients with elevations of CK had undergone electroversion.

Electrolytes

Calcium <7.0 or >12.0 mg/dL
Magnesium <1.5 or >3.0 mg/dL
Potassium <3.3 or >6.0 mEq/L
Sodium <130 or >160 mEq/L

One patient had an abnormally elevated Mg^{++} resulting from being given 3 gram of magnesium sulfate because of an arrhythmia. There were 2 patients with mildly decreased magnesium levels. Five patients had decreased sodium (2 had received placebo), and there was one patient (#1336 protocol 0014) with an unexplained serum potassium increase from 4.2 mEq/L to 6.4 mEq/L (hemolyzed specimen?). No patient had an abnormal calcium level.

h. Vital signs

There were 15 (3.2%) reports of hypotension (5 were considered serious) in 465 patients receiving ibutilide compared to 2 reports (1.4%) in 139 placebo patients.

Overall, ibutilide appears to have little if any effect on systolic and diastolic blood pressure. In study 0015, blood pressure and pulse were recorded throughout the 24 hours. The mean changes from baseline for systolic and diastolic blood pressure were similar in the placebo and the 2 ibutilide groups (*data obtained from vol. 1.72, 08/21/14-19*). Decreases in pulse, as expected, were greater in the ibutilide groups compared to placebo, reflecting the higher conversion rate to sinus rhythm (*data obtained from vol. 1.72, 08/21/20-22*). These findings were similar to those in the other placebo controlled efficacy study, protocol 0014 (*data obtained from vol. 1.65, 08/14/308-22*).

i. Long term safety

There were no safety analyses beyond the 24-72 hour post study drug evaluation period for protocols 00014 and 0015 in the NDA and Safety Update. Therefore, the sponsor was asked to review the hospital and outpatients charts

for the patients who were randomized into one of these 2 studies. As a result, the sponsor was able to obtain retrospective safety information that was classified as serious and/or necessitated a change in dose or discontinuation of an antiarrhythmic medication up to 3 months after the patient completed the study. Findings from each of the 2 studies are discussed below.

Protocol 0014

This was a double blind, placebo controlled, dose response, efficacy study. Long term data were obtained from 188 of the 200 randomized patients.

Deaths: there were 6 deaths up to 3 months post study.

Deaths occurring up to 3 months after patient completed study 0014

patient identification	drug group (mg/kg)	cause of death
1218/	placebo	carcinoma
1116/	ibut 0.005	cardiopulmonary arrest
2113/	ibut 0.010	cardiopulmonary arrest/VT
2121/	placebo	ven. fibrillation
1344/	ibut 0.010	lung carcinoma
2209/	ibut 0.025	lung carcinoma

data from informational amendment 022, Vol 2, pg 221-241

Overall, there were 2 (5.4%, 2/37) deaths in the placebo group and 4 (2.7%, 4/146) in the ibutilide group. There is no imbalance in the occurrence of death up to 3 months after the ibutilide infusion.

Serious medical events

The table below shows the serious safety reported for all randomized patients that occurred up to 3 months after completing study 0014, focusing on the subset of cardiovascular events and, in particular, ventricular tachyarrhythmias.

Number and percent of patients who experienced
a serious medical event post study 0014

	placebo n=37		ibutilide n=146	
	n	%	n	%
any event	19	51.4	63	43.1
cardiovascular event	13	35.1	46	31.5
ventricular tachyarrhythmia+	2	5.4	3	2.1

+includes sustained and non sustained monomorphic and polymorphic VT, ventricular fibrillation, and ventricular tachycardia.
data from International amendment 002, Vol., 2, pg 214-60

There was no substantial difference between the serious medical events including cardiovascular events in the patients who had received ibutilide compared to those who received placebo. There was one report of elevated liver enzymes, classified as severe, that occurred in a 73 year old female patient (#1301, Ellenbogen, ibutilide 0.015 mg/kg). No details, other than that the condition was unresolved, are available.

Protocol 0015

This was a double blind, placebo controlled efficacy study. Long term data were obtained from 248 out of 266 randomized patients.

Deaths: there were 9 deaths reported up to 3 months post study.

Deaths occurring up to 3 months after patient completed study 0015

patient identification	drug group (mg/kg)	cause of death
1212/	ibut 1/0.5	lung carcinoma
9009/	placebo	not stated
1048/	ibut 1/0.5	heart failure
2149/	ibut 1/0.5	congestive heart failure
1175/	ibut 1/1	CNS neoplasm/pneumonia
2068/	placebo	malignant arrhythmia
2196/	ibut 1/0.5	cardiopulmonary arrest
1015/	ibut 1/1	congestive heart failure
2141/	ibut 1/1	respiratory distress/ventricular fibrillation

data from informational amendment 002, Vol 3, pg 224-54

Overall, there were 2 (2.5%, 2/81) deaths in the placebo group and 7 (4.2%, 7/167) in the ibutilide group. This difference in deaths is probably not relevant and it conflicts with the findings in study 0014.

Serious medical events

The table below shows the serious cardiovascular events (CHF and VT) and respiratory events reported for nearly all randomized patients in protocol 0015 that occurred up to 3 months after completing the study. This is limited to the subsets of cardiovascular events: ventricular tachyarrhythmias and congestive heart failure, and respiratory events.

Number and percent of patients who experienced a serious medical event post study 0015

	placebo n=81		ibutilide n=167	
	n	%	n	%
any event.	37	45.7	75	44.9
cardiovascular event	25	30.9	63	37.7
congestive heart failure	1	1.2	12	7.2
ventricular tachyarrhythmia+	0	0	5	3.0
respiratory event	3	3.7	14++	8.3

+includes sustained and non sustained monomorphic and polymorphic VT, ventricular fibrillation, and ventricular tachycardia.
++ includes respiratory arrest (1), aspiration pneumonia (1), lung carcinoma (3), cough (1), dyspnea (5), lung edema (2), hemoptysis (1), obstructive lung disease (1), pneumonia (1).
data from informational amendment 022, Vol 3, pg 817-25.

There is no difference between placebo and ibutilide patients for the reported occurrence of any serious medical event during this post study period. However, ibutilide patients had more congestive heart failure, ventricular tachyarrhythmias and respiratory events than the placebo patients. These findings are probably inconsequential.

Combining both studies gives a placebo death rate of 3.4% (4/118) and an ibutilide death rate of 3.5% (11/313). The combined cardiovascular event rates were 32.2% (38/118) for placebo and 34.8% (109/313) for ibutilide. In conclusion, there is no convincing evidence that ibutilide infused for 10 minutes once or twice causes any long term adverse effects.

Maryann Gordon 9-8-95

Maryann Gordon, M.D.

CHEMIST'S REVIEW

DEC 19 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-491 **CHEM.REVIEW #:** 6 **REVIEW DATE:** 18-Dec-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-Oct-94	28-Oct-94	01-Nov-94
AMENDMENT	04-Dec-95	05-Dec-95	08-Dec-95

NAME & ADDRESS OF APPLICANT: The Upjohn Company
7171 Portage Road
Kalamazoo, MI 49001

DRUG PRODUCT NAME

Proprietary: Corvert Injection
Nonproprietary/USAN: Ibutilide fumarate
Code Name/#: U-70226E
CAS-122647-32-9 (salt)
CAS-122647-31-8 (ibutilide)
Chem.Type/Ther.Class: 1 S

ANDA Suitability Petition/DESI/Patent Status:

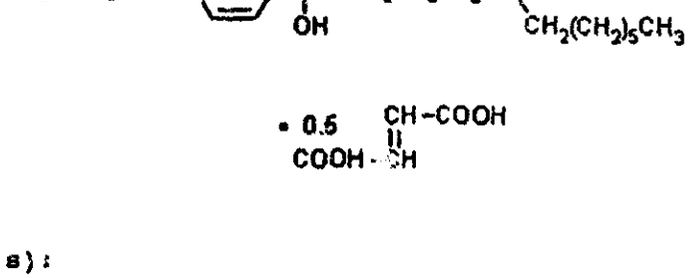
Patent and exclusivity information

Patent # 5,155,268 — Five (5) year after the approval, 13 October 2009 (for 1 mg/10 mL Corvert Injection)

PHARMACOL.CATEGORY/INDICATION: Treatment of atrium fibrillation and flutter

DOSAGE FORM: Injection
STRENGTHS: 0.1 mg/mL
ROUTE OF ADMINISTRATION: Intravenous
DISPENSED: __x__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name(s):

N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]ph nyl]methanesulfonamide, (E)-2-butenedioate (1:0.5) (hemifumarate salt)

Molecular Formula: $C_{22}H_{36}N_2O_5S$ Molecular Weight: 442.62

SUPPORTING DOCUMENTS:

DMF 4266 The Upjohn Co. (Type I)

[redacted] Page 4

[redacted] (if applicable):

[redacted]: Microbiology consult was submitted. Deficient.

[redacted]:

Ibutilide fumarate has not been registered anywhere in the world to treat atrial flutter or atrial fibrillation.

The drug substance and drug product are manufactured by The Upjohn Company.

EER (FUR) was requested on 10/4/95. Acceptable 10/6/95.

Methods validation was requested on 12/30/94. DDA and Detroit results are reported. 12/4/95 - response to methods validation questions.

[redacted]:

In general, the methods are acceptable for the regulatory purposes.

cc:
Orig. NDA 20-491
HFD-110/Division File
HFD-110/CunninghamD/12/18/95
HFD-110/CSO
District

R/D Init. by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20491R06.NDA

12/19/95

PHARMACOLOGIST'S REVIEW

CLINICAL PHARMACOLOGY REVIEW

NDA 20-491

CORVERT™ INJECTION

(Ibutilide Fumarate Injection)

Victor F.C. Raczkowski, M.D., M.S.

Division of Cardio-Renal Drug Products

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DOSE-ESCALATION STUDIES IN HEALTHY VOLUNTEERS:

ELECTROPHYSIOLOGICAL STUDIES:

Clinical Pharmacology Review

NDA 20-701
Corvert™ Injection (ibutilide fumarate injection)
Sponsor: The Upjohn Company
Formulation: 0.1 mg/ml solution
Proposed Indication: Acute Termination of Atrial Fibrillation or Atrial Flutter
Reviewer: Victor F.C. Raszkowski, M.D., M.S.; Division of Cardio-Renal Drug Products; HFD-110

Victor F. C. Raszkowski

OVERVIEW AND COMMENTARY

1. Indication, Formulation, and Preclinical Data

Ibutilide fumarate is a new molecular entity with predominantly class III antiarrhythmic properties. The sponsor proposes that the drug be indicated for the rapid conversion of atrial fibrillation or atrial flutter to sinus rhythm. The drug is formulated as an isotonic, sterile, aqueous solution and is intended to be infused intravenously. Ibutilide fumarate has one chiral center. It is a racemic mixture containing an equal ratio of the two enantiomers: U-82208 (dextrorotatory) and U-82209 (levorotatory).[1]

In isolated adult cardiac myocytes, ibutilide fumarate prolongs the duration of the action potential. In vivo, it increases the atrial and ventricular effective refractory periods. The antiarrhythmic effects of ibutilide are thought to be due to these electrophysiological properties. However, in contrast to most other class III antiarrhythmic agents (which block outward potassium currents), voltage clamp studies show that ibutilide activates a slow inward current that is carried mostly by sodium and calcium.[2]

2. Organization, Scope, and Pagination of this Review

Briefly, this review summarizes nine clinical pharmacology studies. Final study reports for seven of these studies were submitted with the original NDA on 27 October 1994. Final study reports for two electrophysiological studies were submitted to the NDA on 12 April 1995.[3]

The preceding "Overall Table of Contents" gives the location, in the appendices, for the reviews of each of these studies (see appendix "A" through appendix "I"). Each appendix, and therefore each study, has a detailed "Table of Contents." References to a page number within each appendix refers only to pages within that particular study. "Reviewer's Comments" may be found at the end of the review for each of these studies. As this review is intended to complement those of the biopharmaceutical reviewer and of the safety reviewer, pharmacokinetic data and safety data are summarized for each study.

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1 Note: U-82208F and U-82209E are the hemifumarate salts of the enantiomers of ibutilide. For example, see protocol P-7550-0008 in Appendix E.

2 For details, see the preclinical review by the pharmacologist.

3 Submitted as amendment number 31.

As outlined in the preceding "Overall Table of Contents," the nine studies can be broken down into four groups:

- Two studies were double-blind, placebo-controlled, dose escalation trials that were performed in healthy men (Protocol P-7550-0001: ten-minute infusion, and Protocol P-7550-0001: eight-hour infusion).

- Two electrophysiological studies were completed. The first was a randomized, placebo-controlled study that evaluated the electrophysiological and hemodynamic effects of escalating doses of ibutilide in patients undergoing invasive electrophysiological evaluation (Protocol P-7550-0007). The second was an open-label study of the electrophysiological effects of escalating doses of ibutilide in patients with hemodynamically stable ventricular tachycardia (VT). This study was not randomized and had no placebo control (Protocol P-7550-0013).

- Three single-dose pharmacokinetic (PK)/pharmacodynamic (PD) studies were performed. One study compared the PK and PD of a single dose of racemic ibutilide fumarate with single doses of its two enantiomers: U-92,208E and U-92,209E. This study was performed in healthy men and was a randomized, double-blind, three-way crossover study (Protocol P-7550-0008). A second study evaluated the metabolism and excretion of a single dose of ^{14}C-ibutilide fumarate in healthy men. This was an open-label study with no concurrent control group (e.g., no placebo group) and no randomization (Protocol P-7550-0016). A third study compared the PK and PD of a single dose of ibutilide fumarate in healthy men and women. This also was an open-label study with no concurrent control group (e.g., no placebo group) and no randomization (Protocol P-7550-0022)

- Two studies were terminated. One study was discontinued after one patient had participated (Protocol P-7550-0004). Another study was discontinued after two patients were treated under the protocol (Protocol P-7550-0018). Given the limited information available from these two studies, in this overview they will be considered no further.

3. Hemodynamics

Three studies evaluated the hemodynamic effects of ibutilide. In the subjects included in these studies and at the dosages studied, ibutilide did not appear to have direct adverse effects on cardiovascular function (e.g., direct depression of myocardial function by negative inotropic effects).

The best hemodynamic data were obtained in one of the electrophysiology studies (Protocol P-7550-0007). Invasive hemodynamic measurements were made of cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure. These parameters did not appear to change from baseline in a consistent dose-related way either in the stratum of patients with a left ventricular ejection fraction (LVEF) less than 35%, in the stratum of patients with a LVEF ≥35%, or overall when these two strata were combined. These parameters generally changed from baseline to a similar extent in patients treated with ibutilide and in patients treated with placebo.

Although patients with a LVEF <35% were included in this trial, reliance on this surrogate physiological measure as a measure of clinically-meaningful cardiac impairment overstates the extent of cardiac disease in this patient sample. Patients with congestive heart failure, angina pectoris, hypertension, or a history of drug-induced torsades de pointes were excluded from participation. Patients were required to be hemodynamically stable, to have 1:1 atrioventricular (AV) conduction, and a baseline QTc of less than 0.440 sec[k].

Consequently, the generalizeability of this trial is limited to relatively healthy patients, even if it included patients with a LVEF <35%. This lack of data on the hemodynamic effects of intravenous ibutilide in patients with substantial mechanical cardiac impairment or with substantial electrical cardiac impairment are major shortcomings both for this trial and for the overall development program of the drug. For example, it would be of great practical value to know how patients with congestive heart failure or patients with advanced degrees of heart block respond to or handle the drug. In the absence of these data, the pharmacodynamic effects, the safety, and the effectiveness of ibutilide in these populations remain largely speculative, as do instructions for use in these populations.

In a second study, impedance plethysmography was used to measure changes in cardiac output, ventricular ejection time, and ejection velocity index (Protocol P-7550-0001: eight hour infusion). During the eight-hour infusion, changes in these parameters in the ibutilide-treatment groups were similar to changes in the placebo group. However the sponsor seeks to obtain approval for administration of ibutilide fumarate over ten minutes, not over eight hours as in this protocol. Thus, the immediate relevance of these results to the proposed ten-minute regimen is uncertain. Moreover, the subjects included in the study were all healthy men with normal myocardial function. This is a population in whom adverse cardiovascular effects are less likely to be detected, compared to patients with structural cardiac disease (e.g., after a myocardial infarction) or to patients with mechanical cardiac abnormalities (e.g., congestive heart failure). Finally, the sensitivity, specificity, accuracy, and reproducibility of impedance plethysmography for detection of changes in these hemodynamic indices have not been well characterized.

Similarly, in a third study, impedance plethysmography was used to measure changes in hemodynamic function (Protocol P-7550-0001: ten minute infusion). Although ten minutes is the duration of the infusion in the proposed labeling, the data in this study are inadequate to draw meaningful conclusions about the hemodynamic effects of ibutilide. That is, the small number of subjects in the placebo-comparison group (n=2) restricts the power of any statistical analyses. The ability to detect differences of groups from the placebo group is greatly limited. As with the eight-hour infusion, the subjects included in this study were all healthy men with normal myocardial function. Impedance plethysmography has the limitations listed above.

4. Electrophysiology

Two invasive studies evaluated the electrophysiological effects of ibutilide fumarate (Protocol P-7550-0007 and Protocol P-7550-0013). Four other studies evaluated the effects of ibutilide on the QT and QTc intervals as measured with signal-averaged electrocardiograms (Protocol P-7550-0001: ten-minute infusion; Protocol P-7550-0001: eight-hour infusion; Protocol P-7550-0008, and Protocol P-7550-0022). The remaining studies evaluated the effects of ibutilide on electrocardiographic intervals, particularly the QT and QTc interval, as measured with 12-lead electrocardiograms.

4.1 Invasive electrophysiological assessments

In the two invasive electrophysiological studies (Protocol P-7550-0007 and Protocol P-7550-0013), ibutilide fumarate appeared to depress sinus node function somewhat. In both of these studies, ibutilide fumarate significantly prolonged the maximal sinus node recovery time (maximal SNRT)

at all doses tested.[4] Ibutilide also appeared to prolong the sinus node recovery time (SNRT) and the corrected sinus node recovery times (CSNRT) to some extent in both studies. It prolonged the basic cycle length (BCL) inconsistently in study P-7550-0007 but not in study P-7550-0013. These effects on sinus node function may be of greater significance (i.e., a safety concern) in patients with intrinsically abnormal sinus node function (e.g., sick sinus syndrome), a group that was not systematically evaluated during the development of the drug.

Similarly, in these two studies ibutilide appeared to depress AV nodal function to some extent, but these effects also generally were not marked. Ibutilide prolonged both the AV and VA Wenckebach cycle lengths to a minor degree in both studies, and it also appeared to prolong the AH interval somewhat in study P-7550-0007. As with its effects on sinus node function, ibutilide's effects on AV nodal function may be of greater significance (i.e., a safety concern) in patients with intrinsically abnormal AV nodal function (e.g., advanced degrees of AV block), a group that was not systematically evaluated during the development of the drug.

In these studies and as expected of a class III antiarrhythmic agent, ibutilide significantly prolonged the duration of the atrial and ventricular monophasic action potentials (MAPs), and it significantly increased the atrial and ventricular effective refractory periods (ERPs). In general, these effects were dose-related and were greater at the higher doses of ibutilide. In study P-7550-0013, the changes from baseline of the MAP/ERP ratio at a given paced cycle length were often significantly and positively correlated with the changes from baseline of the MAP/ERP ratio at the other paced cycle lengths.

Ibutilide did not appear to alter HV conduction in either study, and the drug did not appear to alter atrial or ventricular thresholds.

Finally, in study P-7550-0013, ibutilide was evaluated for its ability to inhibit the reinduction of sustained monomorphic ventricular tachycardia (VT). Overall, sustained monomorphic VT could not be reinduced during the ibutilide infusion in 44% (21 of 48) of the evaluable patients. However, this result is difficult to interpret in the absence of a concurrent placebo-control group or, in fact, of *any* concurrent control group. Moreover, any putative effect of ibutilide to prevent the reinduction of sustained monomorphic tachycardia did not show a dose response. That is, the difference in the "success" rate of inhibiting reinduction of VT across the three dose groups did not even remotely approach statistical significance (p=0.8324).

4.2 Signal-Averaged Electrocardiograms (ECGs) and 12-Lead Electrocardiograms

In virtually all of the studies, and as expected of an antiarrhythmic agent with class III antiarrhythmic properties, ibutilide prolonged the QT and QTc intervals. This was demonstrated both in studies that used signal-averaged ECGs to measure intervals as well as in studies using 12-lead ECGs. Generally speaking, prolongation of the QT and QTc intervals appeared to be dose-related. That is, (a) at higher doses, prolongations were generally greater than prolongations at the lower doses; (b) at the higher doses, significant prolongations generally began earlier than prolongations at the lower doses, and; (c) at the higher doses, significant prolongations generally lasted longer than prolongations at the lower doses.

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[4] For background on the meaning of various electrophysiological terms, see the reviews of the two invasive electrophysiology studies in Appendix C (Protocol P-7550-0007) and Appendix D (Protocol P-7550-0013). Background information on each term is given in the corresponding section describing the electrophysiological results.

In the invasive electrophysiological study P-7550-0013, QT intervals were measured with 12-lead ECGs and correlation analyses were performed on electrophysiological data at a paced cycle length (PCL) of 600 msec. At the end of the loading dose, the prolongation of the QTc interval was somewhat related to changes in the duration of the ventricular monophasic action potential (VMAP). Although less correlated, at the end of the loading dose the prolongation of the QTc interval was weakly related to changes in the ventricular effective refractory period (VERP). Prolongation of the QTc interval did not generally appear to be correlated with changes in the atrial effective refractory period (AERP).

Ibutilide fumarate does not appear to have marked effects on the PR interval or on QRS duration, at least when measured with relatively insensitive 12-lead electrocardiograms.

4.3 Commentary on the Significance of Prolongation of the QT Interval and the QTc Interval

During the clinical development of ibutilide fumarate, the sponsor generally excluded subjects (or patients) from participation in trials if their baseline QTc interval was greater than the upper limit of normal (e.g., 0.440 sec*). Thus, baseline QTc intervals were used as (unvalidated) predictors of adverse events.

Similarly, during the trials subjects (or patients) were also discontinued from the studies if their QTc interval increased from baseline, regardless if they were experiencing a concurrent adverse event or not. Thus, changes from baseline of the QTc interval were also used as surrogate markers for adverse drug events. For example, dose escalation studies in healthy men were discontinued not at doses that caused adverse events, but rather because of QTc prolongation. Thus, dose exploration with ibutilide fumarate may have been terminated prematurely. (i.e., Protocol P-7550-0001: ten-minute infusion, and Protocol P-7550-0001: eight-hour infusion).

Certainly, one of the most serious adverse effects of drugs that prolong the QTc interval is the possible development of polymorphic ventricular tachycardias (e.g., torsades de pointes). However, some drugs that markedly prolong the QTc interval, such as amiodarone, are not associated with a greatly increased risk of torsades de pointes. Conversely, some drugs that are associated with a high incidence of torsades de pointes prolong the QTc only slightly. Furthermore, for those drugs in which QTc prolongation is associated with torsades de pointes, the relationship is not necessarily causal. In those cases, prolongation of the QTc interval may instead be a marker of a drug effect that also increases the likelihood of torsades de pointes.

Stated differently, the length of the baseline QTc interval and the change from baseline of the QTc interval are often not good quantitative predictors of the likelihood of adverse events like torsades de pointes. Prolongation of the QTc interval does seem to have some relationship to these adverse events, but the relationship is not necessarily causal, direct, or quantitative. Hence, parameters that correlate with lengthening of the QTc interval (e.g., such as plasma concentrations of drug) may not be good predictors of the adverse or beneficial effects of the drug. This lack of predictive ability is one of the primary problems with the use of surrogate endpoints as markers for clinically-meaningful drug effects.

This may be the case with ibutilide. Although the drug prolongs the QTc interval and increases the likelihood of polymorphic ventricular tachycardia, the relationship between these two parameters, if any, is unclear. Thus with ibutilide neither the length of the baseline QTc interval, nor the change in the length of the interval from baseline, are particularly predictive of either the drug's benefit (i.e., the termination of atrial fibrillation/flutter) nor of the drug's risks (e.g., induction of polymorphic ventricular tachycardia). Thus, sophisticated analyses based on QTc-interval

prolongation (e.g., Emax models) are not particularly helpful in the overall risk/benefit assessment of the drug.

5. Pharmacokinetics[5]

In healthy volunteers, ibutilide has a high systemic plasma clearance (averaging approximately 29 ml min^{-1}) which approximates hepatic blood flow, and it has a large volume of distribution (averaging approximately 11 l/kg). The apparent elimination half-life is approximately six hours. The pharmacokinetics of ibutilide appear to be linear with respect to the administered dose over the range of 0.01 mg/kg to 0.10 mg/kg.[6]

As evaluated in study P-7550-0008, the two enantiomers of ibutilide have clearances and volumes of distribution that are both similar to each other and to those of ibutilide fumarate (the racemic mixture). There was no evidence of in vivo racemization as only the administered enantiomer was detected in plasma following treatment with either U-82,208E or U-82,209E.

As evaluated in study P-7550-0022, no differences in pharmacokinetic parameter estimates were found between male and female subjects. In that study, after a ten-minute infusion of ibutilide fumarate (0.01 mg/kg), postinfusion plasma concentrations of the (+)- and (-)-enantiomers as well as total racemic ibutilide decreased rapidly with at least two rapid-distribution phases. Nearly identical concentrations of U-82,208E and U-82,209E were achieved after dosing in both male and female subjects. As in study P-7550-0008, racemic ibutilide and its enantiomers exhibited similar pharmacokinetic properties; all components demonstrated a high systemic clearance, approximating liver blood flow and a large volume of distribution.

As evaluated in study P-7550-0016, within seven days of a single 1-mg dose of radiolabeled ibutilide in healthy men, all of the radiolabeled dose was accounted for after excretion in urine and feces. On average, 82% ± 2% and 19% ± 1% of the dose was recovered in urine and feces respectively. No radioactivity was detected in expired air samples. Eight ibutilide-related metabolites (previously identified in rat, dog, and monkey) as well as unchanged ibutilide were detected in urine and accounted for 89% ± 4% of the radioactivity present in urine. Six metabolites and unchanged ibutilide were detected in fecal samples from the two subjects evaluated, and accounted for 97% of the radioactivity present in the fecal samples. Low levels of radioactivity were measured in blood an plasma. Unchanged ibutilide accounted for the radioactivity in plasma at early time points, and four metabolites were detected in later samples.

The sponsor concluded that metabolism of ibutilide in humans appears to proceed primarily through a pathway consisting of ϖ-oxidation of the heptyl side-chain followed by β-oxidation of the heptyl side-chain of ibutilide. Initial (ϖ-1)-oxidation of the heptyl side-chain and the associated one-carbon-loss pathway is a less significant metabolism pathway in humans. Metabolites resulting from these degradative oxidation processes and unchanged ibutilide are then eliminated principally through urinary excretion (about 82% of the dose).

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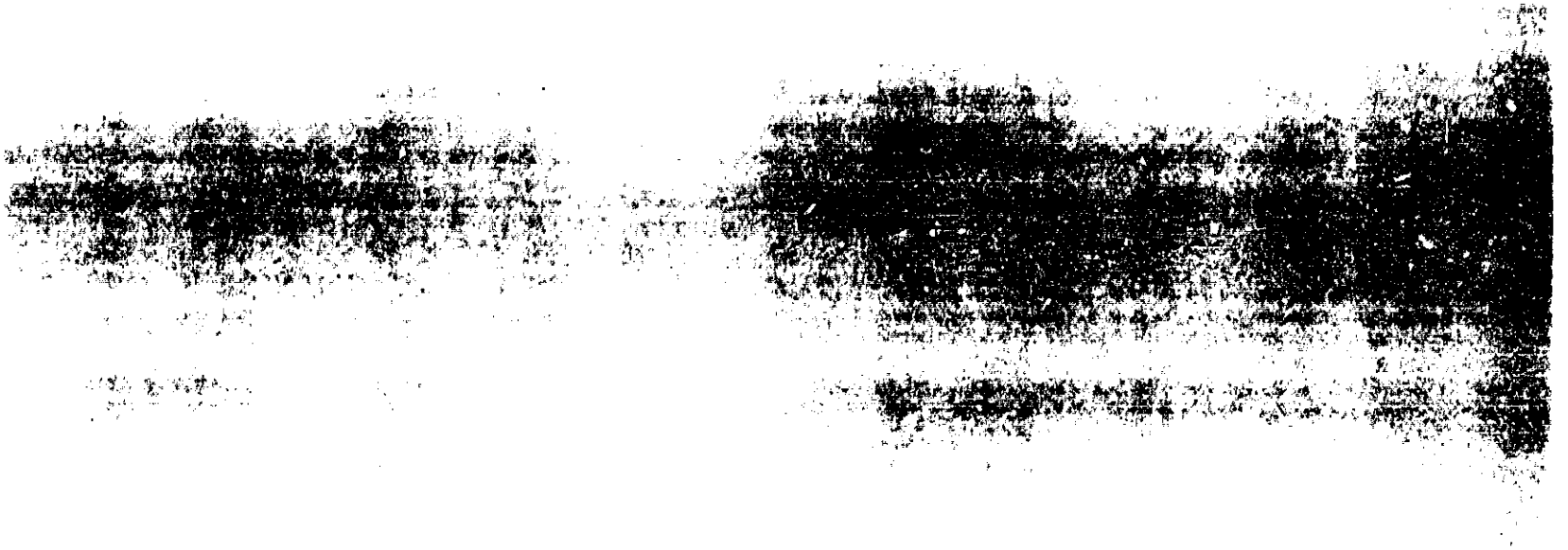
[5] For a complete assessment of the pharmacokinetic results, see the evaluation by the pharmaceutical reviewer.

[6] See Protocol P-7550-0001: ten-minute infusion and Protocol P-7550-0001: eight-hour infusion.



APPENDIX A

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Double-Blind, Placebo-Controlled, Dose-Escalating Tolerance Study of a Ten-Minute Intravenous Infusion of Ibutilide Fumarate (U-70,226E) in Normal Male Volunteers (Protocol BC843, P-7550-0001).

1. DESCRIPTION OF THE STUDY

1.1 Title

Double-Blind, Placebo-Controlled, Dose-Escalating Tolerance Study of a Ten-Minute Intravenous Infusion of Ibutilide Fumarate (U-70226E) in Normal Male Volunteers **(Protocol BC843, P-7550-0001).**

1.2 Objectives

1.2.1 Primary Objective

As specified in the protocol, the primary objective of this study was to determine the tolerance of single intravenous doses of ibutilide fumarate.

1.2.2 Secondary Objectives

The study had two prespecified secondary objectives:

- to determine the pharmacokinetics of single intravenous doses of ibutilide fumarate, and;
- to determine the effect of ibutilide fumarate on the QTc interval of the ECG

1.3 Experimental Design

This was a double-blind, placebo-controlled study of escalating doses of ibutilide that was performed at the Upjohn Research Clinic. As originally planned, the effects of single intravenous doses of ibutilide were to be evaluated in six sequential dosing groups (0.001, 0.003, 0.01, 0.03, 0.1, and 0.25 mg/kg). Each dosing group was to be comprised of 11 normal, healthy men between 18 and 50 years of age, so that up to 66 volunteers were to be enrolled. Within each dosing group, the men were to be randomly allocated to treatment with a single, ten-minute infusion of either ibutilide fumarate (n=8) or of placebo (n=3). As the study was actually conducted, however, four sequential dosing groups (0.001, 0.003, 0.01, and 0.03 mg/kg) were evaluated. Use of concomitant medications was forbidden, whereas smoking was permitted.

1.4 Drug Administration

Ibutilide (Lot #25,561) was supplied in 10 ml clear glass ampules in a concentration of 2.5 mg/ml. The solution was isotonic and buffered with acetate to a pH of 4.6. The solution was diluted to a volume of 10 ml and infused intravenously over ten minutes. A standard diluent was not specified. Matching ampules of placebo containing only the vehicle were also supplied.

1.5 Evaluations

Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- Blood for safety laboratories (hematology, chemistry) and urine for complete urinalysis
- Blood for prolactin levels
- Blood samples for drug levels

- Urine for drug levels
- Signal-averaged ECGs (for assessment of QTc=QT/√RR)
- Impedance plethysmography (for assessment of ventricular ejection time, ejection velocity index, and cardiac output)
- Twelve-lead electrocardiograms (ECGs)
- Twenty-four hour electrocardiographic (Holter) monitoring
- Vital signs (pulse, respiration, temperature) and supine blood pressure
- Medical events

The subjects were also monitored continuously by cardiac telemetry. See the "Activities Schedule" on page 3 for a summary of study evaluations.

Activities Schedule

Activity	Screen	(-24 Hours)	Predose	Hours														
				0	.17	.25	0.5	0.75	1	2	3	4	6	8	10	12	24	48
History/Physical Exam	x																	
Cardiac Telemetry		←																→
Screening/Safety Labs	x		x									x					x	x
Prolactin Levels			x						x	x		x					x	
Plasma Drug Levels			x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Urine for Drug Levels		←																→
Signal Averaged ECG's			x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs		x	x		x		x		x	x		x		x		x	x	
Medical Events			x		x		x		x	x		x		x			x	
Urine Drug Screen	x	x																

2. RESULTS

2.1 Disposition of Subjects

Forty-three (43) subjects enrolled in the trial. Forty-one (41) subjects completed the ten-minute infusion and the 48-hour follow-up. Two subjects (#8 and #39) were assigned subject numbers but decided not to participate in the study. Two other subjects (#17 and #29) received doses of ibutilide inconsistent with their order of randomization.[1] Explanations for these inconsistencies were not provided by the sponsor.

Number of Subjects in Each Dosing Group

			Ibutilide (mg/kg)				
	Not Dosed	Placebo	0.001	0.003	0.01	0.03	Total
Group 1	1	2	8				11
Group 2		2		8			10
Group 3		3			8		11
Group 4	1	2				8	11
Total	2	9	8	8	8	8	43

2.2 Demographics and Baseline Characteristics

Of the 41 treated subjects, 36 were white, 2 were black, and 3 were of "other" races. The 41 treated subjects had a mean age of 30 years (range: 19 to 48 years), a mean weight of 78.3 kg (54.2 to 78.3 kg), and a mean height of 176.9 cm (156.2 to 190.5 cm). The baseline characteristics of the subjects are summarized in the table on page 5.

[1] Subject #17 should have received 0.003 mg/kg of ibutilide, but instead received 0.01 mg/kg.
Subject #29 should have received 0.01 mg/kg, but instead received 0.03 mg/kg.

Baseline Characteristics of Subjects by Treatment Group

		Ibutilide (mg/kg)			
	Placebo (n=9)	0.001 (n=8)	0.003 (n=8)	0.01 (n=8)	0.03 (n=8)
Race (W/B/O)[a]	9/0/0	8/0/0	7/1/1	8/0/0	5/1/2
Weight (lbs)	185.3	170.4	164.7	169.5	161.75
Blood Pressure (mmHg)					
Systolic	114.7	118.2	111.7	112.1	109.8
Diastolic	67.5	66.2	64.6	61.6	64.5
Pulse (beats/min)	56.9	52.4	55.5	57.2	54.0
12-Lead EKG					
Intervals					
PR (sec)	0.17	0.16	0.17	0.17	0.17
QRS (sec)	0.10	0.10	0.10	0.10	0.10
QT (sec)	0.41	0.42	0.41	0.41	0.42
heart rate (beats/min)	57.0	54.1	54.4	60.4	57.4
Signal-Averaged EKG					
Intervals					
PR (msec)	142.8	152.6	165.6	167.0	155.9
QRS (msec)	78.8	77.75	77.5	88.75	77.2
QT (msec)	408.1	412.1	399.4	398.1	417.8
QTc ($sec^{\frac{1}{2}}$) x 1000	406.2	385.0	390.1	403.4	398.0
heart rate (beats/min)	60.3	52.5	57.7	62.0	55.1
Impedance Plethysmography					
cardiac output (l/min)	6.72*				5.23**
ejection velocity index (ohm/sec)	1.340*	N/A+	N/A+	N/A+	1.275**
ventricular ejection time (sec)	0.338*				0.344**

[a] Number of subjects by race: W/B/O = White/Black/Other
* n=2
** n=8
\+ not assessed

2.3 PHARMACOKINETIC RESULTS[2]

During the 10-minute infusion, plasma concentrations of ibutilide rose transiently to high levels. Concentrations declined rapidly after the infusion. See the figure on page 7.[3] The sponsor concluded that ibutilide has a high systemic plasma clearance (averaging approximately

[2] For a complete assessment of the pharmacokinetic results, see the evaluation by the biopharmaceutical reviewer.

[3] From NDA page 06/04/18

29 ml min^{-1}/kg), which approximates hepatic blood flow, and that it has a large volume of distribution (averaging approximately 11 l/kg). The sponsor also concluded that the apparent elimination half-life is approximately 6 hours, and that the pharmacokinetics of ibutilide are linear with respect to the administered dose and the duration of the infusion. See the table below (note: this table also includes data from a related study in which ibutilide was infused over 8 hours rather than 10 minutes).[4]

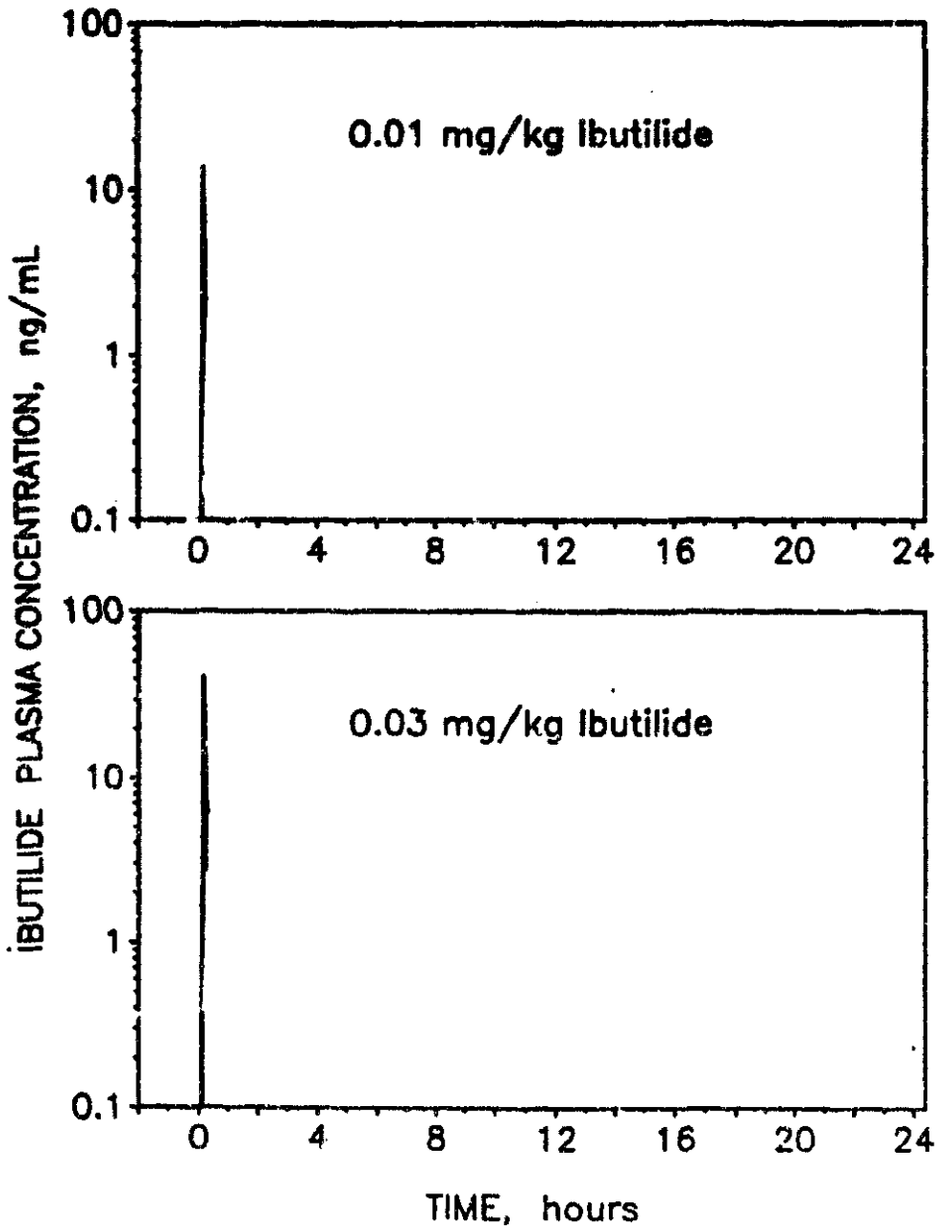
Ibutilide Pharmacokinetic Parameter Estimates [Mean (% CV)] and Statistical Analysis

Dose, mg/kg	0.01	0.03	0.03	0.06	0.10	ANOVA
Infusion Duration	10 min	10 min	8 hours	8 hours	8 hours	p-value
No. of Subjects	8	6	6	5	8	---
C_{max}, ng/mL	8.8 (26%)	38.5 (36%)	2.0 (25%)	3.3 (26%)	5.2 (14%)	0.0001
$AUC_{0-\infty}$, ng*h/mL	5.7 (15%)	18.5 (31%)	21.5 (29%)	36.3 (27%)	55.3 (17%)	0.0001
CL, mL min^{-1}/kg	29.8 (17%)	29.7 (32%)	24.5 (22%)	29.1 (22%)	30.9 (16%)	0.4709
V_{ss}, L/kg	11.5 (25%)	13.7 (45%)	9.6 (28%)	11.8 (35%)	10.5 (24%)	0.3339
Half-life, hours	5.9	6.9	6.1	6.7	5.7	0.3108*

* ANOVA p-value from comparison of the elimination rate constant values.

[4] From NDA page 06/04/14

Figure 2A. Composite Plots of Individual Subject Ibutilide Plasma Concentrations Following 10-minute Intravenous Infusion of Ibutilide



2.4 PHARMACODYNAMIC RESULTS

2.4.1 Blood pressure and pulse

Data for blood pressure and pulse were highly variable. As evaluated by analysis of variance, mean changes from baseline (for blood pressure and pulse) were similar among the treatment groups, and did not give any evidence for a drug effect.

2.4.2 Impedance plethysmography

Cardiac output, ejection velocity index, and ventricular ejection time were evaluated in eight subjects in the group receiving 0.03 mg/kg of ibutilide and in two of the subjects in the group receiving placebo. Because of the small size of the placebo-comparison group (n=2), no conclusions can be drawn from the plethysmography data. That is, the near absence of a control group precludes any meaningful conclusions from being drawn.

2.4.3 24-hour electrocardiographic monitoring

All results were recorded as normal. No consistent, statistically-significant changes from baseline were noted across dose levels for maximal heart rate, minimal heart rate, premature ventricular contractions (PVCs), or premature atrial contractions (PACs).

2.4.4 12-lead electrocardiograms

As shown in the table on the next page, the QT interval was significantly prolonged one hour[5] after the beginning of the infusion in the 0.003, 0.01, and 0.03 mg/kg dose groups. The mean increases from baseline in these groups, respectively, were 0.02, 0.06, and 0.15 sec. By comparison, the mean increase in the QT interval in the placebo group at one hour was 0.01 sec. The PR and QRS intervals did not change in any consistent way as the dose of ibutilide was increased.

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[5] 12-lead ECGs were obtained at baseline and at 1 and 24 hours.

Protocol EC861 (P7550/5001); U-70,226F
Basic Statistics on Change from Baseline - ECG Intervals

QT Interval

		N	Baseline	Mean Change	Standard Error	P-value*
Group (mg/kg)	Studytime					
.001	Hour 1	8	0.42	0.00	0.01	
	Hour 24	8	0.42	-0.01	0.01	
.005	Hour 1	8	0.41	0.02	0.01	0.007
	Hour 24	8	0.41	-0.01	0.01	
.01	Hour 1	8	0.41	0.04	0.01	0.000
	Hour 24	8	0.41	0.03	0.01	
.03	Hour 1	8	0.42	0.15	0.02	0.000
	Hour 24	8	0.42	0.00	0.01	
Placebo	Hour 1	9	0.41	0.01	0.00	0.065
	Hour 24	9	0.41	0.01	0.01	

2.4.5 Signal-averaged electrocardiograms

Of the parameters analyzed on the signal-averaged electrocardiograms (PR, QRS, QT and QTc intervals and heart rate), only the QT and QTc intervals showed consistent significant changes from baseline after drug administration. The table on the next page summarizes the changes from baseline in the QTc interval by time for each dose group. Values with a statistically significant ($p<0.05$) change from baseline are denoted with an asterisk. Baseline values are shown in the table on page 5.

At 30 minutes in the 0.01 and 0.03 mg/kg groups, the QTc interval had increased from baseline on average by 13% and 43%, respectively. The greatest QTc prolongation was observed at the additional measurement made at the end of the 0.03 mg/kg infusion (10 min); at that time the mean increase in the QTc interval was 0.201 sec* (50%) over baseline.

As shown by (1) analysis of variance (ANOVA) for differences among dose levels, and (2) regression analysis to test for dose response, ibutilide prolonged the QT and QTc intervals for at least six hours after the beginning of the infusion. The PR and QRS intervals were not affected. See the tables on page 12.

Pair-wise comparisons to test for differences between each dose level also showed that the higher doses of ibutilide (0.01 and 0.03 mg/kg) consistently prolong the QTc interval. The figure on page 13 shows absolute values of the QTc interval at different doses, and the figure on page 14 shows changes of the QTc interval from baseline at different doses. Also, changes from baseline in the QTc interval are shown in the table on page 14.

MEAN CHANGE FROM BASELINE IN QTc INTERVAL (msec) BY TIME AND DOSE GROUP

	0.001 mg/kg	0.003 mg/kg	0.01 mg/kg	0.03 mg/kg	Placebo
Min 30	34	23*	74*	172*	-15
Hour 1	22	21*	46*	117*	-6
Hour 2	28*	9	39*	93*	-11
Hour 3	31	8	21*	53*	-14
Hour 4	19*	-1	11	37*	-15
Hour 6	14*	8	12	48*	2
Hour 8	12	9	24*	22*	7
Hour 10	26*	-6	17*	6	8
Hour 12	19*	10	6	23	2
Hour 24	10	1	10	3	1

Summary of AOV for differences among dose levels.

Variable	Probability Levels			
	PR Interval	QRS Interval	QT Interval	QTc Interval
Baseline	0.196	0.564	0.404	0.197
Change to 30 minutes	0.454	0.394	<0.001	<0.001
Change to 1 hour	0.032	0.772	<0.001	<0.001
Change to 2 hours	0.011	0.467	<0.001	<0.001
Change to 3 hours	0.480	0.988	<0.001	<0.001
Change to 4 hours	0.746	0.220	<0.001	0.003
Change to 6 hours	0.107	0.697	0.036	0.006
Change to 8 hours	0.417	0.980	0.284	0.514
Change to 10 hours	0.339	0.677	0.500	0.151
Change to 12 hours	0.266	0.373	0.125	0.606
Change to 24 hours	0.064	0.669	0.096	0.928

Summary of regression of changes on dose levels.

Variable	Probability Levels			
	PR Interval	QRS Interval	QT Interval	QTc Interval
Change to 30 minutes	0.313	0.950	<0.001	<0.001
Change to 1 hour	0.086	0.773	<0.001	<0.001
Change to 2 hours	0.367	0.388	<0.001	<0.001
Change to 3 hours	0.574	0.903	<0.001	<0.001
Change to 4 hours	0.965	0.759	<0.001	0.007
Change to 6 hours	0.406	0.211	0.002	0.002
Change to 8 hours	0.393	0.501	0.180	0.168
Change to 10 hours	0.088	0.295	0.298	0.690
Change to 12 hours	0.070	0.764	0.831	0.303
Change to 24 hours	0.379	0.325	0.789	0.945

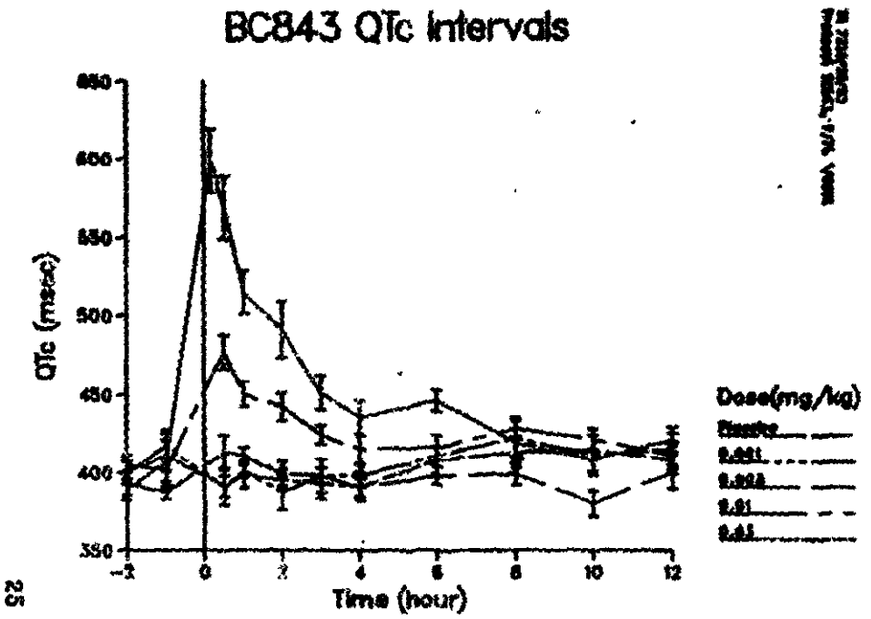
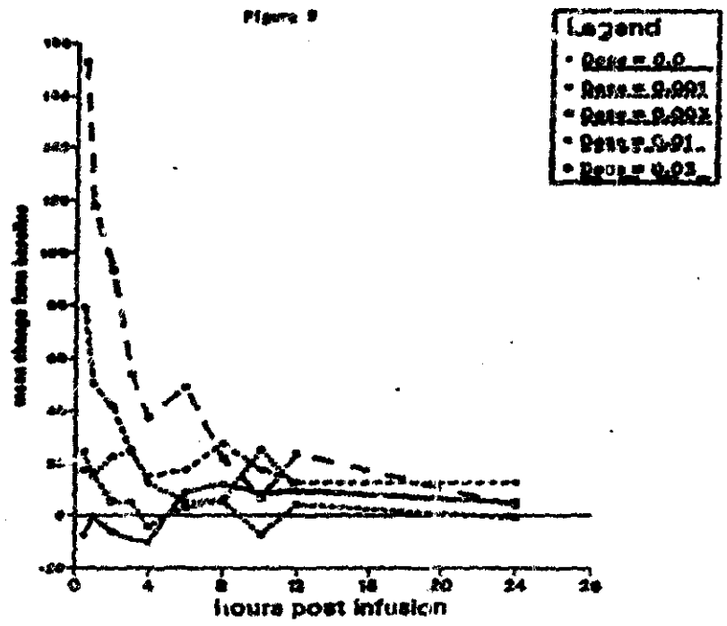

BC843 QTc Intervals
QTc (msec)
Time (hour)
Dose(mg/kg)

Figure 9



BCH43: Mean Change(LS means) from Baseline of Corrected QT Interval

Table 6. Least Squares Means for Change in QTc Interval.

Variable	Dose					
	Placebo	0.001	0.003	0.010	0.030	
Change to 30 minutes	-7.36	24.5	12.4	79.3	172.9	
Change to 1 hour	-0.17	11.0	16.6	50.4	118.0	
Change to 2 hours	-6.11	22.3	5.3	42.0	93.4	
Change to 3 hours	-9.02	15.5	5.0	24.1	53.8	a
Change to 4 hours	-10.16	12.6	-0.1	14.9	37.9	b
Change to 6 hours	2.00	5.2	3.0	17.3	49.3	
Change to 8 hours	11.96	6.0	5.5	27.8	22.3	
Change to 10 hours	2.62	25.3	-7.2	17.7	6.5	c
Change to 12 hours	9.37	9.5	4.1	12.7	23.9	
Change to 24 hours	4.97	5.3	-1.1	12.4	1.5	

Means joined by an underline do not differ at the p=0.03 level.

a - At 3 hours Placebo differs from all others except 0.003; and 0.003 and 0.03 differ; no others differ.

b - At 4 hours 0.03 and 0.001 do not differ.

c - At 10 hours -.001 and 0.003 differ.

2.5 SAFETY RESULTS[6]

No serious adverse events were reported. No patient withdrew from the trial because of an adverse event. None of the adverse events were severe; all were of mild or moderate intensity.

3. REVIEWER'S COMMENTS

This was a randomized, double-blind, placebo controlled study that evaluated the pharmacodynamic effects and the pharmacokinetics of 10-minute infusions of ibutilide fumarate in healthy men. Forty-one (41) subjects were randomly allocated to treatment in sequential groups with either escalating doses ibutilide fumarate 0.001 mg/kg (n=8), 0.003 mg/kg (n=8), 0.01 mg/kg (n=8), or 0.03 mg/kg (n=8) or to treatment with placebo (pooled n=9). Two subjects were assigned numbers but decided not to participate in the study.

General: The design of this study was adequate to obtain reliable pharmacokinetic, pharmacodynamic, and safety data for the studied population. Of the 41 treated subjects, 36 (87.8%) were white, 2 (4.9%) were black, and 3 (7.3%) were of "other" races. Only healthy men took part in this "phase I" study design, women, elderly subjects, and pediatric subjects were excluded. Hence, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to patients with different demographic characteristics (e.g., subjects with age, sex, or racial differences), with cardiac abnormalities (e.g., structural, mechanical, or electrical abnormalities), or with impaired function of other organs (e.g., renal or hepatic insufficiency).

The different doses of ibutilide were evaluated sequentially, rather than concurrently. Thus, effects of the drug may be confounded with the effects of time (i.e., "period effects").

Dose exploration: As outlined in the original protocol, the sponsor originally planned not only to study doses of 0.001, 0.003, 0.01, and 0.03 mg/kg, but also planned to evaluate doses of 0.1 mg/kg and 0.25 mg/kg. However, as the study was performed, the effects of these two higher doses were not evaluated--presumably because the QT and QTc intervals became prolonged when the lower doses were administered to the subjects. Thus, the effects and tolerability of 10-minute infusions greater than 0.03 mg/kg remain unknown. The failure to explore the effects of these higher doses has at least two consequences:

- possible associations of QTc prolongation with arrhythmogenesis were not assessed;
- at these higher doses, *other* possible pharmacodynamic effects or *other* adverse effects of ibutilide were not evaluated.

Stated differently, any *a priori* definition of what constitutes an "acceptable" increase in the QTc interval is subjective. Increased risks of adverse events don't correlate well with the extent of QT prolongation--especially across classes of drugs. Accordingly, the conclusion that any given prolongation of the QTc interval is detrimental will ultimately be based on observation of the effects of that particular drug. This is especially the case for a new drug with a novel mechanism of action. Whereas ibutilide has electrophysiological actions of a class III antiarrhythmic agent, its primary mechanism of action appears to differ from other class III drugs. That is, ibutilide appears

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[6] Safety issues are discussed comprehensively in Dr. Gordon's review.

to prolong the duration of the action potential by increasing the slow inward current, which is carried by Ca^{++} and Na^{+}, rather than by blocking outward potassium currents.

As stated by others: "Although QT prolongation is unquestionably associated with torsades de pointes, prolongation of the QT or QTc interval is not a strong predictor for the occurrence of this arrhythmia. For example, broad QTc-interval prolongation with bepridil, a drug known to induce torsades de pointes occasionally, does not necessarily lead to arrhythmogenesis. Also, despite highly significant prolongation of the QT interval with amiodarone, this drug seldom causes torsades de pointes."[7]

The sponsor seeks to obtain approval for 10-minute infusions of ibutilide fumarate that are not adjusted for body weight. For reference, then, the following table provides the absolute doses administered to subjects of varying weights in the different treatment groups. The lightest subject in the study weighed 52.7 kg (116.0 lbs), and the heaviest weighed 91.8 kg (202.0 lbs).

Absolute Dose of Ibutilide Fumarate (mg) Received by Subjects
Over Ten Minutes
by Treatment Group and Body Weight*

	Treatment group			
Body weight	0.001 mg/kg	0.003 mg/kg	0.01 mg/kg	0.03 mg/kg
40 kg	0.04	0.12	0.4	1.2
50 kg	0.05	0.15	0.5	1.5
60 kg	0.06	0.18	0.6	1.8
70 kg	0.07	0.21	0.7	2.1
80 kg	0.08	0.24	0.8	2.4
90 kg	0.09	0.27	0.9	2.7
100 kg	0.10	0.30	1.0	3.0
110 kg	0.11	0.33	1.1	3.3
120 kg	0.12	0.36	1.2	3.6
130 kg	0.13	0.39	1.3	3.9

* Shaded cells encompass the range of body weights of subjects included in this trial.

Pharmacokinetics: In this study, ibutilide had a systemic plasma clearance of about 29 ml min^{-1}/kg, which approximates hepatic blood flow. The volume of distribution averaged approximately 11 l/kg), and the mean elimination half-life was about six hours. The sponsor concluded that the pharmacokinetics of ibutilide are linear with respect to dose.

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[7] Funck-Bretano C and Jaillon P. Rate-Corrected QT Interval: Techniques and Limitations. Am J Cardiol 1993;72:17B-22B.

Pharmacodynamics: As assessed with both 12-lead and signal-averaged electrocardiograms, the principal pharmacodynamic effect of ibutilide was to prolong the QT and $_{QT_c}$ intervals, consistent with its characterization as a Class III antiarrhythmic agent. Prolongation of these intervals appeared to be dose-related. Maximal prolongation occurred within the first hour following ibutilide administration, and the effect persisted for about six hours. Ibutilide did not appear to have consistent effects on the PR or QRS intervals.

Cardiac output, ejection velocity index, and ventricular ejection time were evaluated by impedance plethysmography in some subjects. No meaningful conclusions can be made about the effects of ibutilide on these parameters because of the small number of subjects in the placebo-comparison group with these evaluations (n=2). Furthermore, the sensitivity, specificity, accuracy, and reproducibility of impedance plethysmography have not been well characterized for the assessment of changes in these cardiac indices.

Safety: No serious adverse events were reported. No patient withdrew from the trial because of an adverse event. None of the adverse events were severe, all were of mild or moderate intensity.

APPENDIX B

TABLE OF CONTENTS

Double-Blind, Placebo-Controlled, Dose-Escalating Tolerance Study of an Eight-Hour Intravenous Infusion of Ibutilide Fumarate (U-70226E) in Normal Male Volunteers (Protocol BC843, P-7550-0001).

1. DESCRIPTION OF THE STUDY

1.1 Title

Double-Blind, Placebo-Controlled, Dose-Escalating Tolerance Study of an Eight-Hour Intravenous Infusion of Ibutilide Fumarate (U-70226E) in Normal Male Volunteers **(Protocol BC843, P-7550-0001).**

1.2 Objectives

1.2.1 Primary Objective

As specified in the protocol, the primary objective of this study was to determine the tolerance of single intravenous doses of ibutilide fumarate.

1.2.2 Secondary Objectives

The study had two prespecified secondary objectives:

- to determine the pharmacokinetics of single intravenous doses of ibutilide fumarate, and;
- to determine the effect of ibutilide fumarate on the QTc interval of the ECG

1.3 Experimental Design

This study was conducted according to Protocol BC843, P-7550-0001. That protocol was amended to allow for an eight-hour infusion at doses of 0.01, 0.03, 0.06, 0.10, 0.15, and 0.25 mg/kg. Data for these subjects are presented here.

1.4 Drug Administration

Ibutilide (Lot #25,561) was supplied in 10 ml clear glass ampules in a concentration of 2.5 mg/ml. The solution was isotonic and buffered with acetate to a pH of 4.6. The solution was infused intravenously over eight hours. A standard diluent was not specified. Matching ampules of placebo containing only the vehicle were also supplied.

1.5 Evaluations

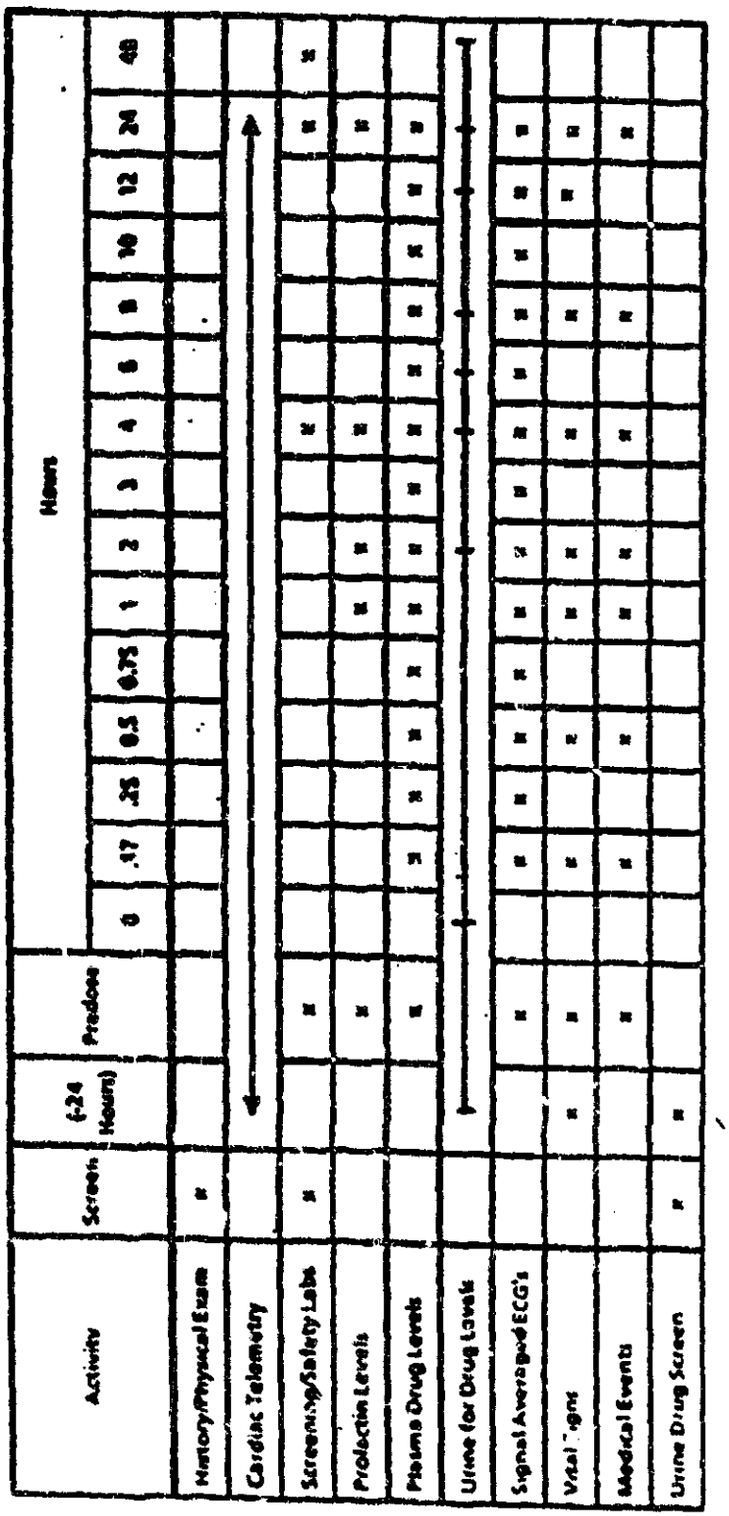
Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- Blood for safety laboratories (hematology, chemistry) and urine for complete urinalysis
- Blood for prolactin levels
- Blood samples for drug levels
- Urine for drug levels
- Signal-averaged ECGs (for assessment of QTc=QT/√RR)
- Impedance plethysmography (for assessment of ventricular ejection time, ejection velocity index, and cardiac output)
- Twelve-lead electrocardiograms (ECGs)
- Twenty-four hour electrocardiographic (Holter) monitoring

- Vital signs (pulse, respiration, temperature) and supine blood pressure
- Medical events

The subjects were also monitored continuously by cardiac telemetry. See the "Activities Schedule" on the next page for a summary of study evaluations.

Activities Schedule



Activity	Screen	(-24 Hours)	Predose	Hours																				
				0	.17	.25	0.5	0.75	1	2	3	4	6	8	10	12	24	48
History/Physical Exam	x																	
Cardiac Telemetry		↔																
Screening/Safety Labs	x		x									x					x	
Prolactin Levels			x						x	x		x					x	
Plasma Drug Levels			x			x	x	x	x	x	x	x	x	x	x	x	x	
Urine for Drug Levels		↔																
Signal Averaged ECG's			x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs		x	x		x		x		x	x		x	x	x		x	x	
Medical Events			x		x		x		x	x		x	x	x			x	
Urine Drug Screen	x	x																

2. RESULTS

2.1 Disposition of Subjects

Thirty-nine (39) subjects enrolled in the trial. Thirty-eight (38) subjects completed the eight-hour infusion and the 48-hour follow-up. One subject (#51) was assigned a number but decided not to participate in the study.

Number of Subjects in Each Dosing Group

			Ibutilide (mg/kg)				
	Not Dosed	Placebo	0.01	0.03	0.06	0.10	Total
Group 1	1	1	6				8
Group 2		3		6			9
Group 3		3			8		11
Group 4		3				8	11
Total	1	10	6	6	8	8	39

2.2 Demographics and Baseline Characteristics

Of the 38 treated subjects, 36 were white, 1 was black, and 1 was of an "other" race. The 38 treated subjects had a mean age of 25 years (range: 18 to 50 years), a mean weight of 76.3 kg (62.0 to 99.5 kg), and a mean height of 178.0 cm (163.8 to 193.0 cm). The baseline characteristics of the subjects are summarized in the table on the next page.

2.3 PHARMACOKINETIC RESULTS[1]

The sponsor states that during the 8-hour infusion, plasma concentrations of ibutilide approached steady-state conditions. Concentrations declined rapidly after the infusion. See the figure on page 7.[2] The sponsor concluded that ibutilide has a high systemic plasma clearance (averaging approximately 29 ml min^{-1}/kg), which approximates hepatic blood flow, and that it has a large volume of distribution (averaging approximately 11 l/kg). The sponsor also concluded that the apparent elimination half-life is approximately 6 hours, and that the pharmacokinetics of ibutilide are linear with respect to both the administered dose and the duration of the infusion. See the table on page 6 (note: this table also includes data from a related study in which ibutilide was infused over 10 minutes rather than 8 hours).[3]

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[1] For a complete assessment of the pharmacokinetic results, see the evaluation by the biopharmaceutical reviewer.

[2] From NDA page 06/04/10

[3] From NDA page 06/04/14

Baseline Characteristics of Subjects by Treatment Group

		Ibutilide (mg/kg)			
	Placebo (n=10)	0.01 (n=6)	0.03 (n=6)	0.06 (n=6)	0.10 (n=6)
Race (W/B/O)[a]	10/0/0	5/0/1	6/0/0	7/1/0	6/0/0
Weight (lbs)	162.35	177.6	175.8	186.5	153.1
Blood Pressure (mmHg)					
Systolic	118.7	120.4	121.2	114.6	116.4
Diastolic	67.3	68.3	64.4	65.9	69.6
Pulse (beats/min)	56.3	57.25	55.9	57.25	60.1
12-Lead EKG					
Intervals					
PR (sec)	0.16	0.16	0.15	0.16	0.15
QRS (sec)	0.10	0.10	0.11	0.10	0.10
QT (sec)	0.41	0.42	0.42	0.42	0.40
heart rate (beats/min)	59.4	59.2	56.2	56.25	60.5
Signal-Averaged EKG					
Intervals					
PR (msec)	156.9	148.25	136.7	154.6	146.7
QRS (msec)	74.4	78.25	68.9	76.8	66.9
QT (msec)	400.0	410.25	406.8	415.4	395.1
QTc ($sec^{1/2}$) x 1000	387.85	414.6	402.7	396.9	386.0
heart rate (beats/min)	57.15	63.0	59.25	55.4	58.6
Impedance Plethysmography					
cardiac output (l/min)	5.95	5.94	7.06	6.43	6.53
ejection velocity index (ohm/sec)	1.23	1.22	1.55	1.20	1.51
ventricular ejection time (sec)	0.316	0.333	0.330	0.335	0.327

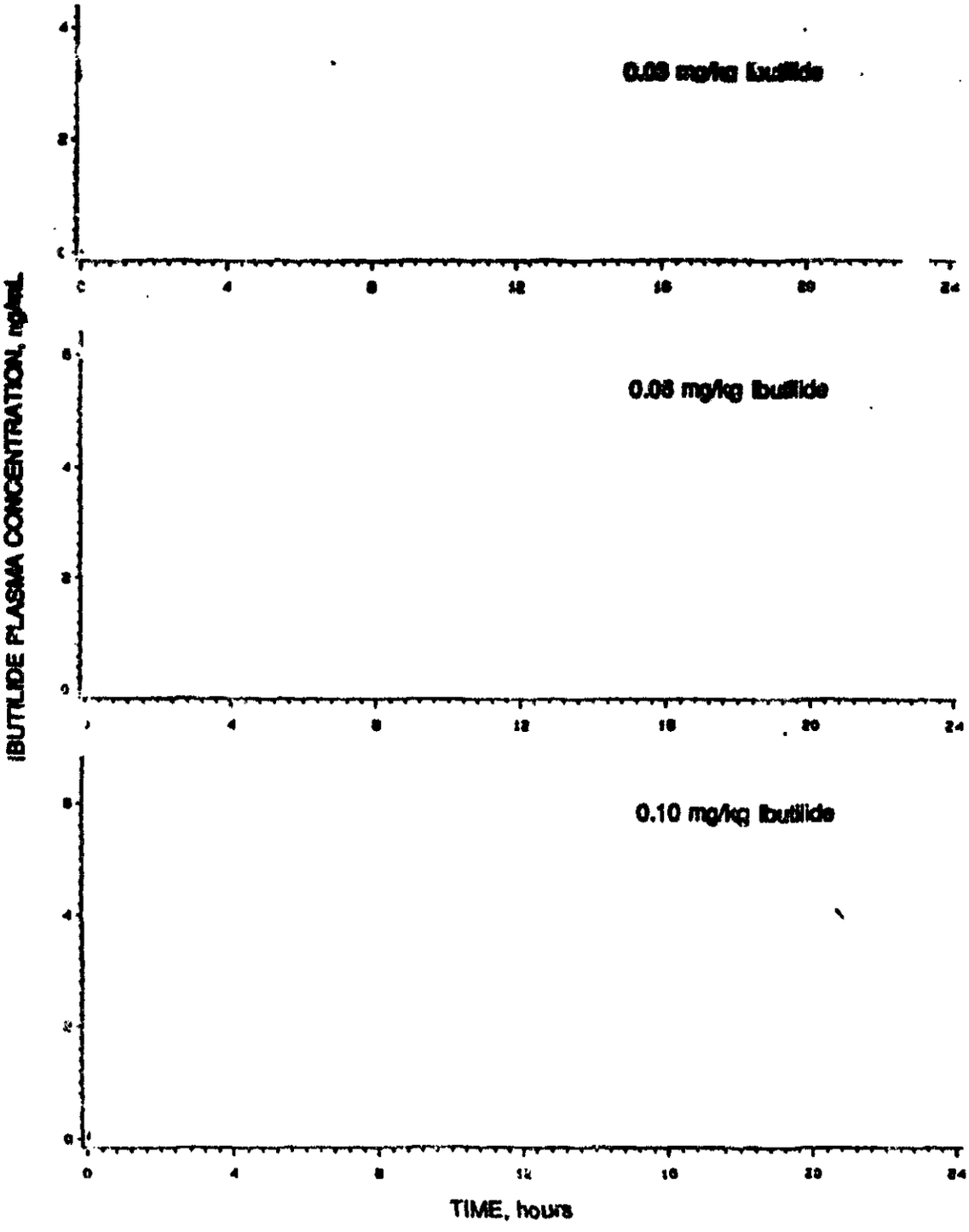
[a] Number of subjects by race: W/B/O = White/Black/Other

Ibutilide Pharmacokinetic Parameter Estimates [Mean (% CV)] and Statistical Analysis

Dose, mg/kg	0.01	0.03	0.03	0.06	0.10	ANOVA
Infusion Duration	10 min	10 min	8 hours	8 hours	8 hours	p-value
No. of Subjects	8	8	6	8	8	---
C_{max}, ng/mL	0.8 (30%)	2.2 (38%)	2.0 (25%)	3.3 (26%)	5.2 (14%)	0.0001
$AUC_{0-\infty}$, ng•h/mL	5.7 (15%)	18.5 (31%)	21.5 (29%)	36.3 (27%)	55.3 (17%)	0.0001
CL, mL min^{-1}/kg	29.8 (17%)	29.7 (32%)	24.5 (22%)	29.1 (22%)	30.9 (16%)	0.4709
V_{ss}, L/kg	11.5 (25%)	13.7 (45%)	9.6 (28%)	11.8 (25%)	10.5 (24%)	0.3339
Half-life, hours	5.9	6.9	6.1	6.7	5.7	0.3106*

* ANOVA p-value from comparison of the elimination rate constant values.

Figure 8B. Composite Plots of Individual Subject Ibutilide Plasma Concentrations Following 8-hour Intravenous Infusion of Ibutilide



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2.4 PHARMACODYNAMIC RESULTS

2.4.1 Blood pressure and pulse

Data for blood pressure and pulse were highly variable. As evaluated by analysis of variance, mean changes from baseline (for blood pressure and pulse) were similar among the treatment groups and did not give any evidence for a drug effect.

2.4.2 Impedance plethysmography

At several times during the eight hours of the infusion, cardiac output increased from baseline significantly more in the groups receiving the two highest doses of ibutilide (0.06 and 0.10 mg/kg) than in the group receiving placebo. However, changes from baseline in ejection velocity index and ventricular ejection fraction in each of the ibutilide-treatment groups were never significantly different from the corresponding changes in the placebo-treatment group.

2.4.3 24-hour electrocardiographic monitoring

All results were recorded as normal. No consistent, statistically-significant changes from baseline were noted across dose levels for maximal heart rate, minimal heart rate, premature ventricular contractions (PVCs), or premature atrial contractions (PACs).

2.4.4 12-lead electrocardiograms

The QT interval was prolonged seven hours[4] into the infusion in the 0.01, 0.03, 0.06, and 0.10 mg/kg dose groups. The mean increases from baseline in these groups, respectively, were 0.01, 0.03, 0.05, and 0.06 sec. The increase in the 0.03 mg/kg dose group was statistically significant, and the increase in the 0.06 mg/kg dose group approached significance (p=0.080). By comparison, the QT interval in the placebo group decreased from baseline by a mean of 0.02 sec, a decrease that was statistically significant. The PR interval, the QRS interval, and the heart rate did not significantly change from baseline in any of the treatment groups.

2.4.5 Signal-averaged electrocardiograms

Of the parameters analyzed on the signal-averaged electrocardiograms (PR, QRS, QT and QTc intervals and heart rate), only the QT and QTc intervals showed consistent, significant, dose-related changes from baseline after drug administration. The table on page 10 summarizes the changes from baseline in the QTc interval by time for each dose group. Values with a statistically significant ($p<0.05$) change from baseline are denoted with an asterisk. Baseline values are shown in the table on page 5.

At the end of the infusion (eight hours), the mean QTc intervals had significantly increased from baseline in the 0.03, 0.06, and 0.10 mg/kg groups by 17%, 23% and 38%, respectively. In contrast, in the placebo group the QTc interval had decreased from baseline by 5% (p=0.081) at eight hours.

Regression analyses provided evidence of a dose response for prolongation of both the uncorrected and corrected QT intervals by ibutilide. Regression analyses were computed for change from

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[4] 12-lead ECGs were obtained at baseline and at 7 and 24 hours.

baseline as a function of dose. The p values for these regression analyses were less than 0.05 at every time point from 1 hour to 16 hours (time zero = the start of the infusion of study drug).

Analysis of variance (and pair-wise comparisons) for differences among dose levels showed that compared to placebo, the three higher doses of ibutilide (0.03, 0.06, and 0.10 mg/kg) each consistently and significantly prolonged the QTc interval. For example, the effect of the highest dose of ibutilide (0.10 mg/kg) remained significantly greater than the effect of placebo from one through 14 hours. The dose of 0.06 mg/kg remained significantly greater than the effect of placebo through 9.5 hours, and the dose of 0.03 mg/kg remained significantly greater through 9.0 hours. Although not at each time point, the 0.01 mg/kg also intermittently prolonged the QTc interval through 8.5 hours when compared to placebo. In contrast to these effects on the QT and QTc intervals, the PR and QRS intervals were not affected differently by ibutilide or placebo.

The figure on page 11 shows absolute values of the QTc interval at different doses, and the figure on page 12 shows changes of the QTc interval from baseline at different doses.

MEAN CHANGE FROM BASELINE FOR QTc INTERVAL (msec) BY TIME AND DOSE GROUP

	0.01 mg/kg	0.03 mg/kg	0.06 mg/kg	0.10 mg/kg	Placebo
Hour 1	3	34*	48*	95*	-6
Hour 2	13	43	80*	129*	-1
Hour 4	-5	47*	67*	119*	-6
Hour 6	26	76*	79*	162*	-5
Hour 7	1	45*	83*	132*	-6
Hour 8	-6	67*	92*	148*	-18
Hour 8, Min 15	-5	50*	80*	134*	-14
Hour 8, Min 30	14	35*	60*	132*	-16
Hour 9	-8	46*	56*	111*	-6
Hour 9, Min 30	11	22*	56*	104*	-11
Hour 10	-2	31*	45*	67*	-4
Hour 11	-1	31	47*	56*	6
Hour 12	18	28	21*	59*	13
Hour 14	9	26	22*	58*	4
Hour 16	-18*	16	16	19*	-2
Hour 20	-5	14	39	20	-7
Hour 24	-24	-8	4	9	0

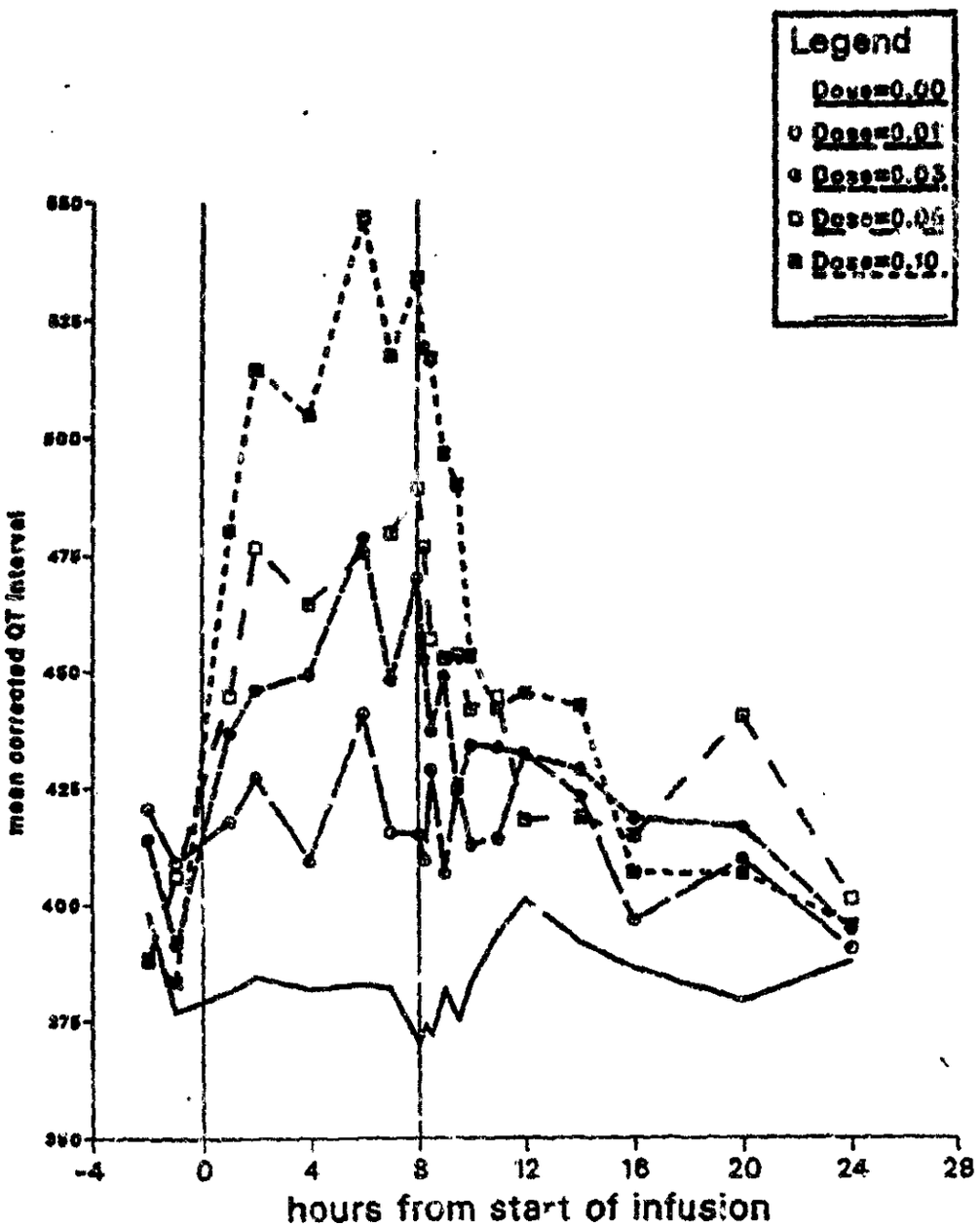

Figure 9 BCB43 (8 hour infusions): Corrected QT Interval
Mean Observed Values

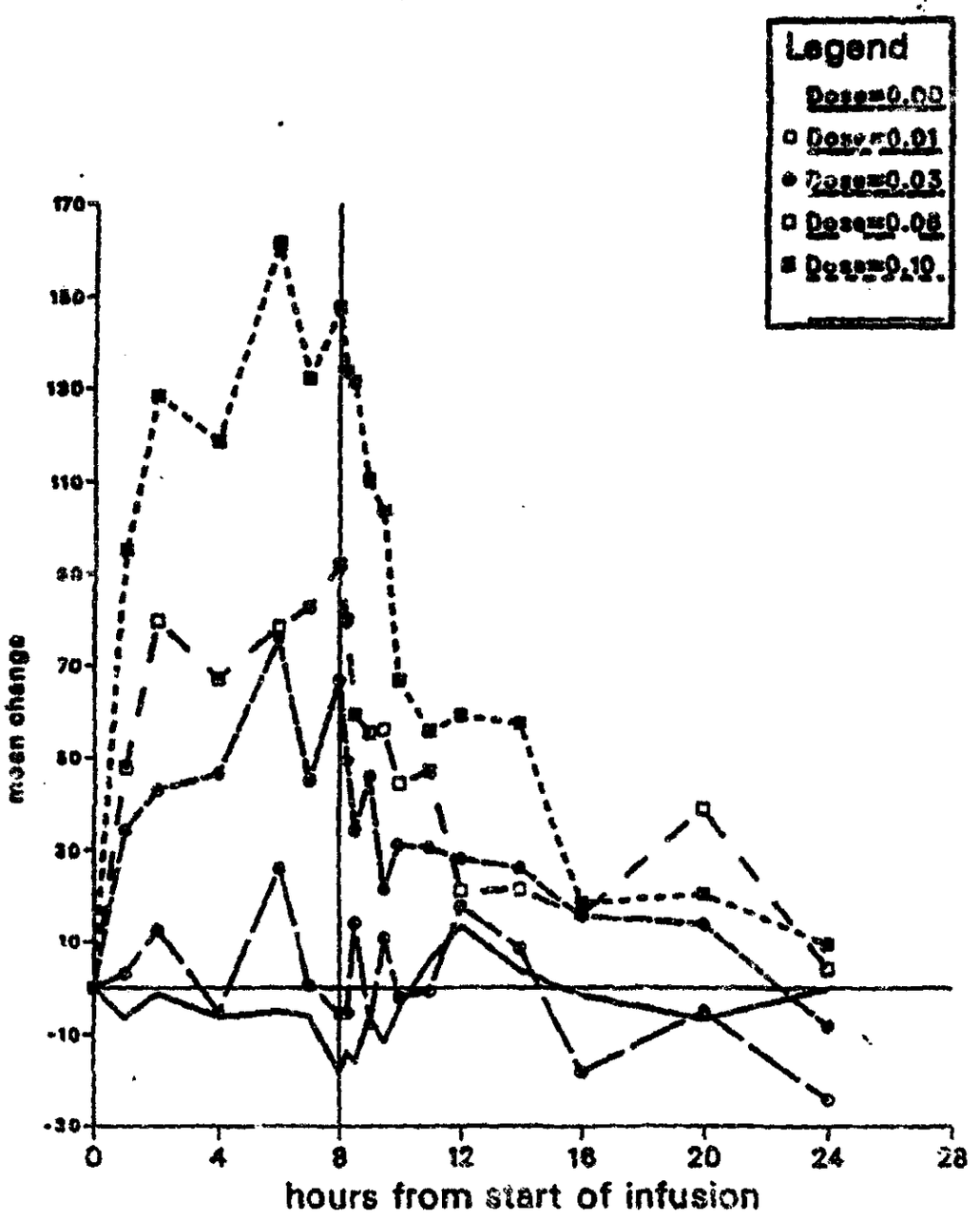

Figure 12 BC843 (8 hour infusion): Corrected QT Interval
Mean Change from Baseline

2.5 SAFETY RESULTS[5]

No serious adverse events were reported. No patient withdrew from the trial because of an adverse event. None of the adverse events were severe; all were of mild or moderate intensity.

3. REVIEWER'S COMMENTS

This was a randomized, double-blind, placebo-controlled study that evaluated the pharmacodynamic effects and the pharmacokinetics of eight-hour infusions of ibutilide fumarate in healthy men. Thirty-eight (38) subjects were randomly allocated to treatment in sequential groups with either escalating doses Ibutilide fumarate 0.01 mg/kg (n=6), 0.03 mg/kg (n=6), 0.06 mg/kg (n=8), or 0.10 mg/kg (n=8) or to treatment with placebo (pooled n=10). An additional subject in the first dose group was assigned a number but decided not to participate in the study.

General: The design of this study was adequate to obtain reliable pharmacokinetic, pharmacodynamic, and safety data for the studied population. Of the 38 treated subjects, 36 (87.8%) were white and 2 (4.9%) were black. Only healthy men took part in this "phase I" study. By design, women, elderly subjects, and pediatric subjects were excluded. Hence, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to patients with different demographic characteristics (e.g., subjects with age, sex, or racial differences), with cardiac abnormalities (e.g., structural, mechanical, or electrical abnormalities), or with impaired function of other organs (e.g., renal or hepatic insufficiency).

The different doses of ibutilide were evaluated sequentially, rather than concurrently. Thus, effects of the drug may be confounded with the effects of time (i.e., "period effects").

Dose exploration: As outlined in the original protocol, the sponsor originally planned not only to study doses of 0.01, 0.03, 0.06, and 0.10 mg/kg, but also planned to evaluate doses of 0.15 mg/kg and 0.25 mg/kg. However, as the study was performed, the effects of these two higher doses were not evaluated–presumabiy because the QT and QTc intervals became prolonged when the lower doses were administered to the subjects. Thus, the effects and tolerability of eight-hour infusions higher than 0.10 mg/kg remain unknown. As was the case with the ten-minute infusion, the failure to explore the effects of these higher doses has at least two consequences:[6]

- possible associations of QTc prolongation with arrhythmogenesis were not assessed;
- at these higher doses, *other* possible pharmacodynamic effects or other adverse effects of ibutilide were not evaluated.

The sponsor seeks to obtain approval for doses of ibutilide fumarate that are not adjusted for body weight. For reference, then, the table below provides the absolute doses administered to subjects of varying weights in the different treatment groups. (Note that the sponsor seeks to obtain approval for the administration of ibutilide fumarate over 10-minutes, not over eight-hours as in this protocol. Hence, the immediate relevance of this study for the proposed 10-minute regimen is

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[5] Safety issues are discussed comprehensively in Dr. Gordon's review.

[6] For additional comments, see the "Reviewer's Comments" (Section 3) of Protocol P-7550-0001 (ten-minute infusion). The Reviewer's Comments begin on page 15 of the review of that study.

uncertain.) The lightest subject in the study weighed 60.9 kg (134 lbs) and the heaviest weighed 98.4 kg (216.5 lbs).

Absolute Dose of Ibutilide Fumarate (mg) Received by Subjects Over Eight Hours by Treatment Group and Body Weight*

	Treatment group			
Body weight	0.01 mg/kg	0.03 mg/kg	0.06 mg/kg	0.10 mg/kg
40 kg	0.4	1.2	2.4	4.0
50 kg	0.5	1.5	3.0	5.0
60 kg	0.6			
70 kg				
80 kg				
90 kg				9.0
100 kg	1.0			10.0
110 kg	1.1	3.3	6.6	11.0
120 kg	1.2	3.6	7.2	12.0
130 kg	1.3	3.9	7.8	13.0

* Shaded cells encompass the range of body weights for subjects included in this trial.

Varying the rate of the infusion: Whereas the evaluation of different durations of ibutilide infusion is desirable (as was done in this study), the duration of the ibutilide infusion was otherwise not systematically assessed in the drug-development program. As noted in my review of "Protocol 0014", the duration of the infusion was not varied during drug development in patients with atrial fibrillation or with atrial flutter.[7] All of these patients with atrial fibrillation or atrial flutter received 10-minute infusions. As stated in that review, the drug was administered relatively quickly over 10 minutes, yet the median and mean times for the successful termination of the arrhythmia were never less than 10 minutes. Hence, the full dose of the drug had already been administered before the majority of patients successfully converted. If the drug had been infused more slowly, then concentration-response relationships might have been demonstrated.

For example, had ibutilide been infused over several hours instead of over 10 minutes in that study, concentration-responses both for conversion of the arrhythmia and for safety might have been demonstrated. Moreover, these concentration-responses might *not* have overlapped: longer infusions might have allowed for a dissociation between the "desirable" effects of ibutilide (i.e.,

[7] Protocol 0014" (P-7550-0014) was one of the major clinical trials submitted in support of efficacy of ibutilide fumarate. See my memorandum dated 22 September 1995, section 4.5, pages 43-44. This memorandum was part of the FDA background package that was sent to the Cardiovascular and Renal Drugs Advisory Committee prior to their meeting on 19 October 1995.

conversion of atrial fibrillation or atrial flutter to sinus rhythm) and the adverse effects of the drug (e.g., proarrhythmia). Had the drug been administered over several hours, similar conversion rates might have been achieved in the absence of as many proarrhythmic events.

Pharmacokinetics: In this study, ibutilide had a systemic plasma clearance of about 29 ml min^{-1}/kg, which approximates hepatic blood flow. The volume of distribution averaged approximately 11 l/kg, and the mean elimination half-life was about six hours. The sponsor concluded that the pharmacokinetics of ibutilide are linear with respect to dose and to the duration of the infusion.

The sponsor's assertion that "during the 8-hour infusion, plasma concentrations of ibutilide approached steady-state conditions" is inaccurate, given an elimination half-life of about six hours. With a half-life of six hours, steady state would be reached in about 18-30 hours (i.e., in 3-5 half-lives).

Pharmacodynamics: As noted immediately above and contrary to the sponsor's assertions, this study did not evaluate the pharmacodynamics of ibutilide at steady state.

As assessed with both 12-lead and signal-averaged electrocardiograms, the principal pharmacodynamic effect of ibutilide was to prolong the QT and QTc intervals, consistent with its characterization as a Class III antiarrhythmic agent. Prolongation of these intervals appeared to be dose-related. Maximal prolongation occurred 6-8 hours into the ibutilide infusion. At the highest dose (0.10 mg/kg) compared to placebo, statistically significant effects persisted for eight hours. Ibutilide did not appear to have consistent effects on the PR or QRS intervals,.

Cardiac output, ejection velocity index, and ventricular ejection time were evaluated by impedance plethysmography. Changes in these parameters in the ibutilide-treatment groups were similar to changes in the placebo group. However, the sponsor seeks to obtain approval for the administration of ibutilide fumarate over 10-minutes, not over eight-hours as in this protocol. Thus, the immediate relevance of these pharmacodynamic results to the proposed 10-minute regimen is uncertain. Furthermore, the sensitivity, specificity, accuracy, and reproducibility of impedance plethysmography have not been well characterized for the assessment of changes in these cardiac indices.

Safety: No serious adverse events were reported. No patient withdrew from the trial because of an adverse event. None of the adverse events were severe, all were of mild or moderate intensity.

APPENDIX C

TABLE OF CONTENTS

Electrophysiologic and Hemodynamic Effects of Intravenous Ibutilide (U-70,226E) in Patients Undergoing Invasive Study (Protocol P-7550-0007; Technical report 7216-65-001).

1. DESCRIPTION OF THE STUDY

1.1 Title

Electrophysiologic and Hemodynamic Effects of Intravenous Ibutilide (U-70,226E) in Patients Undergoing Invasive Study (Protocol P-7550-0007; Technical report 7216-95-001).

1.2 Objectives

1.2.1 Primary Objectives

The four major objectives specified in the protocol were to determine the effects of intravenous ibutilide on the following:

- atrial and ventricular effective refractory periods (ERP) and monophasic action potential (MAP) durations as a function of heart rate
- the relation of the above parameters to the QT interval of the electrocardiogram in patients undergoing electrophysiologic study
- cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure using a Swan-Ganz catheter
- the relationship of the monophasic action potential duration/ERP ratio to cycle length

1.2.2 Secondary Objectives

The study had two prespecified secondary objectives:

- to assess the effects of ibutilide on other standard electrophysiologic parameters including sinus node recovery times and AV conduction intervals
- to correlate the pharmacokinetics of ibutilide with its electrophysiologic effects.

1.3 Experimental Design

This was a placebo-controlled study of escalating doses of intravenous ibutilide (note: the protocol did not specify explicitly whether investigators were to be blinded, but the study report states that, with the exception of the first patient enrolled, the study was double-blind). The study was to be performed at 4-6 clinical centers. The electrophysiologic and hemodynamic effects of increasing doses of intravenous ibutilide were to be evaluated in three sequential dosing groups, each of which was split into two subgroups on the basis of the left ventricular ejection fraction (LVEF).[1] Within each of the dosing groups, the dosing regimen consisted of a 10-minute infusion (i.e., a "loading" dose), followed by a 30-minute infusion (i.e., a "maintenance" infusion). As originally planned, 48 patients were to be enrolled in the study: 24 with a LVEF at least 35%, and 24 with a LVEF of less than 35%. The eight patients within each dosing subgroup were to be randomly

[1] Left ventricular ejection fraction was to be determined by angiography, radionuclide scan, or echocardiography within 30 days prior to the study.

allocated to treatment with ibutilide fumarate (n=6) or with placebo (n=2). The table below describes the treatment scheme.

To be included in the study, patients were required to be between 18 and 80 years of age and to be undergoing invasive electrophysiologic study for any indication. Patients were required to be in normal sinus rhythm and to be hemodynamically stable, to have 1:1 atrioventricular (AV) conduction, normal serum electrolytes, and a baseline of QTc of less than 0.440 sec[a]. Patients were excluded if they had a systolic blood pressure ≤90 mmHg, a diastolic blood pressure ≥105 mmHg, or if they had symptoms of angina, congestive heart failure, or other signs of distress. Patients with a history of drug-induced torsades de pointes were also excluded. The use of class I or class III antiarrhythmic medications was prohibited within five half-lives prior to enrollment.

Planned Study Design

Group A (LVEF≥35%)			Group B (LVEF<35%)		
	------Dosing Regimen------			------Dosing Regimen------	
n[c]	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)	n[c]	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)
6:2	0.01	0.002	6:2	0.01	0.002
6:2	0.02	0.004	6:2	0.02	0.004
6:2	0.03	0.006	6:2	0.03	0.006

[a] infused over 10 minutes
[b] infused over 30 minutes
[c] number of patients to be treated with ibutilide fumarate:number of patients to be treated with placebo.

Electrophysiologic and hemodynamic measurements were to be performed at baseline (prior to administration of study drug), immediately following the 10-minute loading dose, and during the last half of the maintenance infusion. Hemodynamic measurements were also to be made at the midpoint of the maintenance infusion.

1.4 Drug Administration

Ibutilide was supplied in 10 ml clear glass ampules in a concentration of 2.5 mg/ml. The solution was isotonic and buffered with acetate to a pH of 4.6. For administration to patients, the solution was to be diluted with 5% dextrose in water (D_5W). Matching ampules of placebo containing only the vehicle were also supplied. Drug administration was to be terminated for any of the following reasons: (a) symptomatic hypotension, (b) a change in rhythm or atrioventricular conduction that was not hemodynamically tolerated or that threatened patient safety, (c) development of new bundle branch block or increase in QRS duration of greater than 50%, or; (d) an adverse event that threatened patient safety.

1.5 Evaluations

Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- resting blood pressure (left arm) and heart rate
- electrophysiological (EP) measurements (atrial and ventricular refractory periods, atrial and ventricular monophasic action potentials (MAPs), sinus node recovery times)
- invasive hemodynamic measurements (pulmonary capillary wedge pressure, pulmonary artery pressure, cardiac output)
- 12-lead electrocardiogram
- safety laboratories: blood for safety laboratories (hematology, chemistry, coagulation) and urine for urinalysis and microscopic evaluation
- blood samples for drug levels (obtained through six hours following the end of the maintenance infusion)
- digoxin levels (if applicable)
- medical events

The subjects were also monitored with a continuous electrocardiographic recording. See the table below for a summary of study evaluations:

Activity	Time from beginning of Infusion (min)						Time from end of maintenance infusion Minutes			Hours					
	-30	-10	0	10	25	40	5	15	30	1	2	4	6	24	Post 24
Informed Consent[1]	x														
History/Physical Exam	x														
EP Measurements[2]			x		x										
Hemodynamic Measurements[3]		x	x		x	x	x								
12 Lead ECG[4]	x		x		x	x	x			x	x	x	x	x	
Safety Labs	x													x	
Continuous ECG Recording/Monitoring[5]															
Resting EP/HR	x										x	x	x	x	
Ibutilide Loading Dose															
Ibutilide Maintenance Dose															
Ibutilide Serum Concentrations[4]			x		x	x	x	x	x	x	x	x	x	x	
Digoxin Levels[4] (if applicable)			x				x								
Final Report															x
MEF, MEFSI															x
Safety Follow-Up Report (as needed)															x

1. LV ejection fraction must be obtained prior to enrollment.

2. Atrial and ventricular refractoriness and MAP measurements. Other EP measurements to be made only before ibutilide administration (-10 minutes) and at the end of the 10 minute maintenance infusion (25 minutes to 40 minutes), page 9.

3. Pulmonary artery and pulmonary capillary wedge pressure. (Cardiac output will be measured at baseline (-10 & -30 min) and at the end of the maintenance infusion following the final EP measurements.)

4. 40 minute ECG, serum ibutilide concentrations, and digoxin levels are to be done following the infusion. All other 40 minute measurements (EP & Hemodynamics) are to be done at the end of the maintenance infusion.

5. Only standard single lead ECG monitoring required between 30 minutes and 24 hours after the end of maintenance infusion.

2. RESULTS

As stated in the protocol, the study planned to recruit two groups of patients, those with an LVEF ≥35% and those with an LVEF <35%. Data corresponding two these two groups were to be analyzed separately. However, results from the separate analyses were to be compared qualitatively to see if the findings are consistent in the two groups of patients. In the subsequent sections, the overall results when the strata are combined (i.e. results of the "combined stratum") will also be noted.

2.1 Disposition of Subjects

Patients were enrolled in the study from September 1991 through September 1994 by seven investigators. One investigator did not enroll any patients. Forty-seven (47) patients enrolled in the trial. One patient (#2303) experienced a medical event (nonsustained polymorphic ventricular tachycardia) that led to discontinuation of the infusion of study drug. Nonetheless, all 47 patients completed the planned course of the study, and all were considered evaluable by the sponsor. Of these 47 patients, 12 were randomized to receive placebo, 12 to receive ibutilide fumarate 0.01/0.002 mg/kg, 12 to receive ibutilide fumarate 0.02/0.004 mg/kg, and 11 to receive ibutilide fumarate 0.03/0.006 mg/kg.

2.2 Demographic and Baseline Characteristics

Of the 47 patients enrolled in the trial, 35 received ibutilide fumarate and 12 received placebo. Twenty-five (25) had an LVEF ≥ 35% and 22 had a LVEF < 35%. Forty-one (41) of the patients were male and 6 were female. All six of the women had an ejection fraction of ≥35%. Thirty-nine (39) of the patients were classified as white, 7 as black, and 1 as of an "other" race. The table on the next page describes the demographic and baseline characteristics of the patients by treatment group and by stratum.

The variables of race, sex, age, and weight generally were similar among treatment groups in each of the strata. However, the stratum of patients with an LVEF ≥35% was imbalanced across treatment groups for the variables of age (p=0.0431) and sex (p=0.0359). That is, the mean age of 32 years in the 0.01/0.002 mg/kg group was significantly lower than the mean ages in the placebo group (54.4 years; p=0.0135) and in the 0.03/0.006 mg/kg group (55.3 years; p=0.0133).

Baseline Characteristics of Subjects by Dose Group and by Stratum

		Ibutilide (mg/kg)		
Combined Strata N=47	Placebo (n=12)	0.01/0.002 (n=12)	0.02/0.004 (n=12)	0.03/0.006 (n=11)
LVEF (n) (≥35%/<35%)	7/5	6/6	6/6	6/5
Race (n) (W/B/O)*	10/2/0	10/1/1	10/2/0	9/2/0
Sex (n) (♂/♀)	12/0	9/3	9/3	11/0
Age (years) (mean±s.d.)	59.2 ±16.1	49.5 ±21.5	58.2 ±14.4	60.8 ±13.6
Weight (lbs) (mean±s.d.)	188.6 ±41.2	167.2 ±25.5	180.1 ±48.7	171.0 ±37.1
LVEF ≥35% Stratum N=25				
Number of patients (n)	7	6	6	6
Race (n) (W/B/O)*	6/1/0	5/0/1	6/0/0	5/1/0
Sex (n) (♂/♀)	7/0	3/3	3/3	6/0
Age (years) (mean±s.d.)	54.4 ±16.1	32.0 ±12.8	49.5 ±14.25	55.3 ±16.1
Weight (lbs) (mean±s.d.)	198.8 ±50.35	155.7 ±30.5	172.0 ±30.3	183.8 ±39.5
LVEF <35% Stratum N=22				
Number of patients (n)	5	6	6	5
Race (n) (W/B/O)*	4/1/0	5/1/0	4/2/0	4/1/0
Sex (n) (♂/♀)	5/0	6/0	6/0	5/0
Age (years) (mean±s.d.)	65.8 ±15.2	67.0 ±10.8	66.8 ±8.4	67.4 ±5.9
Weight (lbs) (mean±s.d.)	174.4 ±20.6	178.75 ±13.5	188.3 ±64.35	155.6 ±30.8

* Number of subjects by race/ethnicity: W/B/O = White/Black/Other

2.3 PHARMACOKINETIC RESULTS[2]

Serum or plasma concentration data were available from 32 of the 35 patients who received ibutilide fumarate. The pharmacokinetic results are summarized in the table on the next page. Individual patient profiles of concentration versus time are shown by treatment group on pages 8-9. The relationship of plasma concentration to the length of the QTc interval is shown in the figure on page 10.

As stated by the sponsor, post-infusion concentrations rapidly declined in a multi-exponential fashion, and concentrations were typically around or below 1 ng/ml within 1 hour after the maintenance infusion. However, a high degree of interpatient variability was observed in all dose groups, and the presence of extreme outliers resulted in atypically high measures of variability. In addition, many concentration-time profiles were atypical: some were erratic, and some showed maximum concentrations later than the end of the first infusion. In general, maximum ibutilide plasma concentrations and area under the concentration versus time profile values increased in a dose-related manner with increase in dose and were independent of left ventricular function. The pharmacokinetics of ibutilide were similar in patients with a LVEF <35% relative to patients with a LVEF ≥35%. Pharmacodynamic data were also atypical in regards to previous studies. Although studies in healthy volunteers have shown that infusion of ibutilide fumarate results in prolongation of the QTc interval and this prolongation is directly correlated with ibutilide fumarate dose and ibutilide plasma concentrations, no such correlation was found in this study.

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[2] For a complete discussion of pharmacokinetic issues, see the review by the biopharmaceutical reviewer.

Table 1
Ibutilide Fumarate Pharmacokinetic Parameter Estimates Following Intravenous Infusion in Patients Undergoing Invasive Electrophysiologic and Hemodynamic Study

Parameter		Treatment Group					
		A (0.01 mg/kg/10 min then 0.002 mg/kg/30 min)		B (0.02 mg/kg/10 min then 0.004 mg/kg/30 min)		C (0.03 mg/kg/10 min then 0.006 mg/kg/30 min)	
		LVEF ≥ 35%*	LVEF < 35%	LVEF ≥ 35%	LVEF < 35%	LVEF ≥ 35%	LVEF < 35%
No. of Patients		5	5	6	6	5	5
C_{max} (ng/mL)	Mean ± SD Median Range	11.1 ± 7.6 11.6	7.9 ± 8.1 3.5	14.5 ± 14.9 9.6	12.9 ± 10.3 10.2	68.2 ± 74.4 54.5	57.4 ± 113 6.9
T_{max} (h)	Mean ± SD Median Range	0.17 ± 0.02 0.17	0.17 ± 0 0.17	0.22 ± 0.10 0.17	0.47 ± 0.34 0.42	0.22 ± 0.11 0.17	0.17 ± 0 0.17
$AUC_{0-\infty}$ (ng•h/mL)	Mean ± SD Median Range	8.7 ± 3.0 8.2	6.0 ± 2.1 5.1	14.3 ± 6.2 12.0	13.5 ± 10.2 11.6	31.8 ± 20.9 26.9	24.3 ± 31.3 11.3
λ_z (h^{-1})	Mean ± SD Median Range	0.14 ± 0.03 0.14	0.14 ± 0.01 0.15	0.16 ± 0.04 0.18	0.13 ± 0.09 0.18	0.13 ± 0.02 0.13	0.18 ± 0.05 0.17
$t_{1/2}$ (h)†		4.9	4.9	4.4	3.9	5.2	3.6

*LVEF = Left ventricular ejection fraction
†Harmonic mean value

Individual Patient Profiles of Plasma Concentration versus Time

Figure 1. Individual patient ibutilide plasma concentration-time profiles following 0.01 mg/kg/10 min then 0.002 mg/kg/30 min intravenous infusions of ibutilide fumarate

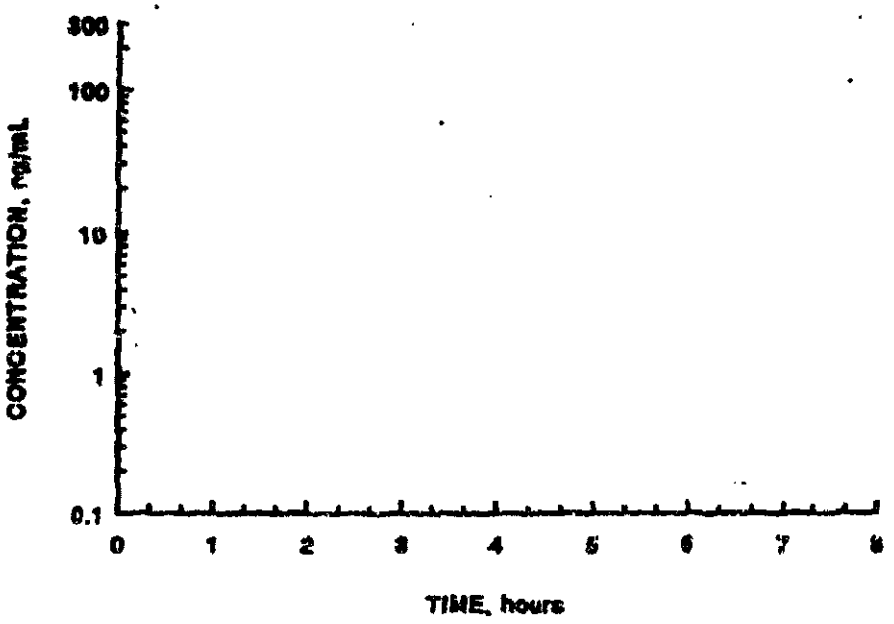
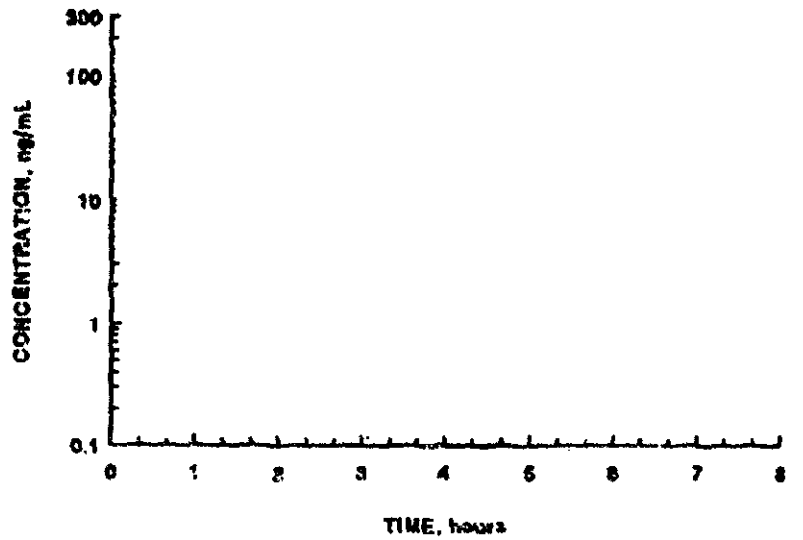


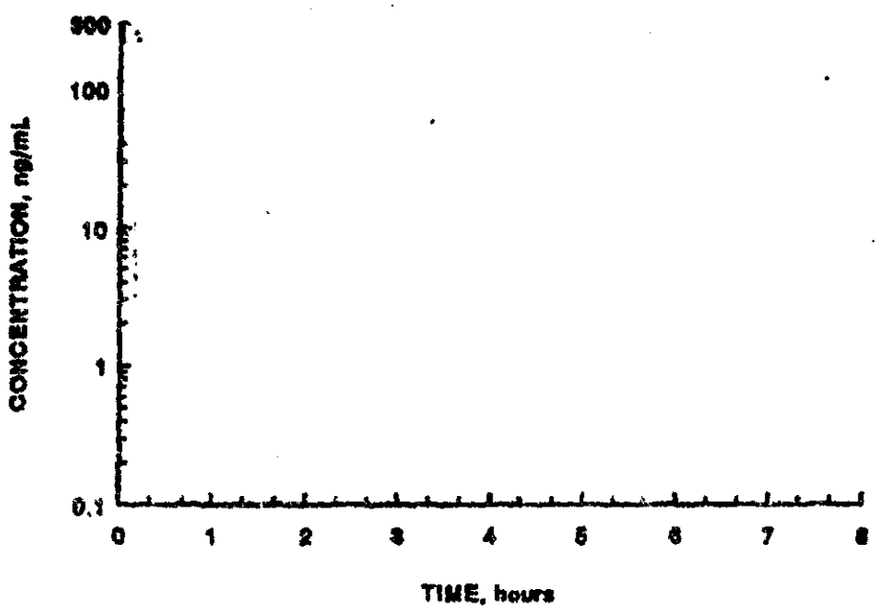
Figure 2. Individual patient ibutilide plasma concentration-time profiles following 0.02 mg/kg/10 min then 0.004 mg/kg/30 min intravenous infusions of ibutilide fumarate



Solid lines represent patients in the LVEF≥35% stratum;
dashed lines represent patients in the LVEF<35% stratum.

Individual Patient Profiles of Plasma Concentration versus Time (continued)

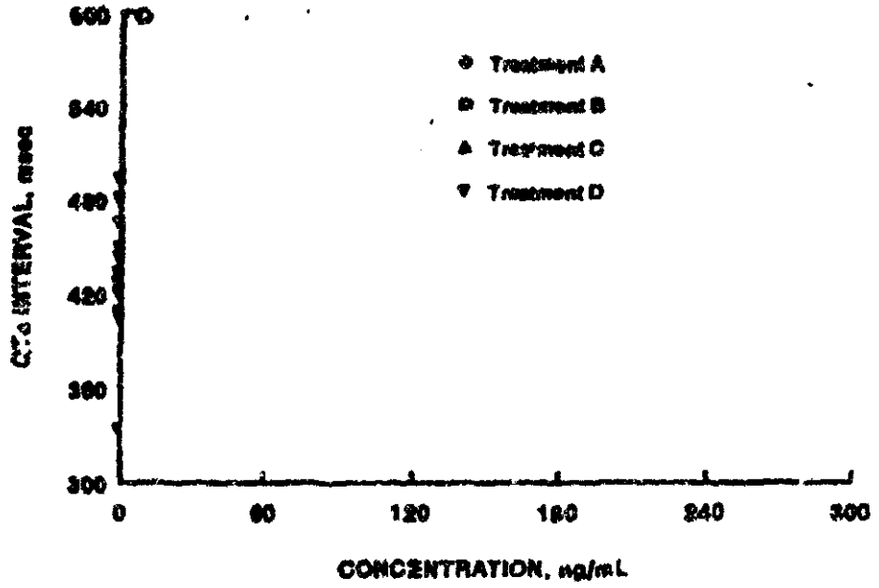
Figure 3. Individual patient ibutilide plasma concentration-time profiles following 0.03 mg/kg/10 min then 0.006 mg/kg/30 min intravenous infusions of ibutilide fumarate



Solid lines represent patients in the LVEF≥35% stratum; dashed lines represent patients in the LVEF<35% stratum.

QTc Interval versus Plasma Concentration

Figure 4. Individual patient QTc interval versus loutilide plasma concentration at the end of the first infusion (loading dose)



2.4 PHARMACODYNAMIC RESULTS

2.4.1 Invasive hemodynamic measurements

Invasive hemodynamic measurements were made of cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure.

2.4.1.1 Cardiac output

The figures on page 21 show the cardiac output by dose group over time in the stratum of patients with a LVEF ≥35% (top figure) and in the stratum of patients with a LVEF <35% (bottom figure).

Similarity at baseline: At baseline the mean cardiac output was 5.40 L/min in the stratum of patients with a LVEF ≥35%, 4.87 L/min in the stratum of patients with a LVEF <35%, and 5.15 L/min when the strata were combined. The cardiac output was similar at baseline across dose groups, both within each ejection-fraction stratum and overall when the strata were combined.

Changes from baseline: Mean cardiac output decreased significantly from baseline in the 0.03/0.006 mg/kg dose group within the stratum of patients with a LVEF ≥35% (mean change = -0.57 L/min, p=0.0130) and in the 0.03/0.006 mg/kg dose group within the combined stratum (mean change = -0.37 L/min, p=0.0360).

Nonetheless, the mean cardiac output changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo. At Minutes 25-40 the mean cardiac output across dose groups was 5.15 L/min in the stratum of patients with a LVEF ≥35%, 4.83 L/min in the stratum of patients with a LVEF <35%, and 5.05 L/min overall when the strata were combined.

2.4.1.2 Mean pulmonary artery pressure

The figures on page 22 show the pulmonary artery pressure by dose group over time in the stratum of patients with a LVEF ≥35% and in the stratum of patients with a LVEF <35%.

Similarity at baseline: At baseline the mean pulmonary artery pressure was 17.5 mmHg in the stratum of patients with a LVEF ≥35%, 22.2 mmHg in the stratum of patients with a LVEF <35%, and 19.7 mmHg when the strata were combined. The mean pulmonary artery pressure was similar at baseline across dose groups, both within each ejection-fraction stratum and overall when the strata were combined.

Changes from baseline: At each of the three time points after baseline (i.e., at Minutes 10, 25, and 40), the mean pulmonary artery pressure changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo.

For patients with a LVEF ≥35%, the mean pulmonary artery pressures across dose groups at Minutes 10, 25, and 40 were 17.3, 17.8, and 18.0 mmHg, respectively. For patients with a LVEF <35%, the mean pulmonary artery pressures across dose groups at Minutes 10, 25, and 40 were 24.6, 24.8, and 25.0 mmHg, respectively. For patients in the combined strata, the mean pulmonary artery pressures across dose groups at Minutes 10, 25, and 40 were 20.4, 21.2, and 21.2 mmHg, respectively.

2.4.1.3 Pulmonary capillary wedge pressure

The figures on page 23 show the pulmonary capillary wedge pressure by dose group over time in the stratum of patients with a LVEF ≥35% and in the stratum of patients with a LVEF <35%.

Similarity at baseline: At baseline the mean pulmonary capillary wedge pressure was 11.0 mmHg in the stratum of patients with a LVEF ≥35%, 12.6 mmHg in the stratum of patients with a LVEF <35%, and 11.8 mmHg when the strata were combined. The mean pulmonary capillary wedge pressure was similar at baseline across dose groups, both within each ejection-fraction stratum and overall when the strata were combined.

Changes from baseline: At each of the three time points after baseline (i.e., at Minutes 10, 25, and 40), the mean pulmonary capillary wedge pressure changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo.

For patients with a LVEF ≥35%, the mean pulmonary capillary wedge pressures across dose groups at Minutes 10, 25, and 40 were 10.3, 10.4, and 10.8 mmHg, respectively. For patients with a LVEF <35%, the mean pulmonary capillary wedge pressures across dose groups at Minutes 10, 25, and 40 were 13.5, 14.5, and 14.4 mmHg, respectively. For patients in the combined strata, the mean pulmonary capillary wedge pressures across dose groups at Minutes 10, 25, and 40 were 11.6, 12.2, and 12.4 mmHg, respectively.

2.4.2 Electrophysiological measurements

Electrophysiological measurements were made of basic cycle length, sinus node recovery time, Wenckebach cycle length, length of the atrial and ventricular effective refractory periods, duration of atrial and ventricular monophasic action potentials, atrial and ventricular thresholds, and length of the AH and HV intervals. QT and QTc intervals were measured from surface electrocardiograms.

2.4.2.1 Effects of ibutilide on functional tests of the sinoatrial node (SAN)

2.4.2.1.1 Basic cycle length

Background: The basic cycle length is the interval between consecutive, spontaneous electrocardiographic depolarizations. A basic cycle length of 1000 msec corresponds to a heart rate of 60 beats per minute, and a basic cycle length of 600 msec corresponds to a heart rate of 100 beats per minute.

Similarity at baseline: At baseline the mean basic cycle length was 838 msec in the stratum of patients with a LVEF ≥35%, 802 msec in the stratum of patients with a LVEF <35%, and 821 msec overall when the strata were combined. Across dose groups, the basic cycle lengths were similar at baseline in the stratum of patients with an LVEF ≥35% and in the combined stratum.

However, in the stratum of patients with an LVEF <35%, the basic cycle length at baseline differed significantly across dose groups (p=0.0227). The mean in the 0.03/0.006 mg/kg dose group (963 msec) was significantly longer than the mean in the 0.01/0.002 mg/kg dose group (716 msec; p=0.0091) and significantly longer than the mean in the 0.02/0.004 mg/kg dose group (732 msec; p=0.0057). See the table on page 24.

Changes from baseline: Changes in the basic cycle length from baseline were similar across dose groups (including the placebo group) in the stratum of patients with an LVEF <35% and overall when the strata were combined. However, in the stratum of patients with a LVEF ≥35%, changes from baseline differed significantly across dose groups (p=0.0062). In this stratum, the mean increase in the basic cycle length in the 0.03/0.006 mg/kg dose group (220 msec) was significantly greater than each of the following: (a) the mean increase in the placebo group (9 msec, p=0.0103); (b) the mean decrease in the 0.01/0.002 mg/kg group (-74 msec, p=0.0011), and; (c) the mean increase in the 0.02/0.004 mg/kg group (41 msec, p=0.0316). See the table on page 24. The heart rates that correspond to these basic cycle lengths are shown in the table on page 25.

2.4.2.1.2 Corrected sinus node recovery time (CSNRT)

Background: The sinus node recovery time (SNRT) is the interval from the last paced atrial beat to the first spontaneous atrial depolarization that originates in the sinus node. In this trial, sinus node recovery times were evaluated following pacing for 30 seconds at five paced cycle lengths (600, 500, 450, 400, and 350 msec). Because the SNRT depends on the basic sinus rate, it is often expressed as the corrected sinus node recovery time (i.e., the SNRT minus the basic cycle length). The upper limit of normal for the SNRT ranges from about 1400 msec to 1550 msec, and the upper limit of normal for the corrected sinus node recovery time (CSNRT) ranges from approximately 500 msec to 550 msec.

Similarity at baseline: At baseline, the mean CSNRT was 246 msec when the patients were paced at a cycle length of 600 msec, 243 msec at a paced cycle length (PCL) of 500 msec, 209 msec at a PCL of 450 msec, 236 msec at a PCL of 400 msec, and 203 msec at a PCL of 350 msec. The CSNRTs were similar at baseline across dose groups (within each of the paced cycle lengths) in the stratum of patients with an LVEF ≥35%.

The CSNRTs were also generally similar at baseline across dose groups in the stratum of patients with a LVEF <35% and overall when the strata were combined (i.e. when patients were paced at cycle lengths of 600 msec or 400 msec). However, in the stratum of patients with an LVEF <35% at a paced cycle length of 500 msec, the CSNRT at baseline differed significantly across dose groups (p=0.0036). The mean CSNRT in the 0.03/0.006 mg/kg dose group (87 msec) was significantly shorter than the mean in the placebo group (335 msec, p=0.0139) and the mean in the 0.01/0.002 mg/kg dose group (365 msec; p=0.0051). The mean CSNRT in the 0.02/0.004 mg/kg dose group (77 msec) was also significantly shorter at baseline than the mean in the placebo group (335 msec; p=0.0083) and the mean in the 0.01/0.002 mg/kg dose group (365 msec; p=0.0027). See the table on page 26.

Similarly, in the combined stratum at a paced cycle length of 500 msec, the CSNRT at baseline differed significantly across dose groups (p=0.0108). The mean CSNRT in the 0.02/0.004 mg/kg dose group (106 msec) was significantly shorter at baseline than the mean in the placebo group (318 msec, p=0.0030) and the mean in the 0.01/0.002 mg/kg dose group (307.5 msec; p=0.0046). See the table on page 26.

Changes from baseline: At each paced cycle length, the changes from baseline in the CSNRT were similar across dose groups (including the placebo group) in each of the three strata: the stratum of patients with an LVEF<35%, the stratum of patients with an LVEF ≥35%, and the combined stratum. See the table on page 26.

Maximum changes from baseline: As noted by the sponsor, patients differ in their basic cycle lengths, and therefore each patient may need a different overdrive suppression pacing cycle length to distinguish any change in the sinus node recovery time. Thus, the dose-group mean of maximum changes from baseline in CSNRTs across all pacing cycles may better distinguish the effects of treatment. In this analysis, the CSNRT was occasionally significantly prolonged from baseline in each of the dose groups (including the placebo group), but the changes from baseline were generally of a greater magnitude in patients treated with ibutilide than in patients treated with placebo. Maximum changes from baseline in corrected sinus node recovery time at the end of the maintenance infusion are summarized in the table on page 27.

2.4.2.2 Effects of ibutilide on functional tests of the atrioventricular node (AVN)

2.4.2.2.1 AV Wenckebach cycle length; antegrade atrioventricular conduction

Background: Pacing the atria at incrementally faster rates will prolong the AH interval, mostly by delaying conduction through the atrioventricular node. Second-degree AV block of a type 1 pattern occurs at the Wenckebach point, and this progresses to 2:1 AV block. The pacing cycle length at which second degree AV block occurs is generally between 500 and 350 msec. In this study the atria were paced at decrements in cycle length of 10 msec to determine the AV Wenckebach cycle length.

Similarity at baseline: At baseline the mean AV Wenckebach cycle length was 375 msec in the stratum of patients with a LVEF ≥35%, 399 msec in the stratum of patients with a LVEF <35%, and 387 msec overall when the strata were combined. The AV Wenckebach cycle lengths were similar at baseline across dose groups, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the LVEF<35% stratum) and overall when the strata were combined.

Changes from baseline: The AV Wenckebach cycle length changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo. At Minute 10 the mean AV Wenckebach cycle length was 414 msec in the stratum of patients with a LVEF ≥35%, 458 msec in the stratum of patients with a LVEF <35%, and 433 msec overall when the strata were combined.

2.4.2.2.2 VA Wenckebach cycle length; retrograde atrioventricular conduction

Background: A significant percentage of individuals with normal antegrade atrioventricular (AV) conduction will not have ventriculoatrial (VA) conduction. In those with ventriculoatrial conduction, however, pacing the ventricles at incrementally faster rates will prolong VA conduction. In this study the ventricles were paced at decreasing cycle lengths to determine the VA Wenckebach cycle length.

Similarity at baseline: At baseline the mean VA Wenckebach cycle length was 393 msec in the stratum of patients with a LVEF ≥35%, 399 msec in the stratum of patients with a LVEF <35%, and 396 msec overall when the strata were combined. The VA Wenckebach cycle lengths were similar at baseline across dose groups, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the LVEF<35% stratum) and overall when the strata were combined.

Changes from baseline: Changes in the VA Wenckebach cycle length from baseline were similar across dose groups (including the placebo group) only in the stratum of patients with an

LVEF <35%. However, changes from baseline differed significantly across dose groups both in the stratum of patients with a LVEF ≥35% (p=0.0053) and in the combined strata (p=0.0041).

In the stratum of patients with an *LVEF ≥35%*, the mean change in the VA Wenckebach cycle length in the 0.03/0.006 mg/kg dose group (183 msec) was significantly greater than the mean change in the placebo group (-20 msec; p=0.0012) and significantly greater than the mean change in the 0.01/0.002 mg/kg group (75 msec, p=0.0492). In addition, the mean change in the 0.02/0.004 mg/kg group (138 msec) was significantly greater than the mean change in the placebo group (-20 msec; p=0.0062). Similarly, the mean change in the 0.01/0.002 mg/kg group (75 msec) was significantly greater than the mean change in the placebo group (-20 msec; p=0.0495).

In the *combined stratum*, the mean change in the VA Wenckebach cycle length in the 0.03/0.006 mg/kg dose group (150 msec) was significantly greater than the mean change in the placebo group (-14 msec; p=0.0007) and significantly greater than the mean change in the 0.01/0.002 mg/kg group (63 msec, p=0.0447). In addition, the mean change in the 0.02/0.004 mg/kg group (97 msec) was significantly greater than the mean change in the placebo group (-14 msec; p=0.0084). Similarly, the mean change in the 0.01/0.002 mg/kg group (63 msec) was significantly greater than the change in the placebo group (-14 msec; p=0.0379).

2.4.2.3 Effects of ibutilide on the atria

2.4.2.3.1 Atrial effective refractory period (AERP)

Background: The effective refractory period is the period in the cardiac cycle during which another impulse fails to be conducted. In this study according to the protocol, an extra stimulus (S_2) was to be introduced during the atrial refractory period after eight paced beats (at cycle lengths of 600 msec, 500 msec, and 400 msec). The coupling interval was then to be increased by increments of 5 msec until the atrium was captured, thereby defining the AERP.

Similarity at baseline: At baseline the mean atrial effective refractory periods in the combined stratum for paced cycle lengths of 400, 500, and 600 msec were 217, 222, and 225 msec, respectively. Across dose groups at each of these paced cycle lengths, the atrial effective refractory periods were similar, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the LVEF<35% stratum) and overall when the strata were combined.

Changes from baseline: The atrial effective refractory period was prolonged from baseline to a significantly greater extent in patients treated with ibutilide than in patients treated with placebo. These significantly greater effects were fairly consistent in the highest dose group (i.e., 0.03/0.006 mg/kg) and were uncommon in the lowest dose group (i.e., 0.01/0.002 mg/kg). The effects were seen at each paced cycle length, both at Minute 10 and at Minute 25-40. The data are illustrated in the table and in the figure (of the combined stratum) on page 28.

2.4.2.3.2 Duration of atrial monophasic action potentials (AMAPs)

Background: The duration of atrial monophasic action potentials were measured at 90% repolarization and at paced cycle lengths of 400, 500, and 600 msec.

Similarity at baseline: At baseline in the combined stratum, the mean duration of the atrial monophasic action potential was 226 msec when the patients were paced at a cycle length of 400 msec, 239 msec when paced at a cycle length of 500 msec, and 242 msec when paced at a

cycle length of 600 msec. Across dose groups (within each of the paced cycle lengths), the duration of the AMAPs were similar at baseline both within the stratum of patients with a LVEF ≥35% and in the "combined" stratum.

The duration of the AMAPs were also similar at baseline across dose groups in the stratum of patients with a LVEF <35% (i.e., at paced cycle lengths of 400 msec or 600 msec). However, at a paced cycle length of 600 msec, the duration of the AMAPs at baseline differed significantly across dose groups (p=0.0463). The mean duration of the AMAP in the placebo group (335 msec) was significantly longer than the mean duration in the 0.01/0002 mg/kg group (253 msec; p=0.0284) and the mean duration in the 0.03/0.006 mg/kg group (232 msec; p=0.0086).

Changes from baseline: The durations of the atrial monophasic action potentials were prolonged from baseline to a significantly greater extent in patients treated with ibutilide, but almost exclusively only in those patients treated with the highest dose (0.03/0.006 mg/kg). These significant effects were demonstrated most consistently in the combined stratum, occurred at each paced cycle length, and were noted both at Minute 10 and at Minute 25-40. The data are illustrated in the table and in the figure (of data from the combined stratum) on page 30.

2.4.2.3.3 Atrial thresholds

Similarity at baseline: At baseline the mean atrial threshold was 0.50 mA in the stratum of patients with a LVEF ≥35%, 0.58 mA in the stratum of patients with a LVEF <35%, and 0.54 mA overall when the strata were combined. The atrial thresholds were similar at baseline across dose groups, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the LVEF<35% stratum) and overall when the strata were combined. However, the data within each dose group were highly variable, with coefficients of variation ranging from approximately 30% in some strata to about 90% in other strata.

Changes from baseline: The atrial thresholds changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo. Including patients treated with placebo, at Minute 10 the mean atrial threshold was 0.50 mA in the stratum of patients with a LVEF ≥35%, 0.57 mA in the stratum of patients with a LVEF <35%, and 0.53 mA overall when the strata were combined.

Similarly (including patients treated with placebo), at Minute 25-45 the mean atrial threshold was 0.50 mA in the stratum of patients with a LVEF ≥35%, 0.70 mA in the stratum of patients with a LVEF <35%, and 0.59 mA when the strata were combined.

Maximal atrial thresholds in patients treated with active drug: Prior to the infusion of ibutilide (i.e., at baseline), the greatest atrial threshold in a patient with a *LVEF* ≥35% was 1.40 mA. At Minute 10 (following the loading dose of ibutilide) the greatest atrial threshold in any patient was 2.00 mA. At Minute 25-40 (at the end of the maintenance infusion of ibutilide) the greatest atrial threshold in any patient was 2.00 mA.

Prior to the infusion of ibutilide (i.e., at baseline), the greatest atrial threshold in a patient with a *LVEF* <35% was 1.0 mA. At Minute 10 (following the loading dose of ibutilide) the greatest atrial threshold in any patient was 1.00 mA. At Minute 25-40 (at the end of the maintenance infusion of ibutilide) the greatest atrial threshold in any patient was 2.00 mA.

2.4.2.4 Effects of ibutilide on the ventricles

2.4.2.4.1 Ventricular effective refractory period (VERP)

Background: The effective refractory period is the period in the cardiac cycle during which another impulse fails to be conducted. In this study according to the protocol, an extra stimulus (S_2) was introduced during the ventricular refractory period after eight paced beats (at cycle lengths of 600, 500, and 400 msec). The coupling interval was then to be increased by increments of 5 msec until the ventricle was captured, thereby defining the VERP.

Similarity at baseline: At baseline the mean ventricular effective refractory periods in the combined stratum for paced cycle lengths of 400, 500, and 600 msec were 218, 227, and 237.5 msec, respectively. At each of these paced cycle lengths, the ventricular effective refractory periods at baseline were similar across dose groups, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the LVEF<35% stratum) and overall when the strata were combined.

Changes from baseline: The ventricular effective refractory periods were prolonged from baseline to a significantly greater extent in patients treated with ibutilide than in patients treated with placebo. These significantly greater effects were fairly consistent in the two highest dose groups (i.e., 0.03/0.006 mg/kg and 0.02/0.004 mg/kg) but were somewhat more erratic in the lowest dose group (i.e., 0.01/0.002 mg/kg). They occurred at each paced cycle length and both at Minute 10 and at Minute 25-40. These data are illustrated in the table and in the figure (of data from the combined stratum) on page 29.

2.4.2.4.2 Duration of ventricular monophasic action potentials (VMAPs)

Background: The duration of ventricular monophasic action potentials were measured at 90% repolarization and at paced cycle lengths of 400, 500, and 600 msec.

Similarity at baseline: At baseline in the combined stratum, the mean duration of the ventricular monophasic action potential was 241 msec when the patients were paced at a cycle length of 400 msec, 254 msec when paced at a cycle length of 500 msec, and 263 msec when paced at a cycle length of 600 msec. Across dose groups (within each of the paced cycle lengths), the duration of the VMAPs at baseline were similar in both strata (i.e., LVEF ≥35% and LVEF <35%) and were similar when the strata were combined.

Changes from baseline: The durations of the ventricular monophasic action potentials were prolonged from baseline to a significantly greater extent in patients treated with ibutilide than in patients treated with placebo. These significantly greater effects were fairly consistent in the two highest dose groups (i.e., 0.03/0.006 mg/kg and 0.02/0.004 mg/kg) but somewhat more erratic in the lowest dose group (i.e., 0.01/0.002 mg/kg). These significant effects occurred at each paced cycle length, and both at Minute 10 and at Minute 25-40. The data are illustrated in the table and in the figure (of data from the combined stratum) on page 31.

2.4.2.4.3 Ventricular thresholds

Similarity at baseline: At baseline the mean ventricular threshold was 0.39 mA in the stratum of patients with a LVEF ≥35%, 0.38 mA in the stratum of patients with a LVEF <35%, and 0.38 mA overall when the strata were combined. The ventricular thresholds were similar at baseline across dose groups, both within each ejection-fraction stratum (i.e., the LVEF≥35% stratum and the

LVEF<35% stratum) and overall when the strata were combined. However, the data within each dose group were highly variable, with coefficients of variation in the LVEF ≥35% stratum, for example, ranging from approximately 40% to about 130%.

Changes from baseline: The ventricular thresholds changed from baseline to a similar extent in patients treated with ibutilide (i.e., with any of the three doses) and in patients treated with placebo. Including patients treated with placebo, at Minute 10 the mean ventricular threshold was 0.38 mA in the stratum of patients with a LVEF ≥35%, 0.41 mA in the stratum of patients with a LVEF <35%, and 0.40 mA overall when the strata were combined.

Similarly (including patients treated with placebo), at Minute 25-45 the mean ventricular threshold was 0.37 mA in the stratum of patients with a LVEF ≥35%, 0.40 mA in the stratum of patients with a LVEF <35%, and 0.38 mA when the strata were combined.

Maximal ventricular thresholds in patients treated with active drug: Prior to the infusion of ibutilide (i.e., at baseline), the greatest ventricular threshold in a patient with a *LVEF ≥35%* was 2.00 mA. At Minute 10 (following the loading dose of ibutilide) the greatest ventricular threshold in any patient was 1.00 mA. At Minute 25-40 (at the end of the maintenance infusion of ibutilide) the greatest ventricular threshold in any patient was 1.0 mA.

Prior to the infusion of ibutilide (i.e., at baseline), the greatest ventricular threshold in a patient with a *LVEF <35%* was 0.80 mA. At Minute 10 (following the loading dose of ibutilide) the greatest ventricular threshold in any patient was 1.5 MA. At Minute 25-40 (at the end of the maintenance infusion of ibutilide) the greatest ventricular threshold in any patient was 1.0 mA.

2.4.2.5 Effects of ibutilide on conduction intervals

2.4.2.5.1 AH interval

Background: The AH interval is the time from the beginning of the A deflection to the beginning of the His bundle deflection (measured in the same lead). In this trial, the AH interval was evaluated at pacing cycle lengths of 600, 500, 450, 400, and 350 msec. As noted above in section 2.4.2.2.2, pacing the atria at incrementally faster rates will prolong the AH interval, mostly by delaying conduction through the atrioventricular node. Second-degree AV block of a type 1 pattern occurs at the Wenckebach point, and this progresses to 2:1 AV block. The upper limit of normal for the AH interval ranges from about 130 msec to 140 msec, whereas the lower limit of normal in adults is approximately 45 msec to 55 msec.

Similarity at baseline: At baseline, the mean AH interval was 101 msec when the patients were paced at a cycle length of 600 msec, 103 msec at a paced cycle length (PCL) of 500 msec, 121 msec at a PCL of 450 msec, 158 msec at a PCL of 400 msec, and 152 msec at a PCL of 350 msec. The AH intervals were similar at baseline across dose groups (at each of the paced cycle lengths) in each stratum (i.e., LVEF ≥35%, and LVEF <35%) and in the combined strata.

Changes from baseline: Changes in the mean AH intervals from baseline were similar across dose groups (including the placebo group) in the stratum of patients with an LVEF <35% and in the combined stratum at each pacing cycle length. The table on page 32 for data from the combined stratum.

Changes from baseline were generally similar across dose groups in the stratum of patients with an LVEF ≥35%, with the exception of the pacing cycle length of 400 msec (p=0.0040). In this stratum (at this pacing cycle length), the mean change from baseline of the AH interval in the 0.03/0.006 mg/kg dose group (105 msec) was significantly greater than the mean change in the placebo group (-1 msec; p=0.0052) and significantly greater than the mean change in the 0.01/0.002 mg/kg group (-2 msec, p=0.0067). In addition, the mean change in the 0.02/0.004 mg/kg group (77 msec) was significantly greater than the mean change in the placebo group (-1 msec; p=0.0029) and significantly greater than the mean change in the 0.01/0.002 mg/kg group (-2 msec; p=0.0052).

2.4.2.5.2 HV Interval

Background: The HV interval is the time from the beginning of the His deflection to the beginning of ventricular depolarization (measured either as the beginning of the QRS complex in surface leads, or as the beginning of the V deflection in the His bundle electrogram). In this trial, the HV interval was evaluated at pacing cycle lengths of 600, 500, 450, 400, and 350 msec. In adults, the normal range for the HV interval ranges from about 30 msec to 55 msec.

Similarity at baseline: At baseline, the mean HV interval was 56 msec when the patients were paced at a cycle length of 600 msec, 57 msec at a paced cycle length (PCL) of 500 msec, 55 msec at a PCL of 450 msec, 54 msec at a PCL of 400 msec, and 54 msec at a PCL of 350 msec. The HV intervals were similar at baseline across dose groups (at each of the paced cycle lengths) in each stratum (i.e., LVEF ≥35%, and LVEF <35%) and in the combined strata.

Changes from baseline: Changes in the mean HV intervals from baseline were similar across dose groups (including the placebo group) at each of the paced cycle lengths in each stratum and in the combined stratum. Changes from baseline in the combined stratum are shown in the table on page 32.

2.4.2.5.3 QT Interval

Similarity at baseline: At baseline the mean QT interval was 385 msec in the stratum of patients with a LVEF ≥35%, 391 msec in the stratum of patients with a LVEF <35%, and 388 msec overall when the strata were combined. The QT intervals were similar at baseline across dose groups, both within each ejection-fraction stratum and overall when the strata were combined.

Change from baseline: At Minutes 10, 25, and 40 in each stratum, mean changes from baseline in the QT intervals were always greater in the ibutilide treated groups than in the corresponding groups treated with placebo. The average mean changes from baseline in the ibutilide-treatment groups (i.e., the averages across the loading and maintenance infusions at Minutes 10, 25, and 40) were significantly greater than the changes in the placebo group at each dose within each stratum, with the sole exception of the 0.01/0.002 mg/kg dose in the stratum of patients with a LVEF<35%. See the table on page 33 for a summary of these data.

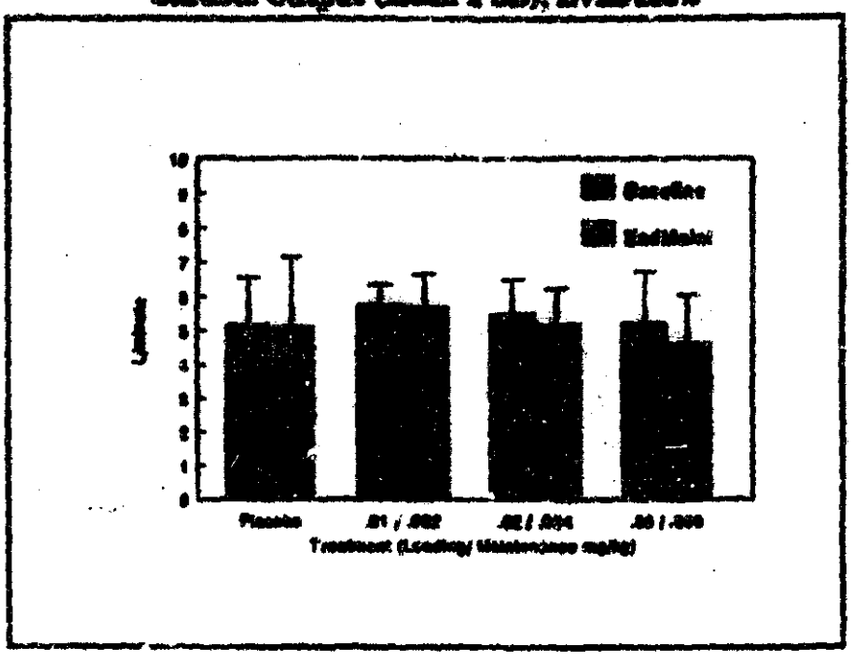
2.4.2.5.4 QTc Interval

Similarity at baseline: At baseline the mean QTc interval was 0.414 sec[N] in the stratum of patients with a LVEF ≥35%, 0.439 sec[N] in the stratum of patients with a LVEF <35%, and 0.426 sec[N] overall when the strata were combined. The QTc intervals were similar at baseline across dose groups, both within each ejection-fraction stratum and overall when the strata were combined.

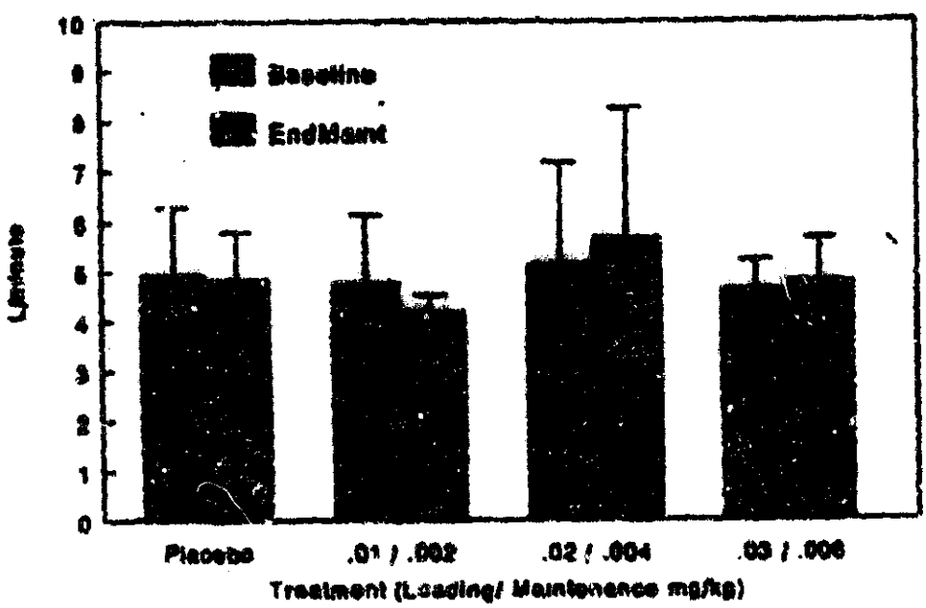
Change from baseline: At Minutes 10, 25, and 40 in each stratum, mean changes from baseline in the QTc intervals were always greater in the ibutilide treated groups than in the corresponding groups treated with placebo. At the 0.03/0.006 mg/kg dose within each stratum, the average mean changes from baseline in the ibutilide-treatment groups (i.e., the averages across the loading and maintenance infusions at Minutes 10, 25, and 40) were significantly greater than the changes in the placebo group. Sometimes the average mean changes from baseline within each stratum in the other two ibutilide-treatment groups (i.e., 0.01/0.002 mg/kg and 0.02/0.004 mg/kg, were also significantly greater than the changes in the placebo group. See the table on page 33 for a summary of these data.

Cardiac Output

Cardiac Output (mean ± SD), LVEF≥35%

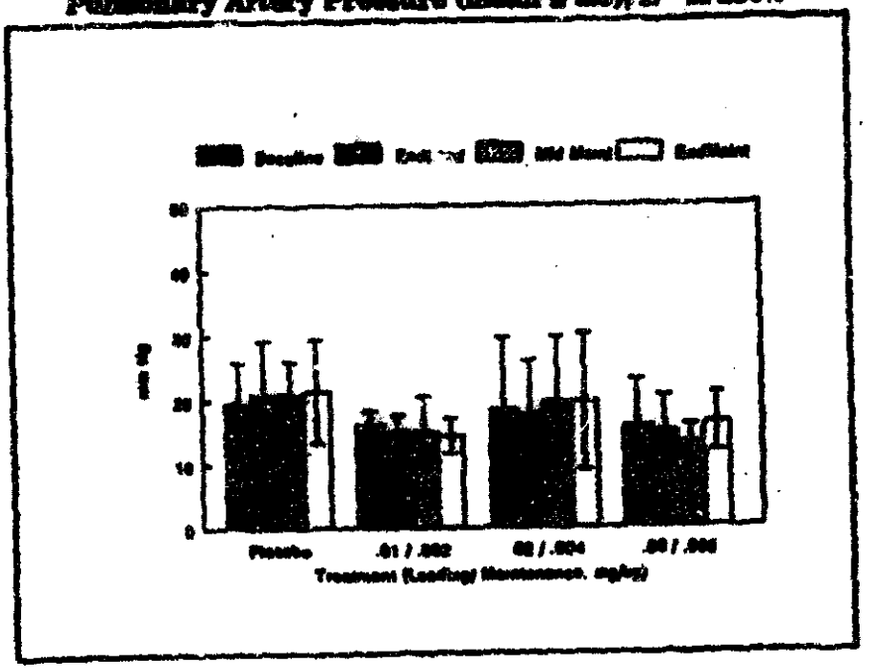


Cardiac Output (mean ± SD), LVEF<35%



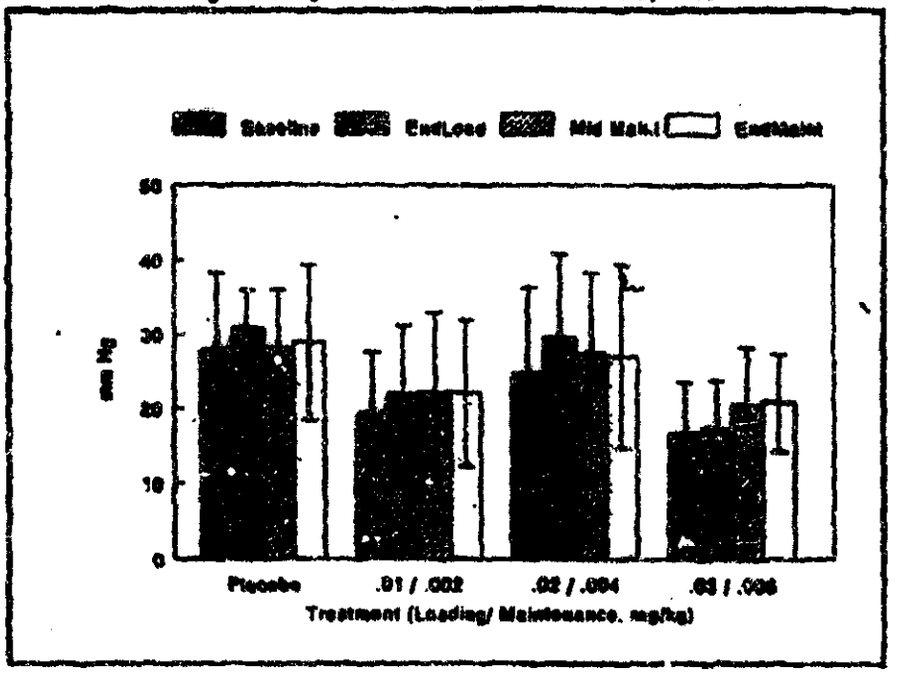
Mean Pulmonary Artery Pressure

Pulmonary Artery Pressure (mean ± SD), LVEF≥35%



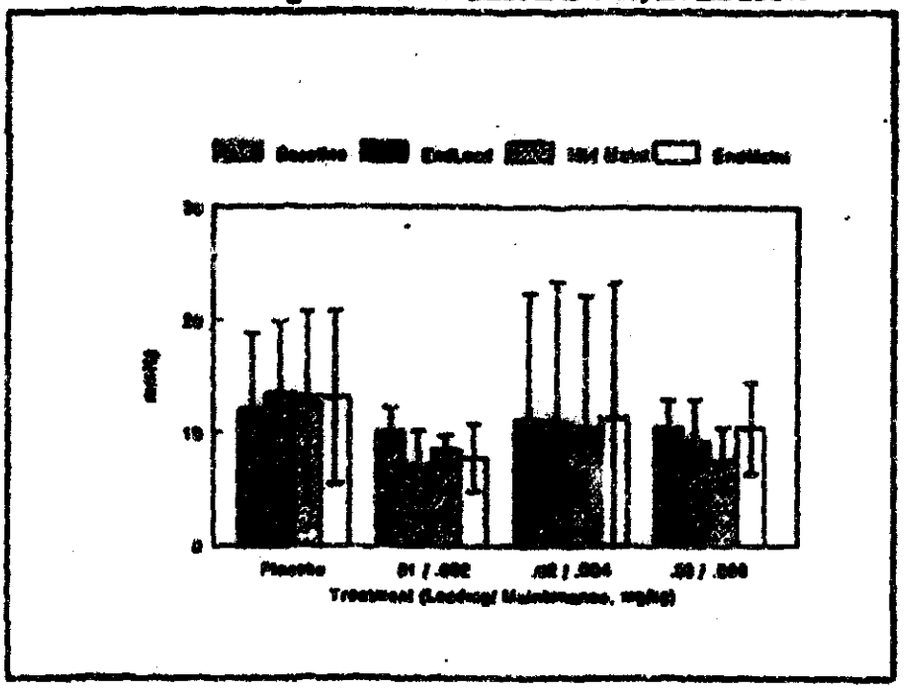
Source: Table K.4

Pulmonary Artery Pressure (mean ± SD), LVEF<35%

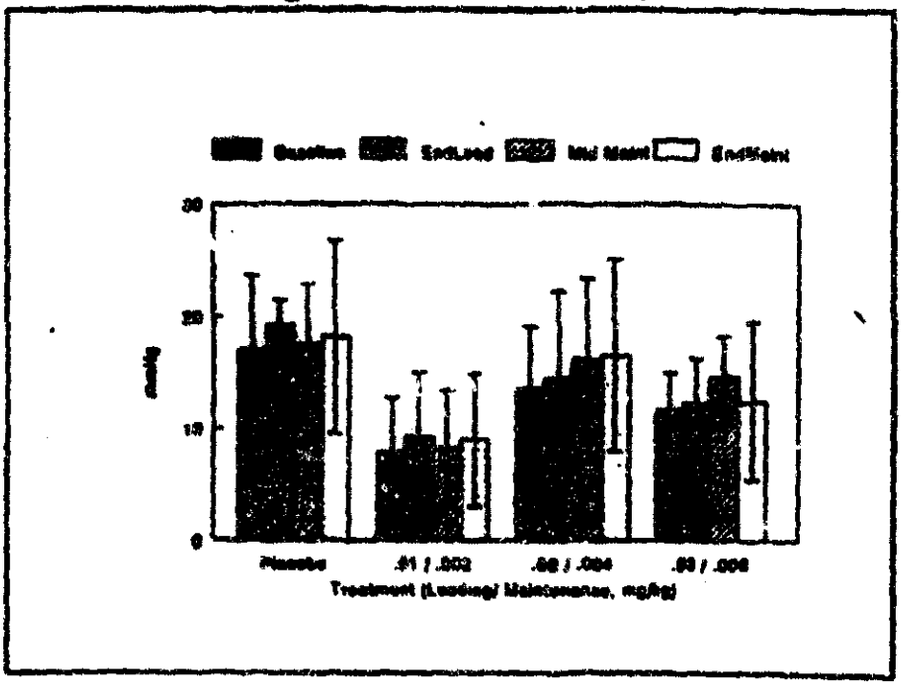


Pulmonary Capillary Wedge Pressure

Cardiac Wedge Pressure (mean ± SD), LVEF≥35%



Cardiac Wedge Pressure (mean ± SD), LVEF<35%



Basic Cycle Lengths

Basic Cycle Length (msec)
Baseline Values and Changes from Baseline to the End of the Maintenance Infusion (mean ± s.d.)

	Ibutilide fumarate (mg/kg)							
	Placebo/Placebo		0.01/0.002		0.02/0.004		0.03/0.006	
	Baseline	▲Baseline	Baseline	▲Baseline	Baseline	▲Baseline	Baseline	▲Baseline
LVEF<35%	830 ± 121	1 ± 124	716 ± 56	49 ± 54	732 ± 183	78 ± 88	963 ± 126	-69 ± 84
LVEF ≥35%	811 ± 153	9 ± 68	818 ± 184	-74 ± 129	860 ± 204	41 ± 87	896 ± 213	220 ± 216
Combined	819 ± 135	6 ± 90	767 ± 140	-13 ± 114	796 ± 196	60 ± 86	910 ± 178	104.5 ± 225

02

Basic Cycle Lengths

Basic Cycle Lengths (msec) and Corresponding Heart Rates (beats/min) at Baseline and at End of Maintenance

Stratum	Dose (mg/kg)	Baseline Mean			End-of-Maintenance Mean		
		N	BCL	HR	N	BCL	HR
LVEF<35%	Placebo	5	830	72	5	831	72
	0.01/0.002	6	716	84	6	764	79
	0.02/0.004	6	732	82	6	811	74
	0.03/0.006	5	963	62	4	930	66
LVEF≥35%	Placebo	7	811	74	7	820	73
	0.01/0.002	6	818	73	6	744	81
	0.02/0.004	6	860	70	6	901	67
	0.03/0.006	6	866	69	6	1087	55
Combined	Placebo	12	819	73	12	825	73
	0.01/0.002	12	767	78	12	754	80
	0.02/0.004	12	796	75	12	856	70
	0.03/0.006	11	910	66	10	1024	59

Corrected Sinus Node Recovery Times

Corrected Sinus Node Recovery Times (msec) at Various Paced Cycle Lengths (PCLs)
Baseline Values and Changes from Baseline (mean ± s.d.)

			Ibutilide fumarate (mg/kg)					
	Placebo/Placebo		0.01/0.002		0.02/0.004		0.03/0.006	
PCL (msec)	Baseline	Δ Baseline	Baseline	Δ Baseline	Baseline	Δ Baseline	Baseline	Δ Baseline
LVEF<35%								
600	290 ± 160	-80 ± 94	372 ± 160	-114 ± 145	145 ± 292	24 ± 315	79 ± 99	101 ± 71
500	335 ± 99	-8.5 ± 64	365 ± 158	-56 ± 150	77 ± 189	107 ± 200	87 ± 57	70 ± 78
450	369 ± 110	111.5 ± 102	219 ± 156	13 ± 153	203 ± 214	-13.5 ± 110	72 ± 19.5	118 ± 130
400	466 ± 308	-208 ± 306	254 ± 201	-55 ± 233	207.5 ± 162	-69.5 ± 318	188 ± 188	134 ± 84
350	339 ± 83	32 ± 139	261 ± 218	-97 ± 345	200.5 ± 170	-96.5 ± 321	88 ± 118	277 ± 348
LVEF ≥35%								
600	340 ± 137	-45 ± 134	193 ± 163	60 ± 215	245 ± 120	-35 ± 170	271 ± 111	-167 ± 331
500	306 ± 95	-71 ± 88	250 ± 55.5	-92 ± 146	134 ± 172	147 ± 175	368 ± 254	-181 ± 603
450	251 ± 155	-33 ± 90	230 ± 81	4 ± 108	86 ± 122	128 ± 136	215 ± 135	143 ± 589
400	243 ± 212	-77 ± 145	137 ± 79	39 ± 183	79 ± 113	137 ± 112	376 ± 388	-126 ± 563
350	195 ± 258	-9 ± 169	82 ± 100	226 ± 327	100 ± 135	9 ± 111	350 ± 285	-158 ± 899
Combined								
600	317 ± 143	-59 ± 115	274 ± 179	-27 ± 198	200 ± 205	-9 ± 229	184 ± 142	-80 ± 236
500	318 ± 94	-49 ± 88	307.5 ± 129	-74 ± 143	106 ± 175	127 ± 180	240 ± 238	-80.5 ± 470
450	300 ± 146	25 ± 116	225 ± 118	8 ± 126	145 ± 177	57 ± 139	158 ± 141	133 ± 446
400	324 ± 261	-117 ± 197	195 ± 158	-12 ± 207	143 ± 149	34 ± 251	301 ± 326	-29 ± 449
350	252.5 ± 212	8 ± 151	161.5 ± 192	65 ± 360	155 ± 157	-61 ± 265	262 ± 274	5 ± 740

Maximum Corrected Sinus Node Recovery Times

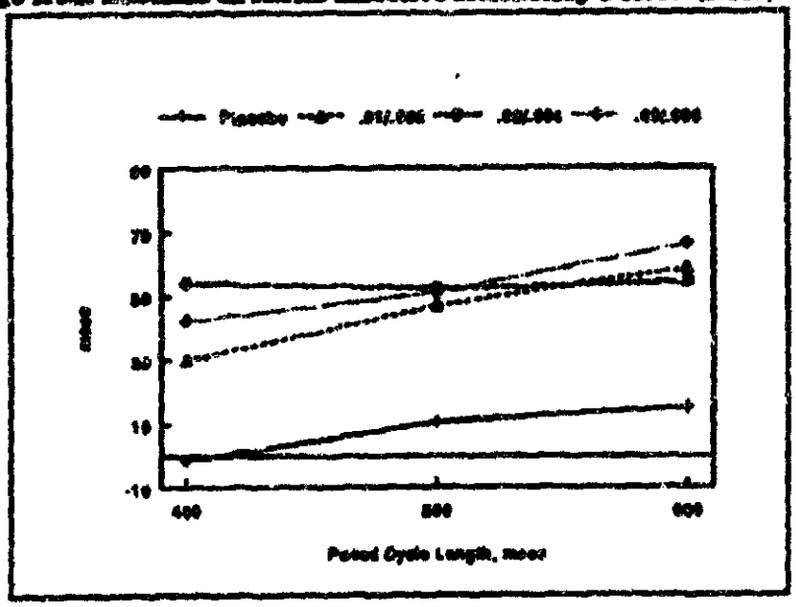
Maximum Change from Baseline in Corrected Sinus Node Recovery Time (msec)

Stratum	Dose (mg/kg)	Baseline Mean	End of Maintenance Mean	Mean Change from Baseline (SD)
LVEF≥35%	Placebo	139.29	210.57	71.29 (93.75)
	0.01/0.002	68.33	315.00	246.67 (303.96)
	0.02/0.004	64.17	282.50	218.33 (157.95)
	0.03/0.006	256.00	438.17	182.17 (691.81)
LVEF<35%	Placebo	316.00	447.50	131.50 (87.78)
	0.01/0.002	234.17	322.00	87.83 (134.36)
	0.02/0.004	100.67	239.50	138.83 (191.79)
	0.03/0.006	24.00	362.00	**338.00*** (174.38)
Combined	Placebo	203.55	296.73	93.18 (92.22)
	0.01/0.002	151.25	316.50	**167.25** (236.91)
	0.02/0.004	82.42	261.00	**178.58** (172.58)
	0.03/0.006	163.20	407.70	**244.50** (459.55)

Bold numbers indicate significant changes from baseline (P≤0.05)
*** Significantly different from placebo (P≤0.05)**
Source: Table L.10

Atrial Effective Refractory Periods

Mean Change from Baseline in Atrial Effective Refractory Period (msec) at Minute 10



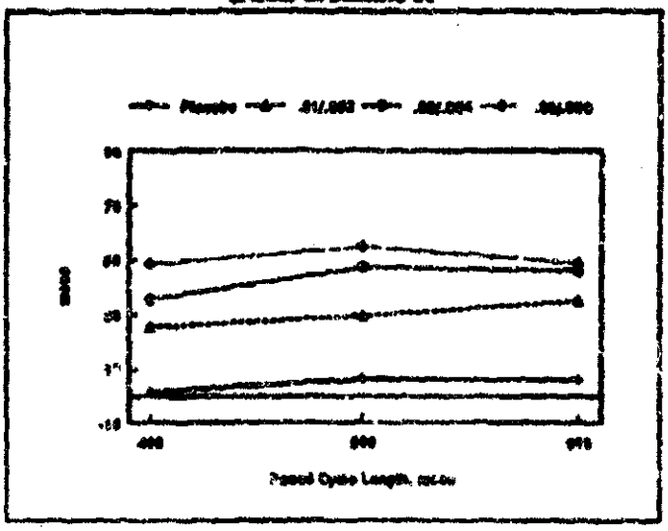
Mean Change from Baseline in Atrial Effective Refractory Periods (msec)

Stratum	Dose (mg/kg)	Minute 10			Minute 55-60		
		Paced Cycle Length (msec)					
		400	500	600	400	500	600
LVEF≥35%	Placebo	-0.50§ (8)	0.57§ (7)	12.00§ (8)	-0.71§ (8)	-0.71§ (7)	10.00§ (8)
	0.01/0.002	12.50 (7)	40.00 (8)	50.50 (8)	1.79§ (8)	18.00§ (8)	32.50§ (4)
	0.02/0.004	50.50* (4)	62.50* (8)	72.50* (8)	76.50*† (8)	68.00* (8)	68.50* (8)
	0.03/0.006	37.50 (8)	50.50* (8)	72.50* (8)	62.50* (8)	97.75*† (8)	97.50*† (8)
	Overall P-value	0.0051	0.0001	0.0001	0.0173	0.0054	0.0008
LVEF<35%	Placebo	6.67 (3)	22.50 (4)	18.00‡§ (3)	10.50 (3)	12.50§ (4)	0.00‡§ (3)
	0.01/0.002	25.00 (5)	40.17 (6)	64.00*§ (6)	35.83 (6)	50.00§ (6)	32.50*§ (6)
	0.02/0.004	25.00 (5)	44.17 (6)	52.50*§ (4)	54.17 (6)	40.00§ (6)	40.00* (4)
	0.03/0.006	20.00 (4)	22.50 (4)	40.00*‡ (4)	60.00 (4)	70.00*†‡ (4)	97.50*† (4)
	Overall P-value	0.0760	0.1349	0.0007	0.1181	0.0164	0.0039
Combined	Placebo	-1.67§ (9)	10.00§ (11)	14.00 †§ (11)	-0.70§ (9)	4.55§ (11)	5.50§ (11)
	0.01/0.002	20.00 (5)	40.00* (6)	58.75* (8)	37.50§ (8)	32.50§ (8)	30.00§ (8)
	0.02/0.004	54.00* (10)	60.27* (11)	54.45* (8)	64.00*† (11)	48.91*§ (11)	60.00*§ (8)
	0.03/0.006	40.00* (10)	51.00* (10)	66.67* (9)	67.00*† (10)	78.50*†‡ (10)	82.50*†‡ (8)
	Overall P-value	0.0114	0.0004	0.0006	0.0026	<0.0001	<0.0001

Data presented as mean change from baseline in msec with number of patients in parentheses.
Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.01/0.002 mg/kg group (P≤0.05)
‡ Significantly different from 0.02/0.004 mg/kg group (P≤0.05)
§ Significantly different from 0.03/0.006 mg/kg group (P≤0.05)
Source: Tables L.42-L.44, L.60.1-L.62.2A

Ventricular Effective Refractory Periods

Mean Change from Baseline in Ventricular Effective Refractory Period (msec) at Minute 10



Source: Tables L.53-L.55

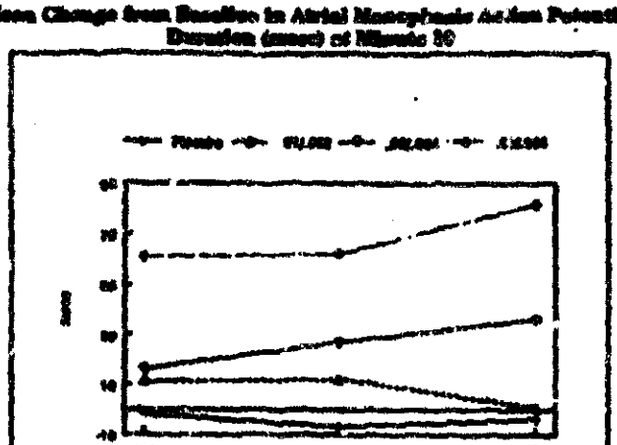
Mean Change from Baseline in Ventricular Effective Refractory Periods (msec)

Stratum	Dose (mg/kg)	Minute 10			Minute 55-60		
		Paced Cycle Length (msec)					
		400	500	600	400	500	600
LVEF≥30%	Placebo	2.00‡§ (7)	7.29‡§ (7)	5.00 (8)	-0.83‡§ (6)	4.29‡§ (7)	-2.33†‡§ (6)
	0.01/0.002	4.00‡§ (8)	18.00‡§ (8)	24.00 (8)	7.50‡§ (8)	14.17‡§ (8)	20.50*§ (8)
	0.03/0.004	20.17*† (6)	42.33*† (6)	41.50 (4)	25.00*† (6)	40.00*† (6)	36.50* (4)
	0.03/0.006	45.00*† (6)	60.83*† (6)	34.17 (6)	30.33*† (6)	50.67*† (6)	37.00*† (6)
	Overall P-value	0.0002	0.0000	0.1864	0.0000	0.0005	0.0003
LVEF<30%	Placebo	0.00*‡§ (5)	4.00*‡§ (5)	0.00*‡§ (5)	-6.00*‡§ (5)	4.00*‡§ (5)	2.00*‡§ (5)
	0.01/0.002	42.50* (6)	40.83* (6)	44.17* (6)	25.00* (6)	30.17*§ (6)	30.50*§ (6)
	0.03/0.004	41.67* (6)	54.00* (6)	50.00* (4)	40.17* (6)	47.00* (6)	57.25* (4)
	0.03/0.006	52.50* (4)	60.00* (4)	70.00* (4)	37.50* (4)	60.00*† (4)	70.00*† (4)
	Overall P-value	0.0001	0.0002	0.0014	0.0004	0.0010	0.0005
Combined	Placebo	1.07‡§ (12)	6.00‡§ (12)	3.91‡§ (13)	-4.00‡§ (11)	4.17‡§ (13)	-1.62‡§ (11)
	0.01/0.002	35.45*§ (11)	30.00 *§ (11)	35.00* (11)	21.25*§ (12)	21.67*§ (12)	25.00*§ (12)
	0.03/0.004	35.42* (12)	47.00*† (12)	46.25* (8)	32.00*† (12)	44.17*† (12)	46.88*† (8)
	0.03/0.006	48.89*† (10)	54.50*† (10)	46.00* (10)	33.00*† (10)	55.00*† (10)	53.50*† (10)
	Overall P-value	<0.0001	<0.0001	0.0010	<0.0001	<0.0001	<0.0001

Data presented as mean change from baseline in msec with number of patients in parentheses.
Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.01/0.002 mg/kg group (P≤0.05)
‡ Significantly different from 0.03/0.004 mg/kg group (P≤0.05)
§ Significantly different from 0.03/0.006 mg/kg group (P≤0.05)
Source: Tables L.53-L.55, L.73.1-L.73.3A

Atrial Monophasic Action Potentials

Mean Change from Baseline in Atrial Monophasic Action Potential Duration (msec) at Minute 10



Source: Tables L.45-L.47

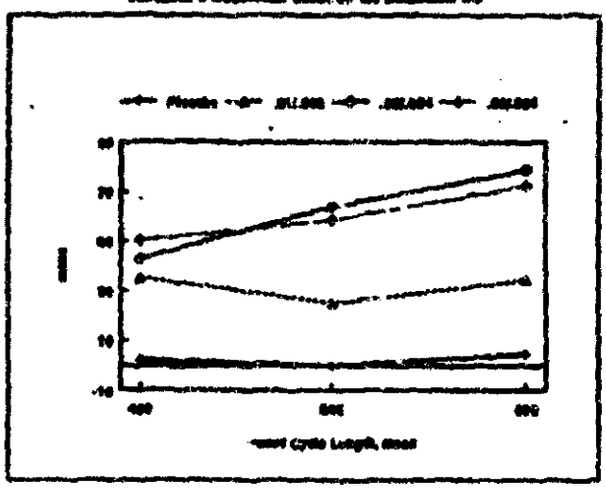
Mean Change from Baseline in Atrial Monophasic Action Potential (msec)

Stratum	Dose (mg/kg)	Minute 10			Minute 55-60		
		Paced Cycle Length (msec)					
		400	500	600	400	500	600
LVEF≥35%	Placebo	5.50 (8)	4.50 (8)	7.50§ (8)	-0.50 (8)	-1.50 (8)	2.00 (8)
	0.01/0.002	10.50 (8)	21.93 (4)	16.50§ (4)	28.75 (4)	18.00 (4)	23.50 (4)
	0.03/0.006	30.50 (8)	37.00 (8)	34.00 (8)	18.00 (8)	36.50 (8)	51.50 (8)
	0.09/0.018	46.67 (9)	48.00 (8)	60.50*† (8)	34.50 (8)	46.00 (8)	62.50 (8)
	Overall P-value	0.0710	0.1254	0.0398	0.2035	0.2964	0.2250
LVEF<35%	Placebo	-18.50 (8)	-26.25 (4)	-17.75 (4)	-36.00 (1)	-37.50 (4)	-30.75 (4)
	0.01/0.002	7.50 (8)	8.00 (8)	-30.00 (3)	20.50 (8)	28.50 (8)	33.00 (8)
	0.03/0.006	1.75 (4)	37.50 (4)	36.50 (2)	1.50 (4)	19.50 (4)	60.50 (2)
	0.09/0.018	50.25 (8)	56.25 (8)	60.00 (4)	40.50 (8)	57.87 (8)	56.25 (8)
	Overall P-value	0.0744	0.4426	0.1363	0.8142	0.2808	0.6576
Combined	Placebo	-1.50§ (8)	-0.57§ (8)	-1.50§ (8)	-14.00 (8)	-15.57 (8)	-11.1196 (8)
	0.01/0.002	11.50§ (8)	13.250 (8)	6.71§ (7)	28.50 (16)	26.94 (11)	28.70§ (9)
	0.03/0.006	18.50§ (8)	27.25 (8)	26.14 (7)	10.67 (9)	27.00 (10)	56.50* (7)
	0.09/0.018	51.50*†‡ (8)	52.11*† (9)	51.50*† (10)	36.50 (8)	50.50 (8)	72.75*† (8)
	Overall P-value	0.0063	0.0618	0.0026	0.1891	0.0020	0.0072

Data presented as mean change from baseline in msec with number of patients in parentheses.
Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.01/0.002 mg/kg group (P≤0.05)
‡ Significantly different from 0.03/0.006 mg/kg group (P≤0.05)
Source: Tables L.45-L.47, I.42.1-I.42.3A

Ventricular Monophasic Action Potentials

Change from Baseline in Ventricular Monophasic Action Potential (msec) at Minute 10



Source: Tables L.56-L.58

Mean Change from Baseline in Monophasic Action Potential Duration (msec)

Stratum	Dose (mg/kg)	Minute 10			Minutes 25-40		
		Paced Cycle Length (msec)					
		400	500	600	400	500	600
LVEF≤30%	Placebo	7.14‡§ (7)	2.286§ (7)	0.000§ (6)	-5.67†‡§ (7)	-13.14†‡§ (7)	-21.67†‡§ (6)
	0.010-0.020	17.00 (5)	13.00‡ (5)	10.00‡ (5)	26.00* (5)	20.17* (6)	20.67* (6)
	0.040-0.064	37.60* (5)	38.80*† (5)	39.60*† (5)	36.20* (5)	31.67* (6)	30.00* (6)
	0.080-0.096	41.20* (5)	51.20* (5)	52.20* (5)	48.17* (6)	50.50* (6)	54.67* (6)
	Overall P-value	0.0207	0.0080	0.0110	0.0014	0.0002	0.0001
LVEF>30%	Placebo	-4.00†‡§ (5)	-5.40†‡§ (5)	-6.000§ (5)	-11.25†‡§ (4)	0.00†‡§ (4)	1.50†§ (4)
	0.010-0.020	30.40* (5)	35.80*§ (5)	36.67§ (3)	50.00* (6)	40.00* (6)	36.75§ (4)
	0.040-0.064	50.20* (4)	65.25*† (4)	63.00* (3)	48.25* (4)	46.50* (4)	117.00*† (2)
	0.080-0.096	66.00* (4)	66.00*† (4)	66.00*† (4)	76.75* (4)	66.00* (4)	74.75* (4)
	Overall P-value	0.0012	0.0010	0.0026	0.0017	0.0007	0.0008
Combined	Placebo	3.00†§ (12)	-0.857†§ (12)	1.00†§ (11)	-7.20†‡§ (11)	-6.91†‡§ (11)	-13.09†‡§ (10)
	0.010-0.020	26.00* (10)	26.00*§ (10)	24.38*§ (8)	40.20* (12)	30.08*§ (12)	27.00*§ (10)
	0.040-0.064	43.60* (10)	54.00*† (10)	55.00*† (7)	42.20* (10)	38.00* (10)	70.83*† (7)
	0.080-0.096	53.50* (10)	58.30*† (9)	59.50*† (10)	60.90* (10)	59.11*† (9)	60.70*† (10)
	Overall P-value	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Data presented as mean change from baseline in msec with number of patients in parentheses.
Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.010-0.020 mg/kg group (P≤0.05)
‡ Significantly different from 0.040-0.064 mg/kg group (P≤0.05)
§ Significantly different from 0.080-0.096 mg/kg group (P≤0.05)
Source: Tables L.56-L.58, L.73.1-L.75.3

Atrial-His (AH) Intervals and His-Ventricular (HV) Intervals

Mean Change from Baseline in A-H and H-V Interval (msec)

	Paced Cycle Length (msec)				
Dose (mg/kg)	**350**	**400**	**450**	**500**	**600**
A-H Interval (msec)					
Placebo	**13.25 (4)**	**-1.14 (7)**	**-21.29 (7)**	**9.33 (9)**	**20.00 (9)**
0.01/0.002	**-17.50 (2)**	**6.60 (5)**	**28.00 (7)**	**13.56 (9)**	**1.13 (8)**
0.02/0.004	**75.50 (2)**	**61.40 (5)**	**40.33 (6)**	**28.71 (7)**	**8.00 (6)**
0.03/0.006	**20.00 (1)**	**13.00 (3)**	**34.75 (4)**	**34.60 (5)**	**21.75 (8)**
H-V Interval (msec)					
Placebo	**3.00 (10)**	**3.64 (11)**	**3.09 (11)**	**1.73 (11)**	**3.50 (10)**
0.01/0.002	**1.67 (3)**	**2.50 (6)**	**1.38 (8)**	**5.67 (9)**	**-1.63 (8)**
0.02/0.004	**4.50 (4)**	**4.67 (6)**	**5.00 (6)**	**5.00 (7)**	**2.83 (6)**
0.03/0.006	**4.80 (5)**	**6.00 (6)**	**5.83 (6)**	**2.86 (7)**	**6.44 (9)**

Data presented as mean change from baseline in msec with number of patients in parentheses.
Bold numbers indicate significant changes from baseline (P≤0.05)
Source: Tables L.50 and L.51

QT Interval and QTc Intervals

QT Interval Mean Change from Baseline and Repeated Measures Means (msec)

Stratum	Dose (mg/kg)	Min 10	Min 25	Min 40	Repeated Measures	Overall P-value
LVEF≥35%	Placebo	0.19	-8.14	-12.88	-6.94†§	0.0124
	0.01/0.002	88.60	67.80	65.20	63.67*	
	0.02/0.004	62.00	68.67	77.80	67.22*	
	0.03/0.006	98.83	68.00	94.80	84.88*	
LVEF<35%	Placebo	9.00	18.00	-1.00	-4.00†§	0.0104
	0.01/0.002	42.33	56.67	38.00	40.13§	
	0.02/0.004	66.40	77.20	74.00	69.33*	
	0.03/0.006	108.80	104.00	104.80	102.87*†	
Combined	Placebo	2.45	4.70	-8.88	-4.18†‡§	0.0001
	0.01/0.002	69.91	61.45	46.60	51.80*§	
	0.02/0.004	64.60	68.45	69.40	64.07*	
	0.03/0.006	99.64	84.38	88.00	90.73*†	

Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.01/0.002 mg/kg group (P≤0.05)
‡ Significantly different from 0.02/0.004 mg/kg group (P≤0.05)
§ Significantly different from 0.03/0.006 mg/kg group (P≤0.05)
Source: Tables L.84, L.87.1-L.87.3

QTc Interval Mean Change from Baseline and Repeated Measures Means (msec)

Stratum	Dose (mg/kg)	Min 10	Min 25	Min 40	Repeated Measures	Overall P-value
LVEF≥35%	Placebo	6.71	-1.14	-7.86	-0.76†§	0.0377
	0.01/0.002	44.60	78.40	78.60	66.53*	
	0.02/0.004	43.33	44.33	73.17	53.61	
	0.03/0.006	104.80	81.67	76.40	90.87*	
LVEF<35%	Placebo	23.25	23.67	6.25	14.67§	0.0058
	0.01/0.002	47.33	51.33	28.00	37.20§	
	0.02/0.004	53.60	67.40	48.50	47.50§	
	0.03/0.006	88.80	91.80	66.00	83.87*†‡	
Combined	Placebo	13.73	8.00	-2.72	2.67†‡§	0.0008
	0.01/0.002	46.09	63.64	52.40	54.17*§	
	0.02/0.004	48.00	54.82	62.60	51.17*§	
	0.03/0.006	96.45	86.27	82.20	89.87*†‡	

Bold numbers indicate significant changes from baseline (P≤0.05)
* Significantly different from placebo group (P≤0.05)
† Significantly different from 0.01/0.002 mg/kg group (P≤0.05)
‡ Significantly different from 0.02/0.004 mg/kg group (P≤0.05)
§ Significantly different from 0.03/0.006 mg/kg group (P≤0.05)
Source: Tables L.85, L.89.1-L.89.3

2.5 SAFETY RESULTS[3]

2.5.1 Overview

No patients enrolled in the study died. No patient withdrew from the trial because of an adverse event. However, the infusion of study drug was discontinued in a patient because of two episodes of nonsustained polymorphic ventricular tachycardia (Patient #2303; 0.03/0.006 mg/kg). In addition, one serious adverse event was reported: a pulmonary embolism in a patient with a LVEF <35% who received ibutilide fumarate 0.01/0.002 mg/kg (Patient #2109). See the patient narratives below for summaries of these cases.

Considering only the cardiovascular system, several adverse events occurred only in patients treated with ibutilide but not with placebo. These included atrial fibrillation (n=2), bradycardia (n=1), bundle branch block (n=2), hypotension (n=3), nonsustained monomorphic ventricular tachycardia (n=1), and nonsustained polymorphic ventricular tachycardia (n=1). Sustained monomorphic ventricular tachycardia occurred in one patient receiving ibutilide (0.02/0.004 mg/kg) and in one patient receiving placebo. The cases of ventricular tachycardia are summarized below in the patient narratives.

2.5.2 Patient Narratives

This section summarizes the clinical course of patients who experienced adverse events that were serious (Patient #2109), that led to discontinuation of the infusion of study medication (Patient #2303), or that were classified as a ventricular tachycardia (Patients #2303, #1102, #2207, #2304). The cases are ranked in the order of the patient number.

Patient #1102: *Nonsustained monomorphic ventricular tachycardia, Right bundle-branch block*; This patient was a 21-year-old white man with a history of supraventricular tachycardia and asthma. His left ventricular ejection fraction was 55%. He received a loading infusion of 0.01 mg/kg ibutilide fumarate and a maintenance infusion of 0.002 mg/kg ibutilide fumarate. At the end of the maintenance infusion, right bundle branch block was noted on the electrocardiogram. Approximately two hours after the end of the infusions, five beats of nonsustained monomorphic ventricular tachycardia were note. Two hours after the infusion the QTc was 0.431 sec[a]. The event was not felt to be serious and the patient recovered without any intervention. The investigator felt that the event was possibly related to the investigational medication.

Patient #2109: *Pulmonary embolism*; This patient was a 69-year old white man with a history of three myocardial infarctions of which the last was four years before admission. Catheterization six days prior to admission showed disease of three valves and abnormal wall function. He was admitted with chest discomfort. On admission he had rare premature ventricular contractions and couplets which progressed to asymptomatic non-sustained ventricular tachycardia. He was treated prophylactically with lidocaine. His ejection fraction was 32% (determined by catheterization). He received the 0.01 mg/k loading dose and the 0.002 mg/kg maintenance infusion of ibutilide fumarate. The day after infusion, the patient was diagnosed with pulmonary emboli (unknown start time) after he complained of severe shortness of breath and was found to have abnormal arterial blood gases and an abnormal perfusion scan. The patient remained hospitalized while

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[3] Safety issues are discussed comprehensively in Dr. Gordon's review.

anticoagulation therapy was undertaken. The symptoms subsided three days later. Neither the investigator nor the principal monitor considered the pulmonary emboli to be caused by ibutilide.

Patient #2207: *Sustained monomorphic ventricular tachycardia*; This 65-year-old white man had a history of coronary artery disease and congestive heart failure. He was undergoing electrophysiological evaluation of ventricular tachycardia. The patient had a left ventricular ejection fraction of 20%. A screening electrocardiogram showed first-degree AV block and a prolonged QTc interval of 0.466 sec[*]. He received a loading dose of 0.02 mg/kg ibutilide fumarate followed by a maintenance infusion of 0.004 mg/kg ibutilide fumarate. Six hours after the end of the infusion the QTc was 0.446 sec[*]. Approximately 11 hours after the end of the infusions the patient was noted to have wide complex tachycardia which was thought to be sustained monomorphic ventricular tachycardia. The patient recovered with no residual effects and this event was neither felt to be serious nor related to the investigational medication.

Patient #2303: *Nonsustained polymorphic ventricular tachycardia*; This patient was a 61 year-old white man with a history of nonsustained ventricular tachycardia (VT) and ischemic cardiomyopathy. He underwent electrophysiological evaluation following complaints of palpitations, lightheadedness, and nonsustained VT. He had an ejection fraction of 15-20%. He was assigned to receive a loading dose of 0.03 mg/kg and a maintenance infusion of 0.006 mg/kg ibutilide fumarate. During infusion, the patient's QT interval increased from 440 to 520 msec. Twelve minutes after the infusion began, during atrial threshold testing, the patient developed polymorphic VT. The atrial pacing was immediately stopped. The VT persisted for 10-12 seconds before it terminated spontaneously. He experienced one more episode of spontaneous nonsustained polymorphic VT that was initiated by a long-short interval and was preceded by QTu alternans. The infusion was terminated. Magnesium was administered and the patient underwent ventricular pacing at a cycle length of 800 msec for 15 minutes. The QT had decreased to 440 msec at Hour 2 and the patient did well thereafter without further complications. The investigator considered the nonsustained polymorphic VT to be related to study medication.

Patient #2304: *Monomorphic ventricular tachycardia*. This 41-year-old white man had a history of two previous myocardial infarctions. He experienced a cardiac arrest three weeks prior to the study, and he had a left ventricular ejection fraction of 30%. He was undergoing electrophysiologic evaluation of ventricular tachycardia. The patient received placebo. Toward the end of the maintenance infusion, the patient developed monomorphic ventricular tachycardia which was terminated by pacing. The patient's QTc was 0.426 sec[*] at baseline and 0.445 sec[*] at minute 25. The event was neither felt to be serious nor related to treatment.

3. REVIEWER'S COMMENTS

This was a randomized, placebo-controlled study that evaluated the electrophysiological effects, hemodynamic effects, and the pharmacokinetics of infusions of ibutilide fumarate in subjects undergoing invasive electrophysiological study.[4] The effects of increasing doses of intravenous ibutilide were evaluated in three sequential dosing groups, each of which was split into two strata on the basis of the left ventricular ejection fraction (LVEF≥35% or LVEF<35%). The patients within each stratum were randomly allocated to treatment with ibutilide fumarate or placebo. Within each of the dosing groups, the dosing regimen consisted of a 10-minute infusion (i.e., a "loading" dose), followed by a 30-minute infusion (i.e., a "maintenance" infusion).

Forty-seven (47) patients enrolled in the study: 25 with a LVEF at least 35%, and 22 with a LVEF of less than 35%. As summarized in the table below, 12 patients received a placebo bolus followed by a placebo maintenance infusion, 12 patients received a bolus of ibutilide fumarate 0.001 mg/kg followed by a maintenance infusion of 0.002 mg/kg, 12 patients received 0.02 mg/kg followed by 0.004 mg/kg, and 11 patients received 0.03 mg/kg followed by 0.006 mg/kg. The table below describes the distribution of the patients by treatment group and LVEF stratum:

Distribution of Subjects by Treatment Group and LVEF stratum

Group A (LVEF≥35%)			Group B (LVEF<35%)		
	——Dosing Regimen——			——Dosing Regimen——	
n[c]	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)	n[c]	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)
6:2	0.01	0.002	6:2	0.01	0.002
6:2	0.02	0.004	6:2	0.02	0.004
6:2	0.03	0.006	5:2	0.03	0.006

[a] infused over 10 minutes
[b] infused over 30 minutes
[c] number of patients treated with ibutilide fumarate : number of patients treated with placebo.

General: The design of this study was adequate to obtain reliable pharmacokinetic, pharmacodynamic, and safety data for the studied population. Of the 47 treated patients, 39 (83.0%) were white, 7 (14.9%) were black, and 1 (2.1%) was of an "other" race. Forty-one (87.2%) of the patients were men, and six (12.8%) were women. Nineteen (40.4%) of the patients were more than 65 years of age, and the most elderly patient was 80 years old. Pediatric patients were excluded from the trial; the youngest patient was 21 years old. Patients were required to have a baseline QTc of less than 0.440 sec[4], and to have 1:1 atrioventricular (AV) conduction. Patients with hypertension, congestive heart failure, angina pectoris, or a history of torsades de pointes were excluded from the trial. The use of class I or class III antiarrhythmic medications was prohibited within five half-lives prior to enrollment.

[4] Note: the protocol did not specify explicitly whether investigators were to be blinded, but the study report states that, with the exception of the first patient enrolled, the study was double-blind.

Hence, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to patients with different demographic characteristics (e.g., subjects with age, sex, or racial differences), cardiovascular disease, cardiac abnormalities (e.g., structural, mechanical, or electrical abnormalities), or with baseline QTc intervals that exceed 0.440 sec[8]. This study does not contribute any information about possible interactions of ibutilide with class I or class III antiarrhythmic agents.

The different doses of ibutilide were evaluated sequentially, rather than concurrently. Thus, effects of the drug may be confounded with the effects of time (i.e., "period effects").

The sponsor is not seeking an indication for the prolonged administration of ibutilide fumarate. Nonetheless, it should be noted that in this study the pharmacodynamics and safety of ibutilide were not evaluated at steady state. That is, the study was not performed at steady-state blood levels, nor at steady-state tissue levels of the drug.

Dose exploration: As planned, the sponsor studied only the three regimens outlined above. The effects of higher doses were not evaluated. Thus, the effects and tolerability of dose regimens with a bolus dose of greater than 0.03 mg/kg and a maintenance infusion of greater than 0.006 mg/kg for thirty minutes remain unknown. The failure to explore the effects of these higher doses has at least two consequences:

- possible associations of QTc prolongation with arrhythmogenesis were not assessed;
- at these higher doses, *other* possible electrophysiological effects, hemodynamic effects, other pharmacodynamic effects, or *other* adverse effects of ibutilide were not evaluated.

The sponsor seeks to obtain approval for 10-minute infusions of ibutilide fumarate that are not adjusted for body weight. For reference, then, the table on the following page provides the absolute doses administered to subjects of varying weights in the different treatment groups. In this trial, the lightest patient was 54.1 kg (119 lbs), and the heaviest was 123.6 kg (272 lbs).

Pharmacokinetics: As stated by the sponsor, post-infusion concentrations rapidly declined in a multi-exponential fashion, and concentrations were typically around or below 1 ng/ml within 1 hour after the maintenance infusion. However, a high degree of interpatient variability was observed in all dose groups, and the presence of extreme outliers resulted in atypically high measures of variability. In addition, many concentration-time profiles were atypical: some were erratic, and some showed maximum concentrations later than the end of the first infusion. In general, maximum ibutilide plasma concentrations and area under the concentration versus time profile values increased in a dose-related manner with increase in dose and were independent of left ventricular function. The pharmacokinetics of ibutilide were similar in patients with a LVEF <35% relative to patients with a LVEF ≥35%. Pharmacodynamic data were also atypical in regards to previous studies. Although studies in healthy volunteers have shown that infusion of ibutilide fumarate results in prolongation of the QTC interval and this prolongation is directly correlated with ibutilide fumarate dose and ibutilide plasma concentrations, no such correlation was found in this study.

Absolute Dose of Ibutilide Fumarate (mg) by Treatment Group and Body Weight[a]

	Treatment group								
Body weight	0.01→0.002 mg/kg			0.02→0.004 mg/kg			0.03→0.006 mg/kg		
	Bolus	Maint[b]	Total	Bolus	Maint[b]	Total	Bolus	Maint[b]	Total
40 kg	0.40	0.08	0.48	0.80	0.16	0.96	1.20	0.24	1.44
50 kg									
60 kg									
70 kg									
80 kg									
90 kg									
100 kg									
110 kg	1.10	0.22	1.32						
120 kg	1.20	0.24	1.44						
130 kg	1.30	0.26	1.56				3.90	0.78	4.68

[a] Shaded cells encompass the range of body weights for patients included in this trial.
[b] Maint = Maintenance

Pharmacodynamics: Invasive hemodynamic measurements were made of cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure. These parameters did not appear to change from baseline in a consistent dose-related way either in patients with a LVEF < 35%, in patients with a LVEF ≥35%, or in patients overall when these strata were combined. These parameters changed from baseline to a similar extent in patients treated with ibutilide and in patients treated with placebo.

Ibutilide appeared to depress sinus node function somewhat, but these effects generally were not marked. Ibutilide appears to prolong the basic cycle length and to prolong the corrected sinus node recovery time to some extent. Ibutilide prolonged the maximal sinus node recovery time. These effects may be of greater significance in patients with intrinsically abnormal sinus node function, a group that was not systematically evaluated during the development of the drug.

Similarly, ibutilide appears to depress AV nodal function to some extent, but these effects also generally were not marked. Ibutilide appears to prolong both the AV and VA Wenckebach cycle lengths to a minor degree, and it also appears to prolong the AH interval somewhat. These apparent effects may be of greater significance in patients with intrinsically abnormal AV nodal function, another group that was not systematically evaluated during the development of the drug.

As expected of a Class III antiarrhythmic agent, ibutilide prolonged the duration of the atrial and ventricular monophasic action potentials, and it increased the atrial and ventricular effective refractory periods. In general, these effects were greater at the higher doses of ibutilide. Similarly,

consistent with its characterization as a Class III antiarrhythmic agent, ibutilide prolonged the QT and QTc intervals (as assessed with 12-lead ECGs). Prolongation of the QT and QTc intervals appeared to be dose-related.

Ibutilide did not appear to alter HV conduction. The drug did not appear to alter atrial or ventricular thresholds.

Safety: No patients enrolled in the study died. No patient withdrew from the trial because of an adverse event. However, the infusion of study drug was discontinued in a patient (randomized to ibutilide fumarate 0.03/0.006 mg/kg) because of two episodes of nonsustained polymorphic ventricular tachycardia. In addition, one serious adverse event was reported: a pulmonary embolism in a patient with a LVEF <35% who received ibutilide fumarate 0.01/0.002 mg/kg.

Considering only the cardiovascular system, several adverse events occurred only in patients treated with ibutilide but not with placebo. These included atrial fibrillation (n=2), bradycardia (n=1), bundle branch block (n=2), hypotension (n=3), nonsustained monomorphic ventricular tachycardia (n=1), and nonsustained polymorphic ventricular tachycardia (n=1). Sustained monomorphic ventricular tachycardia occurred in one patient receiving ibutilide (0.02/0.004 mg/kg) and in one patient receiving placebo. Thus, this trial confirms that ibutilide may induce arrhythmias, some of which may have hemodynamic consequences.

APPENDIX D

TABLE OF CONTENTS

An Open-Label Dose-Ranging Study of Intravenous Ibutilide in Patients with Inducible Ventricular Tachycardia Undergoing Electrophysiologic Study (Protocol P-7580-0013; Technical Report 7210-65-068).

(Continued)

1. DESCRIPTION OF THE STUDY

1.1 Title

An Open-Label Dose-Ranging Study of Intravenous Ibutilide in Patients with Inducible Ventricular Tachycardia Undergoing Electrophysiologic Study (Protocol P-7550-0013; Technical Report 7216-95-002).

1.2 Objectives

1.2.1 Primary Objectives

The four primary objectives specified in the protocol were to determine the effects of intravenous ibutilide on the following:

- the ability to induce ventricular tachycardia by programmed electrical stimulation
- ventricular effective refractory periods (ERP) and the duration of monophasic action potentials
- the relation of the above parameters to the QT interval of the electrocardiogram in patients undergoing electrophysiologic study
- the relationship of monophasic action potential duration/ERP ratio to cycle length

1.2.2 Secondary Objectives

The study had two prespecified secondary objectives:

- to assess the effects of ibutilide on other standard electrophysiologic parameters including sinus node recovery times and AV conduction intervals
- to correlate the pharmacokinetics of ibutilide with its electrophysiologic effects.

1.3 Experimental Design

This was an open-label study of escalating doses of intravenous ibutilide that was to be performed at 3-4 clinical centers in 60 patients with hemodynamically-stable ventricular tachycardia.[1] The effects of increasing doses of intravenous ibutilide on the ability to induce ventricular tachycardia by programmed electrical stimulation (PES) and the effects on electrophysiologic measurements were to be evaluated in three sequential dosing groups of twenty patients. Within each of the dosing groups, the dosing regimen consisted of a 10-minute infusion (i.e., a "loading" dose), followed by a 30-minute infusion (i.e., a "maintenance" infusion). The table on the next page describes the treatment scheme:

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[1] Note: the study was not placebo controlled and was not randomized.

		Dosing Regimen	
	n	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)
Group 1	20	0.005	0.001
Group 2	20	0.01	0.002
Group 3	20	0.02	0.004

[a] Infused over 10 minutes
[b] Infused over 30 minutes

To be included in the study, patients were required to be between 18 and 80 years of age and to be undergoing an invasive electrophysiologic study for documented or suspected ventricular tachycardia. Patients who received ibutilide were required to have sustained ventricular tachycardia (i.e., >30 seconds duration or terminated by pacing) that could be initiated reproducibly by programmed electrical stimulation.[2] Patients were also required to be hemodynamically stable, to have a left ventricular ejection fraction[3] of greater than 20%, normal serum electrolytes, and a baseline of QTc of no more than 0.440 sec[4]. Patients were excluded if they had a systolic blood pressure ≤90 mmHg, a diastolic blood pressure ≥105 mmHg, or if they had symptoms of angina, congestive heart failure, or other signs of distress. Patients with a history of torsades de pointes (from any cause) were excluded. The use of class I or class III antiarrhythmic medications was prohibited within five half-lives prior to enrollment.

Electrophysiologic measurements and programmed electrical stimulation were to be performed at baseline (prior to administration of study drug) and during the maintenance infusion.

1.4 Drug Administration

Ibutilide was supplied in 10 ml clear glass ampules in a concentration of 2.5 mg/ml. The solution was isotonic and buffered with acetate to a pH of 4.6. For administration to patients, the solution was to be diluted with 5% dextrose in water (D_5W). Matching ampules of placebo containing only the vehicle were also supplied. Drug administration was to be terminated for any of the following reasons: (a) decrease of systolic blood pressure to <80 mmHg, (b) a change in rhythm or atrioventricular conduction that was not hemodynamically tolerated or that threatened patient safety, (c) development of new bundle branch block or increase in QRS duration of greater than 50%; (d) an adverse event that threatened patient safety.

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[2] As stated in the original protocol, the ventricular tachycardia must have been initiated at least twice. In a subsequent amendment, however, one induction was sufficient if the patient required electrical cardioversion and the investigator felt that repeated cardioversion was unacceptable.

[3] Left ventricular ejection fraction was to be determined by angiography, radionuclide scan, or echocardiography within 30 days prior to the study.

1.5 Evaluations

Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- resting blood pressure (left arm) and heart rate
- electrophysiological (EP) measurements (atrial and ventricular refractory periods, duration of atrial and ventricular monophasic action potentials (MAPs), sinus node recovery times)
- programmed stimulation for induction of ventricular tachycardia
- 12-lead electrocardiograms
- safety laboratories: blood for safety laboratories (hematology, chemistry, coagulation) and urine for urinalysis and microscopic evaluation
- blood samples for drug levels (obtained through six hours following the end of the maintenance infusion)
- digoxin levels (if applicable)
- medical events

The subjects were also monitored with a continuous electrocardiographic recording. See the table on the next page for a summary of study evaluations.

Activity	Screen	Time from start of loading dose (min)										Time from end of maintenance infusion										
												Minutes				Hours						
		Pre-Treat	0	5	10	15	20	25	30	35	40	5	10	15	30	1	2	4	6	8	16	24
Informed Consent[1]	x																					
History/Physical Exam	x																					
12-Lead Electrocardiogram	x	x			x			x			x				x	x	x	x			.	
EP Measurements[2]		x			x		———															
Programmed Stimulation for VT Induction		x					———															
Safety Labs	x																					x
Continuous ECG Recording/Monitoring[3]		———										———										
Resting BP/HR	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Ibutilide 10-Minute Loading Dose			———																			
Ibutilide 30-Minute Maintenance Infusion					———																	
Ibutilide Plasma Concentrations		x			x			x			x	x		x	x	x	x	x	x			
Digoxin Level (if applicable)		x									x											

[1] LV ejection fraction must be obtained prior to enrollment.

[2] All EP measurements will be made before the loading dose and after the maintenance infusion. Atrial and ventricular refractory periods and MAP duration will be recorded before the loading dose, after the loading dose, and at the end of the maintenance infusion.

[3] Only standard single lead ECG monitoring is required between 30 minutes and 24 hours after the maintenance infusion.

2. RESULTS

2.1 Disposition of Subjects

2.1.1 Enrolled subjects

Fifty-five (55) patients were enrolled in the study from August 1991 through March 1994 by 16 investigators. Four investigators did not enroll any patients. One patient (#224) discontinued the infusion of ibutilide after the loading dose of 0.020 mg/kg and withdrew from the study because of the development of hemodynamically unstable ventricular tachycardia. This patient experienced three episodes of polymorphic ventricular tachycardia, two of which were sustained and one of which was nonsustained.[4]

Of the remaining 54 patients, the infusion of ibutilide was discontinued in five additional patients[5] Three of these five patients (#204, #216, #802) also developed hemodynamically unstable ventricular tachycardia, a fourth patient (#223) experienced prolongation of the QTc interval, and a fifth patient (#220) developed hypotension associated with angina and dyspnea. All five of these subjects completed the planned study course. Each of these occurrences was reported as a medical event, except for the ventricular tachycardia in patient #802. In this patient, the ventricular tachycardia was induced per protocol but required anesthesia to be converted electrically.

The patients were assigned to sequential dose groups of ibutilide fumarate (i.e., patients were not randomly assigned to treatment). Of the 55 enrolled patients, 20 received ibutilide fumarate 0.005/0.001 mg/kg, 20 receive ibutilide fumarate 0.01/0.002 mg/kg, and 15 received ibutilide fumarate 0.02/0.004 mg/kg.

2.1.2 Evaluable subjects

Of the 55 patients enrolled, the sponsor considered seven patients to be nonevaluable for efficacy:

a) Two patients (#101, #102) were considered nonevaluable because polymorphic VT was induced at baseline, rather than monomorphic VT as required by the protocol.

b) Three patients (#220, #223, and #224) were considered nonevaluable because reinduction of VT during the infusion of ibutilide fumarate was not attempted because of adverse events.

c) Two patients (#1500 and #1501) each received 2.5 mg of ibutilide fumarate during the loading dose (0.029 mg/kg and 0.033 mg/kg, respectively), rather than 0.010 mg/kg as per the protocol. They both received the correct maintenance infusion of 0.002 mg/kg over 30 minutes.

2.2 Demographic and Baseline Characteristics

Of the 55 patients enrolled in the trial, 47 were male and 8 were female. Fifty-two (52) of the patients were white and 3 were black. Overall, the patients had a mean (±s.d.) age of 64.9 ±

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[4] See the patient narratives in section 2.5.4.

[5] Overall, including patient #224, the ibutilide infusion was discontinued in six patients.

9.2 years, a mean body weight of 176.7 ± 40.6 pounds, and a mean height of 68.5 ± 3.8 inches. The table below describes the demographic and baseline characteristics of the patients by treatment group.

Each of these baseline characteristics was similar across treatment groups, with the exception of body weight (p=0.0057). The mean body weight in the 0.02/0.004 mg/kg treatment group (201.1 lbs) was significantly greater than the mean weight in the 0.005/0.001 mg/kg treatment group (157.9 lbs; p=0.0014).

Baseline Characteristics of Subjects by Dose Group

	Ibutilide (mg/kg)		
	0.005/0.001 (n=20)	0.01/0.002 (n=20)	0.02/0.004 (n=15)
Race (n) (white/black)	17/3	20/0	20/0
Sex (n) (♂/♀)	17/3	16/4	14/1
Age (years) (mean±s.d.)	68.35 ±6.6	62.65 ±10.9	63.3 ±8.9
Weight (lbs) (mean±s.d.)	157.9 ±34.2	177.3 ±40.7	201.1 ±36.9
Height (inches) (mean±s.d.)	68.2 ±3.5	68.1 ±3.9	69.6 ±3.1

2.3 PHARMACOKINETIC RESULTS[6]

Plasma concentration data were available from 50 of the 55 patients who received ibutilide fumarate in this study. The pharmacokinetic results are summarized in the table on the next page. Individual patient profiles of concentration versus time are shown by treatment group on pages 8-9. The relationship of plasma concentration to the length of the QTc interval or to changes in the QTc interval are shown in the figures on page 10.

As stated by the sponsor, post-infusion concentrations declined rapidly in a multi-exponential fashion, and concentrations were typically around or below 1 ng/ml within 1 hour after the maintenance infusion. However, a high degree of interpatient variability was observed in all dose groups, and the presence of extreme outliers resulted in atypically high measures of variability. In addition, many concentration-time profiles were atypical: some were erratic, and some showed

[6] For a complete discussion of pharmacokinetic issues, see the review by the biopharmaceutical reviewer.

maximum concentrations later than the end of the first infusion. In general, maximum ibutilide plasma concentrations and area under the concentration versus time profile values increased in a dose-related manner with increase in dose. Pharmacodynamic data were also atypical in regards to previous studies. Although studies in healthy volunteers have shown that infusion of ibutilide fumarate results in prolongation of the QTc interval and this prolongation is directly correlated with ibutilide fumarate dose and ibutilide plasma concentrations, no such correlation was found in this study.

Estimates of Pharmacokinetic Parameters

Table 1
Ibutilide Fumarate Pharmacokinetic Parameter Estimates Following Intravenous Infusion in Patients Undergoing Invasive Electrophysiologic Study

Parameter		Treatment Group		
		A (0.005 mg/kg/10 min then 0.005 mg/kg/30 min)	B (0.01 mg/kg/10 min then 0.005 mg/kg/30 min)	C (0.02 mg/kg/10 min then 0.005 mg/kg/30 min)
Number of Patients		19	17	14
C_{max} (ng/mL)	Mean ± SD Median Range	21.9 ± 30.8 1.48	7.91 ± 10.8 4.98	130 ± 210 11.4
T_{max} (h)	Mean ± SD Median Range	0.28 ± 0.16 0.17	0.49 ± 0.55 0.17	0.34 ± 0.15 0.17
$AUC_{0-\infty}$ (ng-h/mL)	Mean ± SD Median Range	16.9 ± 16.4 8.1	10.8 ± 10.1 6.2	48.4 ± 55.8 18.3
λ_z (h^{-1})	Mean ± SD Median Range	0.147 ± 0.151 0.107	0.16 ± 0.10 0.15	0.20 ± 0.15 0.15
$t_{1/2}$ (h)*		4.7	4.3	4.7

*Harmonic mean value

Individual Patient Profiles of Plasma Concentration versus Time

Figure 1. Individual patient ibutilide plasma concentration-time profiles following 0.005 mg/kg/10 min then 0.001 mg/kg/60 min intravenous infusions of ibutilide fumarate

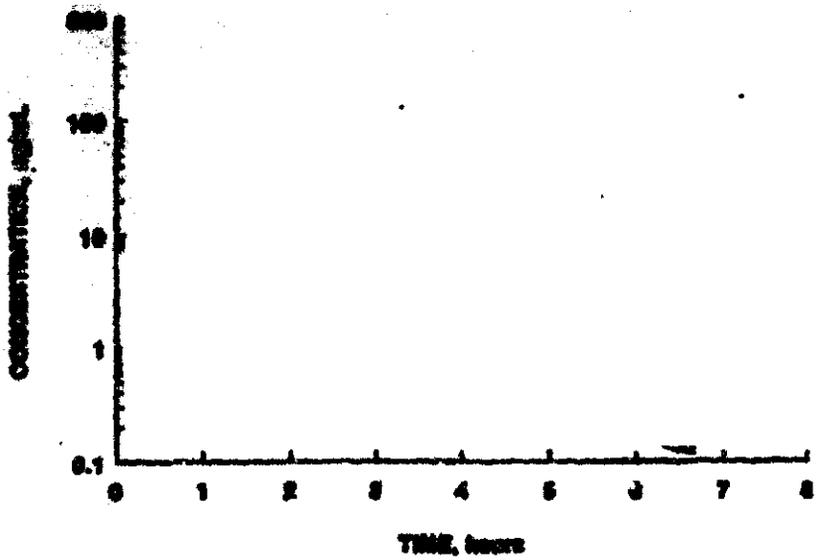
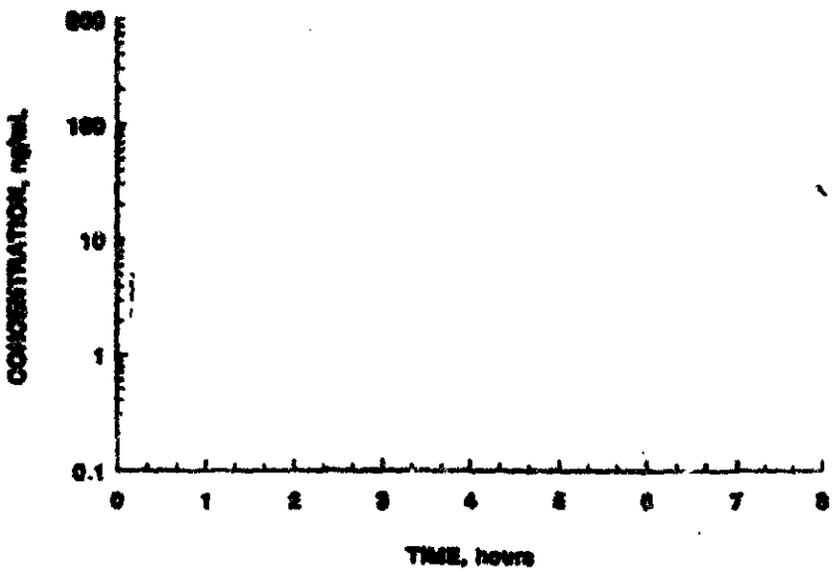
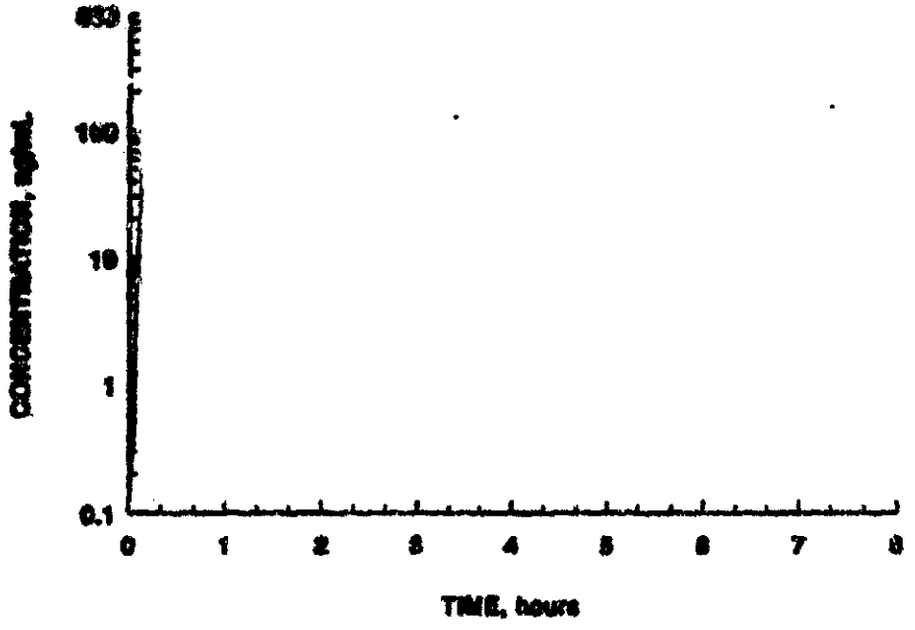


Figure 2. Individual patient ibutilide plasma concentration-time profiles following 0.01 mg/kg/10 min then 0.002 mg/kg/60 min intravenous infusions of ibutilide fumarate



Individual Patient Profiles of Plasma Concentration versus Time (continued)

Figure 9. Individual patient ibutilide plasma concentration-time profiles following 0.02 mg/kg/10 min then 0.004 mg/kg/30 min intravenous infusions of ibutilide fumarate



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QTc Interval and Change in QTc Interval versus Plasma Concentration

Figure 4. Individual patient QTc interval versus fosfidia plasma concentration at the end of the first infusion (loading dose)

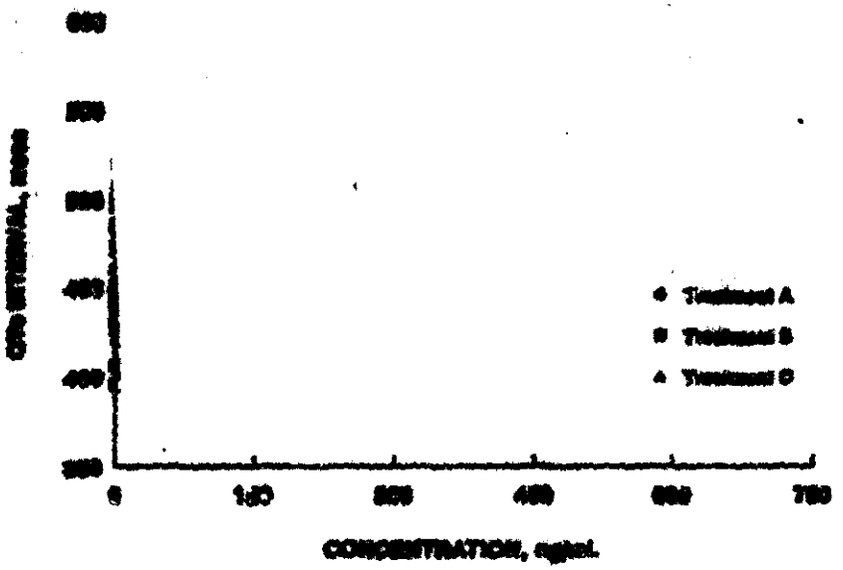
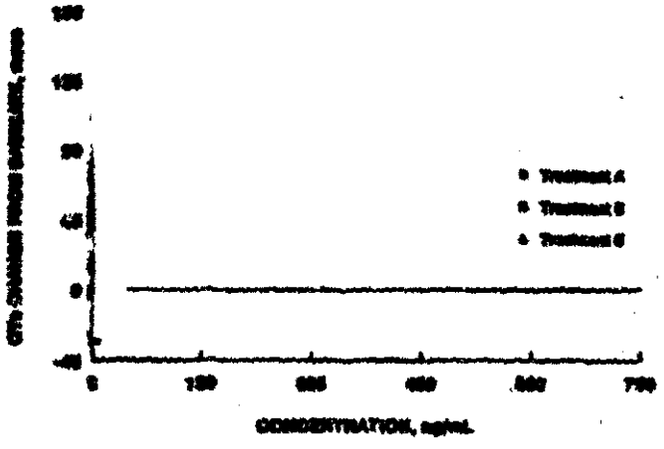


Figure 5. Individual patient change in QTc interval (from predose) versus fosfidia plasma concentration at the end of the first infusion (loading dose)



Treatment A: 0.008 mg/kg/10 min then 0.001 mg/kg/30 min
Treatment B: 0.01 mg/kg/10 min then 0.002 mg/kg/30 min
Treatment C: 0.02 mg/kg/10 min then 0.004 mg/kg/30 min

2.4 PHARMACODYNAMIC RESULTS

2.4.1 Invasive hemodynamic measurements

Invasive hemodynamic measurements were not recorded for this study.

2.4.2 Electrophysiological Data

The data presented in this section are for evaluable patients only (n=46).

Electrophysiological measurements were made of the basic cycle length, the sinus node recovery time, the A-V and V-A Wenckebach cycle lengths, the lengths of the atrial, ventricular, and A-V nodal effective refractory periods, the lengths of the atrial and ventricular monophasic action potentials (at 90% depolarization), the atrial and ventricular thresholds, and the lengths of the AH, HV and QRS intervals. QT and QTc intervals were measured from surface electrocardiograms.

2.4.2.1 Effects of ibutilide on functional tests of the sinoatrial node (SAN)

2.4.2.1.1 Basic cycle length

Background: The basic cycle length is the interval between consecutive, spontaneous electrocardiographic depolarizations. A basic cycle length of 1000 msec (i.e., one second) corresponds to a heart rate of 60 beats per minute, and a basic cycle length of 600 msec corresponds to a heart rate of 100 beats per minute.

Similarity at baseline and Changes from baseline: At baseline the mean basic cycle length was similar across the three dose groups. The basic cycle length did not change significantly from baseline within any of the dose groups, and changes across dose groups were similar. See the table below.

Basic Cycle Length (BCL):
Mean Baseline Values and Mean Changes from Baseline

	Baseline		Δ from baseline (at the end of the maintenance infusion: Minute 20-40)	
	n	BCL[a] (msec)	n	Δ BCL[b] (msec)
0.005 mg/kg / 0.001 mg/kg	17	939.3	15	24.5
0.01 mg/kg / 0.002 mg/kg	16	856.5	13	-11.8
0.02 mg/kg / 0.004 mg/kg	11	894.5	10	33.2
Total	44	883.0	38	14.4

[a] Mean values for the dose groups were not significantly different at baseline: one-way ANOVA p=0.3769.
[b] Changes from baseline were not significantly different across dose groups: one-way ANOVA p=0.659

2.4.2.1.2 Corrected sinus node recovery time (CSNRT)

Background: The sinus node recovery time (SNRT) is the interval from the last paced atrial beat to the first spontaneous atrial depolarization that originates in the sinus node. In this trial, sinus node recovery times were evaluated following atrial pacing for 30 seconds at four paced cycle lengths (600, 500, 400, and 350 msec). Because the SNRT depends on the basic sinus rate, it is often expressed as the corrected sinus node recovery time (i.e., the SNRT minus the basic cycle length). The upper limit of normal for the SNRT ranges from about 1400 msec to 1550 msec, and the upper limit of normal for the corrected sinus node recovery time (CSNRT) ranges from approximately 500 msec to 550 msec.

Similarity at baseline: At baseline, the mean CSNRT was similar across each of the three dose groups at each of the four paced cycle lengths (p values by one-way ANOVA ranged from 0.28 to 0.84). See the top table on page 14.

Changes from baseline: As shown in the top table on page 14, the mean CSNRT changed significantly from baseline in three instances:

- +294 msec within the low-dose group (0.005/0.001 mg/kg) at a PCL of 600 msec (p=0.0434);
- +65 msec within the middle-dose group (0.01/0.002 mg/kg) at a PCL of 400 msec (p=0.0361), and;
- +132.5 msec within the combined dose group at a PCL of 600 msec (p=0.0198).

At each of the paced cycle lengths the changes from baseline were not significantly different across dose groups (p values by one-way ANOVA ranged from 0.0685 to 0.9079).

Maximum changes from baseline: As noted by the sponsor, patients differ in their basic cycle lengths, and therefore each patient may need a different overdrive suppression pacing cycle length to distinguish any change in the sinus node recovery time. Thus, the dose-group mean of maximum changes from baseline in CSNRTs across all pacing cycles may better distinguish the effects of treatment. In this analysis, the CSNRT was significantly prolonged from baseline in each of the individual dose groups, and also when the dose groups were combined. Maximum changes from baseline in corrected sinus node recovery time at the end of the maintenance infusion are summarized in the bottom table on page 14.

2.4.2.2 Effects of ibutilide on functional tests of the atrioventricular node (AVN)

2.4.2.2.1 AV Wenckebach cycle length; antegrade atrioventricular conduction

Background: Pacing the atria at incrementally faster rates will prolong the AH interval, mostly by delaying conduction through the atrioventricular node. Second-degree AV block of a type 1 pattern occurs at the Wenckebach point, and this progresses to 2:1 AV block. The pacing cycle length at which second degree AV block occurs is generally between 500 and 350 msec. In this study the atria were paced at decrements in cycle length of 10 msec to determine the AV Wenckebach cycle length.

Similarity at baseline: At baseline the mean AV Wenckebach cycle length was similar for each of the three treatment groups (p=0.6715). See the top table on page 15.

Changes from baseline: As shown in the top table on page 15, at the end of the maintenance infusion (Minutes 20-40) the AV Wenckebach cycle length increased significantly from baseline in two instances:

- +16.25 msec in the low-dose group (0.005/0.001 mg/kg; p=0.0235), and;
- +37.6 msec within the combined dose group (p=0.0367).

The changes from baseline at the end of the maintenance infusion were not significantly different across dose groups (p=0.3627).

2.4.2.2.2 VA Wenckebach cycle length; retrograde atrioventricular conduction

Background: A significant percentage of individuals with normal antegrade atrioventricular (AV) conduction will not have ventriculoatrial (VA) conduction. In those with ventriculoatrial conduction, however, pacing the ventricles at incrementally faster rates will prolong VA conduction. In this study the ventricles were paced at decreasing cycle lengths to determine the VA Wenckebach cycle length.

Similarity at baseline: At baseline the mean VA Wenckebach cycle length was similar for each of the three treatment groups (p=0.5323). See the bottom table on page 15.

Changes from baseline: As shown in the bottom table on page 15, at the end of the maintenance infusion (Minutes 20-40) the VA Wenckebach cycle length increased significantly from baseline in the high-dose group and in the combined dose group. The increase from baseline also approached significance in the low-dose group:

- +104.0 msec within the high-dose group (0.02 mg/kg / 0.004 mg/kg; p=0.0023)
- +70.8 msec within the combined dose group (p=0.0001)
- +45.0 msec in the low-dose group (0.005 mg/kg / 0.001 mg/kg; p=0.0526).

The changes from baseline at the end of the maintenance infusion were not significantly different across dose groups (p=0.0665).

Corrected Sinus Node Recovery Times (msec):
Mean Baseline Values and Mean Changes from Baseline[a]

	Baseline		Δ from baseline after maintenance infusion (at Minute 20-40)		
Paced Cycle Length	n	mean (msec)	n	mean Δ (msec)	p value
600 msec					
0.005 mg/kg / 0.001 mg/kg	15	250.9	11	**293.3**	**0.0494**
0.01 mg/kg / 0.002 mg/kg	13	305.85	10	47.5	0.3769
0.02 mg/kg / 0.004 mg/kg	9	267.2	9	30.0	0.2883
Total (doses combined)	37	274.2	30	**132.5**	**0.0198**
500 msec					
0.005 mg/kg / 0.001 mg/kg	17	343.1	14	55.3	0.4469
0.01 mg/kg / 0.002 mg/kg	16	249.2	13	22.5	0.3501
0.02 mg/kg / 0.004 mg/kg	11	206.55	10	48.9	0.4761
Total (doses combined)	44	274.8	37	42.05	0.2011
400 msec					
0.005 mg/kg / 0.001 mg/kg	17	423.1	13	-10.3	0.9163
0.01 mg/kg / 0.002 mg/kg	16	255.9	13	**85.2**	**0.0361**
0.02 mg/kg / 0.004 mg/kg	11	204.0	10	-23.7	0.8094
Total (doses combined)	44	307.5	36	13.25	0.7649
350 msec					
0.005 mg/kg / 0.001 mg/kg	14	122.1	11	93.1	0.1589
0.01 mg/kg / 0.002 mg/kg	16	235.1	10	75.4	0.2961
0.02 mg/kg / 0.004 mg/kg	9	207.0	7	-48.3	0.5440
Total (doses combined)	39	186.05	28	51.4	0.2012

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.

Corrected Sinus Node Recovery Times (msec):
Mean Baseline Values and Maximal Mean Changes from Baseline[a,b]

	Baseline		Δ from baseline after maintenance infusion (at Minute 20-40)		
	n	mean (msec)	n	mean Δ (msec)	p value
0.005 mg/kg / 0.001 mg/kg	14	142.2	14	**343.3**	**0.0012**
0.01 mg/kg / 0.002 mg/kg	13	175.7	13	**166.15**	**0.0029**
0.02 mg/kg / 0.004 mg/kg	10	153.8	10	**139.1**	**0.0163**
Total (doses combined)	37	157.1	37	**225.9**	**<0.0001**

[a] Regardless of paced cycle length.
[b] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.

AV Wenckebach Cycle Length (msec):
Mean Baseline Values and Mean Changes from Baseline[a]

	Baseline		Δ from baseline[b]		
	n	mean (msec)	n	mean Δ (msec)	p value
0.005 mg/kg / 0.001 mg/kg	17	482.9	16	16.25	**0.0235**
0.01 mg/kg / 0.002 mg/kg	16	409.75	11	75.45	0.1980
0.02 mg/kg / 0.004 mg/kg	11	410.9	10	90.0	0.2120
Total	44	413.8	37	57.8	**0.0367**

[a] At end of Maintenance Infusion (Minutes 20-40).
[b] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.

VA Wenckebach Cycle Length (msec):
Mean Baseline Values and Mean Changes from Baseline[a]

	Baseline		Δ from baseline[b]		
	n	mean (msec)	n	mean Δ (msec)	p value
0.005 mg/kg / 0.001 mg/kg	6	426.7	4	45.0	0.0526
0.01 mg/kg / 0.002 mg/kg	6	475.0	4	55.0	0.1152
0.02 mg/kg / 0.004 mg/kg	6	406.7	5	104.0	**0.0023**
Total	20	440.0	13	70.8	**0.0001**

[a] At end of Maintenance Infusion (Minutes 20-40).
[b] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.

2.4.2.3 Effects of ibutilide on the atria

2.4.2.3.1 Atrial effective refractory period (AERP)

Background: The effective refractory period is the period in the cardiac cycle during which another impulse fails to be conducted. In this study according to the protocol, an extra stimulus (S_2) was to be introduced during the atrial refractory period after eight paced beats (at cycle lengths of 600 msec and 400 msec). The protocol specified a pause of four seconds between drive trains.

Similarity at baseline: At baseline the mean AERP was similar for each of the three treatment groups at each of the paced cycle lengths ($p=0.7026$ at PCL of 400 msec; $p=0.6007$ at a PCL of 600 msec). See the table on the next page.

Changes from baseline: The atrial effective refractory period was prolonged from baseline in each of the treatment groups. Significant prolongations from baseline occurred in each of the dose

groups, at both of the paced cycle lengths, after the loading dose (at Minute 10), and at the end of the maintenance infusion (at Minute 20-40). These prolongations exhibited a dose-response--prolongations at the higher doses were generally greater than prolongations at the lower doses. See the table below.

Atrial Effective Refractory Period (msec):
Mean Baseline Values and Mean Changes from Baseline[a]

	Baseline		Δ from baseline after loading dose (at Minute 10)			Δ from baseline after maintenance infusion (at Minute 20-40)		
Paced Cycle Length	n	mean (msec)	n	mean Δ (msec)	p value	n	mean Δ (msec)	p value
600 msec								
0.005 mg/kg / 0.001 mg/kg	14	260.0	13	**15.4**[b]	**0.0419**	12	**16.7**[c]	**0.0342**
0.01 mg/kg / 0.002 mg/kg	15	243.3	13	**39.2**	**0.0040**	12	**19.2**[d]	**0.0386**
0.02 mg/kg / 0.004 mg/kg	8	241.25	6	**63.3**[b]	**0.0068**	7	**52.9**[c,d]	**0.0031**
Total (doses combined)	37	249.2	32	**34.1**	**<0.0001**	31	**25.8**	**0.0001**
400 msec								
0.005 mg/kg / 0.001 mg/kg	10	234.0	8	15.0	0.4304	10	19.0	0.2268
0.01 mg/kg / 0.002 mg/kg	14	225.0	11	**31.8**	**0.0455**	10	16.0	0.1595
0.02 mg/kg / 0.004 mg/kg	6	238.3	4	64.75	0.1992	5	32.0	0.1642
Total (doses combined)	30	230.7	23	**31.7**	**0.0103**	25	**20.40**	**0.0182**

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] After the loading dose at a PCL of 600 msec, the prolongation from baseline was significantly greater in the high-dose group compared to the low-dose group (pairwise p=0.0069).
[c] After the maintenance infusion at a PCL of 600 msec, the prolongation from baseline was significantly greater in the high-dose group compared to the low-dose group (pairwise p=0.0161).
[d] After the maintenance infusion at a PCL of 600 msec, the prolongation from baseline was significantly greater in the high-dose group compared to the mid-dose group (pairwise p=0.0241).

2.4.2.3.2 Atrial thresholds

Similarity at baseline: At baseline, the mean atrial threshold was similar for each of the three dose groups (p=0.5536). See the table on the next page.

Changes from baseline: The mean atrial threshold did not change significantly from baseline within any of the treatment groups. Changes from baseline were similar across the treatment groups both after the loading dose at Minute 10 (p=0.5101) and also at the end of the maintenance infusion at Minute 20-40 (p=0.6689). See the table on the next page.

Atrial Threshold (mA):
Mean Baseline Values and Mean Changes from Baseline*

	Baseline		Δ from baseline after loading dose (at Minute 10)			Δ from baseline after maintenance infusion (at Minute 20-40)		
	n	mean (mA)	n	mean Δ (mA)	p value	n	mean Δ (mA)	p value
0.005 mg/kg / 0.001 mg/kg	17	0.87	16	0.11	0.5625	17	0.33	0.4277
0.01 mg/kg / 0.002 mg/kg	18	0.64	15	-0.07	0.1605	13	0.02	0.7246
0.02 mg/kg / 0.004 mg/kg	11	0.72	11	-0.06	0.3800	10	-0.03	0.8872
Total (doses combined)	44	0.75	42	-0.00	0.9591	40	0.14	0.4349

2.4.2.4 Effects of ibutilide on the ventricles

2.4.2.4.1 Ventricular effective refractory period (VERP)

Ventricular effective refractory periods were measured at the right ventricle, both at the apex and at the outflow tract. Because of the small number of patients with measurements at the outflow tract, results will be shown only for the apical measurements. Although not shown, the results from the outflow tract were generally consistent with those from the apex.

Background: The effective refractory period is the period in the cardiac cycle during which another impulse fails to be conducted. In this study according to the protocol, an extra stimulus (S_2) was introduced during the ventricular refractory period after eight paced beats (at cycle lengths of 600, 500, and 400 msec). The protocol specified a pause of 4 seconds between drive trains.

Similarity at baseline: At baseline the mean ventricular effective refractory periods were similar across dose groups at each of the paced cycle lengths (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.4286 to 0.7851). See the table on the next page.

Changes from baseline: The ventricular effective refractory period was significantly prolonged from baseline in each of the treatment groups. These significant prolongations from baseline occurred in each of the dose groups, at each of the paced cycle lengths, after the loading dose (at Minute 10), and at the end of the maintenance infusion (at Minute 20-40). These prolongations exhibited a dose-response: prolongations at the higher doses were generally greater than prolongations at the lower doses. However, the changes from baseline were not significantly different across dose groups. See the table on the next page.

Ventricular Effective Refractory Period at the Right Ventricular Apex (msec):
Mean Baseline Values and Mean Changes from Baseline*

	Baseline		Δ from baseline after loading dose (at Minute 10)			Δ from baseline after maintenance infusion (at Minute 20-40)		
Paced Cycle Length	n	mean (msec)	n	mean Δ (msec)	p value	n	mean Δ (msec)	p value
600 msec								
0.005 mg/kg / 0.001 mg/kg	12	253.3	10	**31.0**	**0.0002**	10	**41.0**	**0.0001**
0.01 mg/kg / 0.002 mg/kg	13	251.5	11	**40.0**	**<0.0001**	12	**40.8**	**0.0008**
0.02 mg/kg / 0.004 mg/kg	8	247.5	5	**50.0**	**0.0151**	5	**48.0**	**0.0151**
Total (doses combined)	33	251.2	26	**38.5**	**<0.0001**	27	**42.2**	**<0.0001**
500 msec								
0.005 mg/kg / 0.001 mg/kg	16	242.5	14	**29.3**	**0.0002**	16	**23.1**	**0.0023**
0.01 mg/kg / 0.002 mg/kg	15	236.0	14	**37.1**	**<0.0001**	14	**37.9**	**<0.0001**
0.02 mg/kg / 0.004 mg/kg	10	233.0	7	**42.9**	**0.0026**	8	**37.5**	**0.0042**
Total (doses combined)	41	237.8	35	**35.1**	**<0.0001**	38	**31.6**	**<0.0001**
400 msec								
0.005 mg/kg / 0.001 mg/kg	16	231.25	14	**25.7**	**0.0005**	16	**29.4**	**0.0001**
0.01 mg/kg / 0.002 mg/kg	16	229.75	14	**34.6**	**<0.0001**	14	**28.9**	**<0.0001**
0.02 mg/kg / 0.004 mg/kg	11	222.7	8	**40.0**	**0.0024**	7	**40.0**	**0.0057**
Total (doses combined)	43	228.5	36	**32.3**	**<0.0001**	37	**31.2**	**<0.0001**

* Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.

2.4.2.4.2 Duration of ventricular monophasic action potentials (VMAPs)

The durations of the ventricular monophasic action potentials were measured at the right ventricle, both at the apex and at the outflow tract. Because of the small number of patients with measurements at the outflow tract, results will be shown only for the apical measurements. Although not shown, the results from the outflow tract were generally consistent with those from the apex.

Background: The duration of ventricular monophasic action potentials were measured at 90% repolarization and at paced cycle lengths of 400, 500, and 600 msec.

Similarity at baseline: At baseline, the mean durations of the ventricular monophasic action potentials were similar across dose groups at each of the paced cycle lengths (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.5973 to 0.9063).

Changes from baseline: The ventricular monophasic action potential was prolonged from baseline in each of the treatment groups. Significant prolongations from baseline occurred in each of the dose groups, at each of the paced cycle lengths, after the loading dose (at Minute 10), and at the end of the maintenance infusion (at Minute 20-40). The prolongations exhibited a dose-response: prolongations at the higher doses were generally greater than prolongations at the lower doses. In some cases, prolongations from baseline were significantly greater in the higher dose groups than in the lower dose groups. See the table on the next page.

Duration of the Ventricular Monophasic Action Potential (msec) at the Right Ventricular Apex: Mean Baseline Values and Mean Changes from Baseline[a]

	Baseline		Δ from baseline after loading dose (at Minute 10)			Δ from baseline after maintenance infusion (at Minute 20-40)		
Paced Cycle Length	n	mean (msec)	n	mean Δ (msec)	p value	n	mean Δ (msec)	p value
600 msec								
0.005 mg/kg / 0.001 mg/kg	14	276.0	10	**20.1**[b,c]	**0.0056**	12	19.4	0.3049
0.01 mg/kg / 0.002 mg/kg	11	267.9	8	**61.9**[b]	**0.0024**	9	**55.4**	**0.0004**
0.02 mg/kg / 0.004 mg/kg	8	268.5	7	**67.1**[c]	**0.0043**	5	**64.6**	**0.0583**
Total (doses combined)	33	271.5	25	**52.2**	**<0.0001**	26	**40.6**	**0.0007**
500 msec								
0.005 mg/kg / 0.001 mg/kg	14	266.6	11	**24.0**	**0.0110**	13	16.4	0.1427
0.01 mg/kg / 0.002 mg/kg	12	260.1	10	**33.5**	**0.0152**	10	23.3	0.1921
0.02 mg/kg / 0.004 mg/kg	8	262.5	7	**61.1**	**0.0028**	6	**49.8**	**0.0014**
Total (doses combined)	34	264.15	28	**36.7**	**<0.0001**	29	**25.7**	**0.0024**
400 msec								
0.005 mg/kg / 0.001 mg/kg	13	257.9	10	**7.6**[d,e]	0.3574	11	8.45	0.5026
0.01 mg/kg / 0.002 mg/kg	14	253.8	11	**37.7**[d]	**0.0090**	12	20.6	0.1909
0.02 mg/kg / 0.004 mg/kg	9	254.9	8	**51.0**[e]	**0.0015**	5	**47.2**	**0.0070**
Total (doses combined)	36	255.6	29	**31.0**	**<0.0001**	28	**20.6**	**0.0196**

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] After the loading dose at a PCL of 600 msec, the prolongation from baseline was significantly greater in the mid-dose group compared to the low-dose group (pairwise p=0.0236).
[c] After the loading dose at a PCL of 600 msec, the prolongation from baseline was significantly greater in the high-dose group compared to the low-dose group (pairwise p=0.0011).
[d] After the loading dose at a PCL of 400 msec, the prolongation from baseline was significantly greater in the mid-dose group compared to the low-dose group (pairwise p=0.0243).
[e] After the loading dose at a PCL of 400 msec, the prolongation from baseline was significantly greater in the high-dose group compared to the low-dose group (pairwise p=0.0039).

2.4.2.4.3 Ventricular thresholds

Ventricular thresholds were measured both at the apex and at the outflow tract. Because of the small number of patients with measurements at the outflow tract, results will be shown only for the apical measurements.

Similarity at baseline: At baseline, the mean apical ventricular threshold was similar for each of the three dose groups (p=0.8318). See the table on the next page.

Changes from baseline: The mean apical ventricular threshold did not change significantly from baseline within any of the treatment groups. Changes from baseline were similar across the treatment groups both after the loading dose at Minute 10 (p=0.2636) and also at the end of the maintenance infusion at Minute 20-40 (p=0.4730). See the table on the next page.

Apical Ventricular Threshold (mA):
Mean Baseline Values and Mean Changes from Baseline*

	Baseline		Δ from baseline after loading dose (at Minute 10)			Δ from baseline after maintenance infusion (at Minute 20-40)		
	n	mean (mA)	n	mean Δ (mA)	p value	n	mean Δ (mA)	p value
0.005 mg/kg / 0.001 mg/kg	16	0.32	14	-0.06	0.0507	15	-0.09	0.1131
0.01 mg/kg / 0.002 mg/kg	17	0.29	16	-0.05	0.3137	16	-0.07	0.1757
0.02 mg/kg / 0.004 mg/kg	11	0.25	8	0.15	0.3320	7	0.27	0.3379
Total (doses combined)	44	0.29	38	-0.01	0.7941	38	-0.01	0.8009

2.4.2.5 Effects of ibutilide on conduction intervals

2.4.2.5.1 AH interval

Background: The AH interval is the time from the beginning of the A deflection to the beginning of the His bundle deflection (measured in the same lead). In this trial, the AH interval was evaluated at pacing cycle lengths of 600, 500, 400, and 300 msec. As noted above in section 2.4.2.2.1, pacing the atria at incrementally faster rates will prolong the AH interval, mostly by delaying conduction through the atrioventricular node. Second-degree AV block of a type 1 pattern occurs at the Wenckebach point, and this progresses to 2:1 AV block. The upper limit of normal for the AH interval ranges from about 130 msec to 140 msec, whereas the lower limit of normal in adults is approximately 45 msec to 55 msec.

Similarity at baseline: At baseline, the AH interval was similar for each of the three dose groups at each of the paced cycle lengths (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.4474 to 0.8594). See the table on the next page.

Changes from baseline: The mean AH interval did not change significantly from baseline within any of the treatment groups at any of the pace cycle lengths. Furthermore, at each of the paced cycle lengths, changes from baseline were similar across the treatment groups (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.1840 to 0.9463). See the table on the next page.

AH Interval (msec)
Mean Baseline Values and Mean Changes from Baseline

	Baseline		A from baseline after maintenance infusion (at Minute 20-40)		
Paced Cycle Length	n	mean (msec)	n	mean Δ (msec)	p value
600 msec					
0.005 mg/kg / 0.001 mg/kg	14	182.9	9	-2.0	0.8758
0.01 mg/kg / 0.002 mg/kg	13	128.7	9	14.9	0.3255
0.02 mg/kg / 0.004 mg/kg	8	140.6	8	9.0	0.2469
Total (doses combined)	35	144.4	26	7.2	0.2980
500 msec					
0.005 mg/kg / 0.001 mg/kg	11	157.9	8	-1.0	0.9372
0.01 mg/kg / 0.002 mg/kg	12	135.9	11	-5.9	0.6486
0.02 mg/kg / 0.004 mg/kg	10	157.5	6	7.3	0.5605
Total (doses combined)	33	149.8	25	-1.2	0.8724
400 msec					
0.005 mg/kg / 0.001 mg/kg	7	150.0	4	-3.0	0.2987
0.01 mg/kg / 0.002 mg/kg	8	141.8	7	5.7	0.6909
0.02 mg/kg / 0.004 mg/kg	8	179.25	4	35.0	0.0787
Total (doses combined)	23	155.1	15	11.2	0.1820
350 msec					
0.005 mg/kg / 0.001 mg/kg	5	142.0	3	10.0	0.2254
0.01 mg/kg / 0.002 mg/kg	6	163.2	3	0.3	0.9922
0.02 mg/kg / 0.004 mg/kg	2	175.0	1	10.0	NA
Total (doses combined)	13	152.2	7	5.9	0.6382

2.4.2.5.2 HV Interval

Background: The HV interval is the time from the beginning of the His deflection to the beginning of ventricular depolarization (measured either as the beginning of the QRS complex in surface leads, or as the beginning of the V deflection in the His bundle electrogram). In this trial, the HV interval was evaluated at pacing cycle lengths of 600, 500, 400, and 350 msec. In adults, the normal range for the HV interval ranges from about 30 msec to 55 msec.

Similarity at baseline: At baseline, the HV interval was similar for each of the three dose groups at each of the paced cycle lengths (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.0652 to 0.2634). See the table on the next page.

Changes from baseline: The mean HV interval did not change significantly from baseline within any of the treatment groups at any of the pace cycle lengths. Furthermore, at each of the paced cycle lengths, changes from baseline were similar across the treatment groups (p values by ANOVA across dose groups at each of the paced cycle lengths ranged from 0.1513 to 0.8409). See the table on the next page.

HV Interval (msec)
Mean Baseline Values and Mean Changes from Baseline

Paced Cycle Length	Baseline		Δ from baseline after maintenance infusion (at Minute 20-40)		
	n	mean (msec)	n	mean Δ (msec)	p value
600 msec					
0.005 mg/kg / 0.001 mg/kg	14	59.4	9	-0.6	0.7902
0.01 mg/kg / 0.002 mg/kg	14	59.4	10	2.5	0.7029
0.02 mg/kg / 0.004 mg/kg	8	62.9	8	4.25	0.0779
Total (doses combined)	36	57.8	27	2.0	0.4177
500 msec					
0.005 mg/kg / 0.001 mg/kg	12	58.4	9	-0.3	0.8374
0.01 mg/kg / 0.002 mg/kg	14	57.7	12	3.8	0.6294
0.02 mg/kg / 0.004 mg/kg	10	65.0	8	4.0	0.1002
Total (doses combined)	36	60.0	29	2.6	0.4285
400 msec					
0.005 mg/kg / 0.001 mg/kg	7	55.3	5	3.0	0.9013
0.01 mg/kg / 0.002 mg/kg	12	54.5	9	0.1	0.9407
0.02 mg/kg / 0.004 mg/kg	9	67.3	6	1.7	0.8020
Total (doses combined)	28	58.8	20	1.3	0.3043
350 msec					
0.005 mg/kg / 0.001 mg/kg	6	55.0	4	6.5	0.2620
0.01 mg/kg / 0.002 mg/kg	12	55.5	8	-0.6	0.7879
0.02 mg/kg / 0.004 mg/kg	6	65.5	5	7.2	0.1004
Total (doses combined)	24	57.9	17	3.35	0.1020

2.4.2.5.3 QT Interval

Similarity at baseline: At baseline, the QT interval was similar for each of the three dose groups (p=0.1169). See the top table on page 24.

Changes from baseline: The QT interval was prolonged from baseline in each of the treatment groups, and significant prolongations from baseline occurred in each group. The prolongations from baseline exhibited a dose-response. That is, (a) at the higher doses, prolongations were generally greater than prolongations at the lower doses; (b) at the higher doses, significant prolongations generally began earlier than the prolongations at the lower doses, and; (c) at the higher doses, significant prolongations generally lasted longer than prolongations at the lower doses. See the bottom table on page 24.

Furthermore, as shown by repeated measures analysis, the prolongations in the QT interval across the loading/maintenance infusions (Minutes 10, 25, and 40) were significantly different (p=0.0002). The average mean change from baseline in the QT interval across the loading/maintenance infusion was significantly greater in the high-dose group (+68 msec) than in the mid-dose group (+34 msec) or the low-dose group (+16 msec).

2.4.2.5.4 QTc interval

Similarity at baseline: At baseline, the QTc interval was similar for each of the three dose groups (p=0.1681). See the top table on page 24.

Changes from baseline: The QTc interval was prolonged from baseline in each of the treatment groups, and significant prolongations from baseline occurred in each group. The prolongations from baseline exhibited a dose-response. That is, (a) at the higher doses, prolongations were generally greater than prolongations at the lower doses; (b) at the higher doses, significant prolongations generally began earlier than the prolongations at the lower doses, and; (c) at the higher doses, significant prolongations generally lasted longer than prolongations at the lower doses. See the bottom table on page 24.

Furthermore, as shown by repeated measures analysis, the prolongations in the QTc interval across the loading/maintenance infusions (Minutes 10, 25, and 40) were significantly different (p=0.0193). The average mean change from baseline in the QTc interval across the loading/maintenance infusion was significantly greater in the high-dose group (+60 sec^{α} x 1000) than in the mid-dose group (+46 sec^{α} x 1000) or the low-dose group (+33 sec^{α} x 1000).

2.4.2.6 Correlations between changes in electrophysiological parameters and changes in the QTc interval

Correlation analyses were performed on electrophysiological data obtained at a paced cycle length of 600 msec. At the end of the loading dose (Minute 10), the prolongation of the QTc interval was somewhat related to changes in the duration of the ventricular monophasic action potential (VMAP). Although less correlated, at the end of the loading dose the prolongation of the QTc interval was weakly related to changes in the ventricular effective refractory period (VERP). Prolongation of the QTc interval did not generally appear to be correlated with changes in the atrial effective refractory period (AERP).

2.4.2.6.1 Atrial effective refractory period (AERP) and QTc

Prolongation of the QTc interval did not generally appear to be correlated with changes in the atrial effective refractory period (AERP). However, in the low-dose group at the end of the loading infusion (Minute 10) the Spearman's correlation coefficient identified a positive trend at the 5% level. The Pearson's correlation coefficient was affected by an outlier. See the table and figure on page 26.

2.4.2.6.2 Ventricular effective refractory period (VERP) and QTc

Prolongation of the QTc interval appeared to be only weakly correlated with changes in the ventricular effective refractory period (VERP). When all dose groups were combined at the end of the loading infusion (Minute 10), the Spearman's correlation coefficient identified a positive trend at the 5% level. The Pearson's correlation coefficient was affected by outliers. See the table and figure on page 27.

QT Interval and QTc Interval: Mean Baseline Values

Study Period	QT Interval n	QT Interval mean (msec)	QTc Interval n	QTc Interval mean ($sec^{1/2}$ x 1000)
Baseline (Minus -10)				
0.005 mg/kg / 0.001 mg/kg	18	402.7	18	425.1
0.01 mg/kg / 0.002 mg/kg	18	427.9	18	436.8
0.02 mg/kg / 0.004 mg/kg	12	371.0	12	418.7

QT Interval and QTc Interval: Mean Changes from Baseline[a]

Study Period	QT change from baseline n	QT change from baseline mean Δ (msec)	QT change from baseline p value	QTc change from baseline n	QTc change from baseline mean Δ ($sec^{1/2}$ x 1000)	QTc change from baseline p value
Minute 10[b]						
0.005 mg/kg / 0.001 mg/kg	18	14.3	0.1641	18	**38.3**	**0.0004**
0.01 mg/kg / 0.002 mg/kg	18	44.4	**0.0008**	18	**50.7**	**0.0024**
0.02 mg/kg / 0.004 mg/kg	11	**69.3**	**0.0044**	11	**87.9**	**0.0005**
Minute 25[c]						
0.005 mg/kg / 0.001 mg/kg	18	**20.4**	**0.0158**	18	**26.9**	**0.0379**
0.01 mg/kg / 0.002 mg/kg	18	**32.1**	**0.0004**	18	**40.1**	**0.0178**
0.02 mg/kg / 0.004 mg/kg	12	**65.0**	**0.0001**	12	**77.0**	**0.0004**
Minute 40[d]						
0.005 mg/kg / 0.001 mg/kg	18	13.5	0.1528	18	**32.5**	**0.0069**
0.01 mg/kg / 0.002 mg/kg	18	**26.8**	**0.0020**	18	**47.4**	**0.0018**
0.02 mg/kg / 0.004 mg/kg	12	**69.0**	**0.0001**	12	**78.75**	**0.0007**
30 minutes after infusion						
0.005 mg/kg / 0.001 mg/kg	18	8.7	0.4073	18	**27.3**	**0.0114**
0.01 mg/kg / 0.002 mg/kg	18	**43.6**	**0.0006**	18	**39.8**	**0.0176**
0.02 mg/kg / 0.004 mg/kg	11	**75.4**	**0.0002**	11	**74.4**	**0.0009**
1 hour after infusion						
0.005 mg/kg / 0.001 mg/kg	18	13.7	0.1089	18	**25.1**	**0.0009**
0.01 mg/kg / 0.002 mg/kg	18	**32.7**	**0.0056**	18	22.6	0.1019
0.02 mg/kg / 0.004 mg/kg	12	**60.3**	**0.0001**	12	**50.3**	**0.0004**
2 hours after infusion						
0.005 mg/kg / 0.001 mg/kg	17	5.2	0.6451	17	14.8	0.2095
0.01 mg/kg / 0.002 mg/kg	18	**20.8**	**0.0445**	18	10.9	0.3053
0.02 mg/kg / 0.004 mg/kg	11	**51.6**	**0.0001**	11	**31.6**	**0.0002**
4 hours after infusion						
0.005 mg/kg / 0.001 mg/kg	18	1.2	0.8823	18	9.5	0.2702
0.01 mg/kg / 0.002 mg/kg	18	11.4	0.1774	18	-1.94	0.8290
0.02 mg/kg / 0.004 mg/kg	12	**30.7**	**0.0019**	12	**17.5**	**0.0138**

a Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
b After the loading dose
c Mid-point of maintenance infusion
d Following maintenance infusion

2.4.2.6.3 Duration of the ventricular monophasic action potential (VMAP) and QTc

Prolongation of the QTc interval was somewhat correlated with changes in the duration of the ventricular monophasic action potential (VMAP). When all dose groups were combined at the end of the loading infusion (Minute 10), both the Spearman's and Pearson's correlation coefficients identified a positive trend at the 5% level. See the table and figure on page 28.

2.4.2.7 Relationship between the ventricular MAP/ERP ratio and the paced cycle length

The changes from baseline of the MAP/ERP ratio at a given paced cycle length were often significantly and positively correlated with the changes from baseline of the MAP/ERP ratio at the other paced cycle lengths. Correlations for within group changes from baseline for the MAP/ERP ratio are shown as follows:

- PCL of 600 msec with PCL of 500 msec: see the top table on page 29;
- PCL of 600 msec with PCL of 400 msec: see the bottom table on page 29;
- PCL of 500 msec with PCL of 400 msec: see the table on page 30.

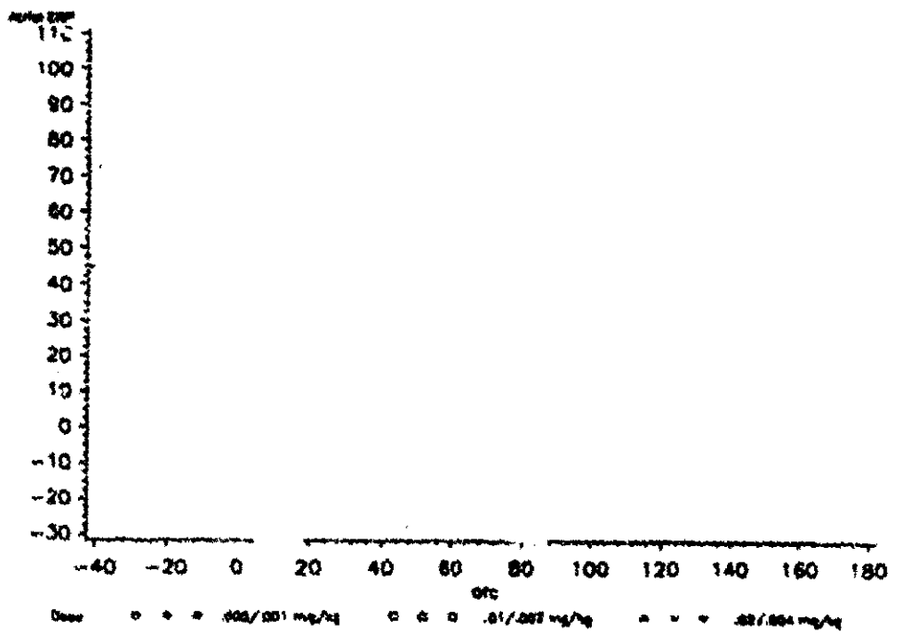
Also, see the figure on page 31.

Correlations for Within Group Change from Baseline for Atrial Effective Refractory Period (AERP) with QTc at a Paced Cycle Length of 600 msec[a]

Treatment Group	n	Pearson correlation coefficient	Spearman correlation coefficient
0.005 mg/kg / 0.001 mg/kg			
After loading dose (Minute 10)	18	0.466	**0.538**[b]
After maintenance infusion (Minute 20-40)	12	0.098	0.266
0.01 mg/kg / 0.002 mg/kg			
After loading dose (Minute 10)	15	-0.082	-0.209
After maintenance infusion (Minute 20-40)	12	0.161	0.189
0.02 mg/kg / 0.004 mg/kg			
After loading dose (Minute 10)	8	-0.180	-0.095
After maintenance infusion (Minute 20-40)	7	0.466	0.109
Doses combined			
After loading dose (Minute 10)	32	0.269	0.294
After maintenance infusion (Minute 20-40)	31	0.269	0.290

[a] Statistically significant changes from baseline (p<0.05) are highlighted with bold characters.
[b] p= 0.0188 (i.e., Prob > |R| under H_0: Rho=0)

Change from Baseline to Minute 10
Atrial ERP (in msec) versus QTc Interval (in msec)

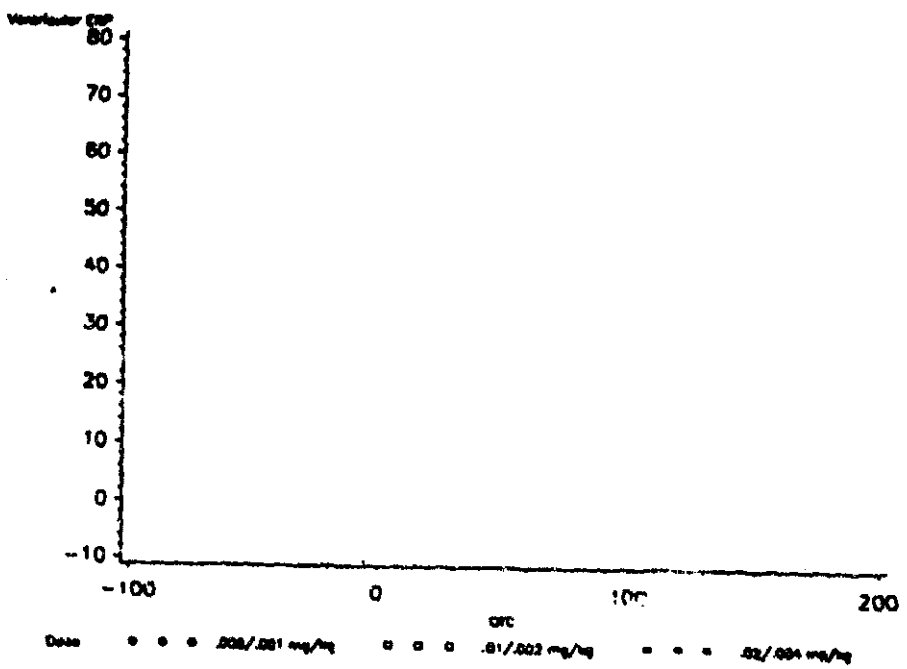


Correlations for Within Group Change from Baseline for Ventricular Effective Refractory Period (VERP) with QTc at a Paced Cycle Length of 600 msec[a]

Treatment Group	n	Pearson correlation coefficient	Spearman correlation coefficient
0.005 mg/kg / 0.001 mg/kg			
After loading dose (Minute 10)	**10**	**0.597[b]**	**0.636[c]**
After maintenance infusion (Minute 20-40)	**10**	**0.647**	**0.709**
0.01 mg/kg / 0.002 mg/kg			
After loading dose (Minute 10)	**11**	**-0.040**	**0.168**
After maintenance infusion (Minute 20-40)	**12**	**-0.263**	**-0.110**
0.02 mg/kg / 0.004 mg/kg			
After loading dose (Minute 10)	**5**	**-0.021**	**-0.200**
After maintenance infusion (Minute 20-40)	**5**	**-0.610**	**-0.300**
Doses combined			
After loading dose (Minute 10)	**26**	**0.269**	**0.299**
After maintenance infusion (Minute 20-40)	**27**	**-0.160**	**-0.104**

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] $p = 0.0746$ (i.e., Prob > |R| under H_0: Rho=0)
[c] $p = 0.0529$ (i.e., Prob > |R| under H_0: Rho=0)
[d] $p = 0.0488$ (i.e., Prob > |R| under H_0: Rho=0)

Change from Baseline to Minute 10
Ventricular ERP (in msec) versus QTc Interval (in msec)

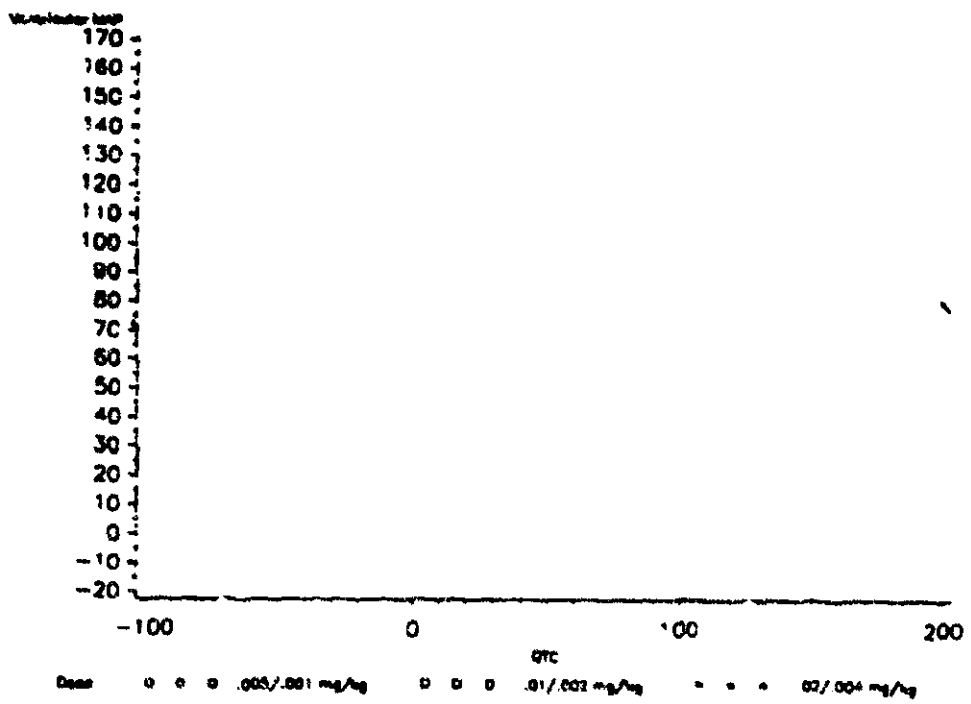


Correlations for Within Group Change from Baseline for Duration of Ventricular Monophasic Action Potential (VMAP) with QTc at a Paced Cycle Length of 800 msec[a]

Treatment Group	n	Pearson correlation coefficient	Spearman correlation coefficient
0.005 mg/kg / 0.001 mg/kg			
After loading dose (Minute 10)	10	0.002	-0.091
After maintenance infusion (Minute 20-40)	12	0.297	0.186
0.01 mg/kg / 0.002 mg/kg			
After loading dose (Minute 10)	8	0.513	0.571
After maintenance infusion (Minute 20-40)	9	0.144	0.166
0.02 mg/kg / 0.004 mg/kg			
After loading dose (Minute 10)	7	0.811	0.149
After maintenance infusion (Minute 20-40)	5	-0.595	-0.600
Doses combined			
After loading dose (Minute 10)	25	0.547[b]	0.573[c]
After maintenance infusion (Minute 20-40)	26	0.269	0.328

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] $p= 0.0046$ (i.e., Prob > |R| under H_0: Rho=0)
[c] $p= 0.0026$ (i.e., Prob > |R| under H_0: Rho=0)

Change from Baseline to Minute 10
Ventricular MAP (in msec) versus QTc (in msec)



Correlations for Within Group Changes from Baseline
of the Ventricular MAP/ERP Ratio:
Paced Cycle Length of 600 msec with Paced Cycle Length of 500 msec[a]

Treatment Group	n	Pearson correlation coefficient	p value[b,c]	Spearman correlation coefficient	p value[b,c]
0.005 mg/kg / 0.001 mg/kg					
After loading dose (Minute 10)	9	0.579	NS	0.667	NS
After maintenance infusion (Minute 20-40)	9	0.922	0.0005	0.883	0.0016
0.01 mg/kg / 0.002 mg/kg					
After loading dose (Minute 10)	7	0.668	NS	0.464	NS
After maintenance infusion (Minute 20-40)	7	0.788	0.0360	0.821	0.0234
0.02 mg/kg / 0.004 mg/kg					
After loading dose (Minute 10)	4	-0.570	NS	-0.400	NS
After maintenance infusion (Minute 20-40)	4	0.212	NS	0.400	NS
Doses combined					
After loading dose (Minute 10)	20	0.447	0.0483	0.417	0.0677
After maintenance infusion (Minute 20-40)	20	0.721	0.0003	0.726	0.0003

[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] Prob > |R| under H_0: Rho=0
[c] NS = not significant

Correlations for Within G[illegible] Changes from Baseline
of the Ventricular MAP/ERP Ratio:
Paced Cycle Length of 600 msec with Paced Cycle Length of 400 msec[a]

Treatment Group	n	Pearson correlation coefficient	p value[b,c]	Spearman correlation coefficient	p value[b,c]
0.005 mg/kg / 0.001 mg/kg					
After loading dose (Minute 10)	8	0.519	NS	0.476	NS
After maintenance infusion (Minute 20-40)	8	0.720	0.0442	0.357	NS
0.01 mg/kg / 0.002 mg/kg					
After loading dose (Minute 10)	8	0.424	NS	0.643	0.0856
After maintenance infusion (Minute 20-40)	9	0.660	0.0530	0.717	0.0296
0.02 mg/kg / 0.004 mg/kg					
After loading dose (Minute 10)	5	0.325	NS	0.500	NS
After maintenance infusion (Minute 20-40)	3	0.167	NS	0.500	NS
Doses combined					
After loading dose (Minute 10)	21	0.370	0.0983	0.469	0.0320
After maintenance infusion (Minute 20-40)	20	0.673	0.0011	0.614	0.0040

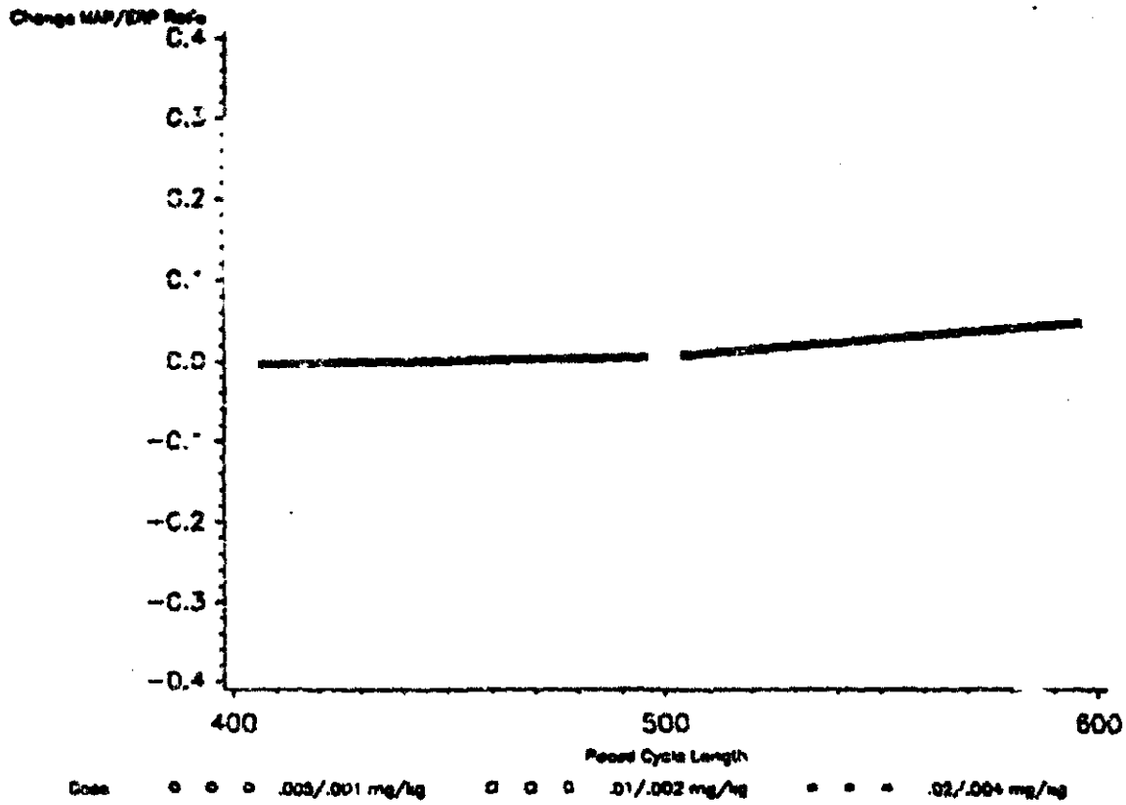
[a] Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
[b] Prob > |R| under H_0: Rho=0
[c] NS = not significant

Correlations for Within Group Changes from Baseline of the Ventricular MAP/ERP Ratio Paced Cycle Length of 600 msec with Paced Cycle Length of 400 msec[a]

Treatment Group	n	Pearson correlation coefficient	p value[b,c]	Spearman correlation coefficient	p value[b,c]
0.005 mg/kg / 0.001 mg/kg					
After loading dose (Minute 10)	10	0.644	0.0449	0.503	NS
After maintenance infusion (Minute 20-40)	11	0.857	0.0029	0.691	0.0304
0.01 mg/kg / 0.002 mg/kg					
After loading dose (Minute 10)	10	0.622	NS	0.709	0.0217
After maintenance infusion (Minute 20-40)	10	0.961	0.0001	0.758	0.0156
0.02 mg/kg / 0.004 mg/kg					
After loading dose (Minute 10)	7	0.374	NS	0.357	NS
After maintenance infusion (Minute 20-40)	6	0.394	NS	0.300	NS
Doses combined					
After loading dose (Minute 10)	27	0.507	0.0070	0.53	0.0045
After maintenance infusion (Minute 20-40)	28	0.836	0.0001	0.647	0.0004

- Statistically significant changes from baseline ($p<0.05$) are highlighted with bold characters.
- Prob > |R| under H_0: Rho=0
- NS = not significant

Change From Baseline to Minute 10
Ventricular MAP/ERP Ratio versus Paced Cycle Length (msec)



2.4.2.8 Effect of ibutilide on the reinduction of ventricular tachycardia

Success was defined as the ability to prevent the reinduction of sustained monomorphic ventricular tachycardia[7] during the infusion of ibutilide fumarate. These reinduction stimuli were to be administered to the same site that successfully induced ventricular tachycardia prior to drug treatment.

Overall, sustained monomorphic ventricular tachycardia could not be induced during the infusion in 44% (21 of 48) of the evaluable patients. Although the success rate increased slightly at each higher dose, the difference in the success rate across the dose groups was not statistically significant (p=0.8324). See the table below.

Number and Percentage of Evaluable Patients (n=48) in whom the Reinduction of Ventricular Tachycardia was Successfully Prevented during the Infusion of Ibutilide

	Success		Failure		Chi-square p value
Treatment Group		%	n	%	
0.005 mg/kg / 0.001 mg/kg (n=18)	7	38.9	11	61.1	
0.01 mg/kg / 0.002 mg/kg (n=18)	8	44.4	10	55.6	
0.02 mg/kg / 0.004 mg/kg (n=12)	6	50.0	6	50.0	0.8324

The number of extrastimuli required at baseline for induction of ventricular tachycardia did not differ between successes and failures. In the success group, 2 of 21 (9.5%) patients required a single extrastimulus, 10 of 21 (47.6%) required double extrastimuli, and 9 of 21 (42.9%) required triple extrastimuli. In the failure group, 4 of 25 (16.0%) required a single extrastimulus, 12 of 25 (48.0%) required double extrastimuli, and 9 of 25 (36.0%) required triple extrastimuli.

Similarly, at baseline the cycle length of the induced ventricular tachycardia was similar between the two groups. The mean cycle length in the success group was 270 msec, and in the failure group was 280 msec.

Furthermore, the ventricular effective refractive period (VERP) changed by a similar amount from baseline to the end of the infusion in patients classified as successes and in those classified as failures (p=0.5241).

Ibutilide was not effective in preventing the reinduction of ventricular tachycardia in 27 or 48 (56%) of patients. Although the reinduced ventricular tachycardia in these patients was on average slower (i.e., the cycle length was longer) than at baseline in each treatment group, these differences were not significant. See the table on the next page.

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[7] Sustained ventricular tachycardia was defined as ventricular tachycardia that lasted 30 seconds, or as ventricular tachycardia that required pacing or cardioversion to be terminated

Mean Cycle Length of Induced Ventricular Tachycardia (VT) in Failures

	Baseline VT (before infusion)	Reinduced VT (during infusion)
Treatment Group	mean cycle length (msec)	mean cycle length (msec)
0.005 mg/kg / 0.001 mg/kg	275	304
0.01 mg/kg / 0.002 mg/kg	292	321
0.02 mg/kg / 0.004 mg/kg	287	300

Finally, of these 27 failures (i.e., patients whose ventricular tachycardia could be induced during the ibutilide infusion), four had ventricular tachycardia that was less inducible, while four had ventricular tachycardia that was more inducible than at baseline. This was determined by an increase or decrease in the number of stimuli required to initiate the ventricular tachycardia.

2.5 SAFETY RESULTS[6]

The major safety findings in this study are summarized below, and are considered in more detail in the following sections:

Deaths: No patients enrolled in the study died.

Serious medical events: Of the 55 patients enrolled in the trial, three experienced serious medical events, all of the cardiovascular system, and all of whom required discontinuation of the infusion.

Discontinuation of the infusion: Of the 55 patients enrolled in the trial, 50 completed the study as planned. Three of the five patients in whom the infusion was discontinued had experienced serious medical events, and two had experienced non-serious medical events.

Ventricular arrhythmias: Overall, six patients exposed to ibutilide experienced a total of seven ventricular arrhythmias classified as adverse events. In two of these patients the ventricular arrhythmias were serious and led to discontinuation of the infusion. The two patients that experienced sustained polymorphic ventricular tachycardia were successfully DC cardioverted.

Most frequent adverse events: Among the 55 patients exposed to ibutilide, the most frequent treatment-emergent medical events were back pain (9.1%, n=5), atrial flutter (5.5%, n=3), chest pain (5.5%, n=3), headache (5.5%, n=3), and sustained monomorphic ventricular tachycardia (5.5%, n=3).

Vital signs: Systolic and diastolic blood pressure decreased significantly from baseline, predominantly in the low dose group. These decreases began at approximately four hours after the infusion and continued through 24 hours after the infusion. The pulse rate decreased significantly from baseline throughout the course of the study, predominantly in the mid-dose and

[6] Safety issues are discussed comprehensively in Dr. Gordon's review. The sponsor did not provide a narrative of safety issues for this trial, and the following has been assembled from the statistical tables.

high-dose groups. These changes in vital signs were felt to be clinically unimportant. Without the benefit of a parallel placebo group these changes are difficult to interpret.

12-lead electrocardiograms: No clinically significant adverse effects were noted of ibutilide on the PR or QRS intervals. The effects of ibutilide on the QT and QTc intervals are discussed above.

Laboratories: No clinically significant laboratory abnormalities were attributable to ibutilide.

2.5.1 Serious medical events

Overall, 5.5% (3 of 55) of the patients in the study experienced serious medical events, all of the cardiovascular system. See the table below. Narratives for these patients may be found in section 2.5.4.

Number of Patients Experiencing
Serious Treatment-Emergent Medical Events*

Medical Event	Low 0.005/0.001 mg/kg (n=20)	Mid 0.01/0.002 mg/kg (n=20)	High 0.02/0.004 mg/kg (n=15)	Total (n=55)
Hypotension	0	0	1 [#220]	1
Sustained monomorphic VT	1 [#204]	0	0	1
Sustained polymorphic VT	0	0	1 [#224]	1

* Patient identification numbers are given in brackets [].

2.5.2 Medical events causing discontinuation of the infusion

Of the 55 patients enrolled in the trial, 50 completed the study as planned. The infusion was discontinued in five patients who experienced eight medical events. The infusion was discontinued in three of these five patients (#204, #220, and #224) because of serious medical events. See the table on the top of the next page. Narratives for the five patients who discontinued the infusion may be found in section 2.5.4.

Number of Patients with
Medical Events Necessitating Discontinuation of Infusion[a,b,c]

Medical Event	Low 0.005/0.001 mg/kg (n=20)	Mid 0.01/0.002 mg/kg (n=20)	High 0.02/0.004 mg/kg (n=15)	Total (n=55)
Sustained polymorphic VT	0	**1 [#216]**	**1 [#224]**	2
Angina	0	0	**1 [#220]**	1
Dyspnea	0	0	**1 [#220]**	1
Hypotension	0	0	**1 [#220]**	1
Nonsustained polymorphic VT	0	0	**1 [#224]**	1
QT segment prolonged	0	0	**1 [#223]**	1
Sustained monomorphic VT	**1 [#204]**	0	0	1

[a] Patient identification numbers are given in brackets [].
[b] Serious adverse events are indicated by bold type.
[c] Some patients experienced more than one adverse event.

2.5.3 Ventricular arrhythmias

Of the 55 patients enrolled in the trial, six experienced a total of seven ventricular arrhythmias that were classified as adverse events. In two of these patients (#204 and #224), the ventricular arrhythmias were serious and led to discontinuation of the infusion. The two patients that experienced sustained polymorphic ventricular tachycardia were successfully DC cardioverted. See the table below. Narratives for the patients who experience ventricular arrhythmias may be found in section 2.5.4.

Number of Patients with Ventricular Arrhythmia[a,b,c]

Arrhythmia	Low 0.005/0.001 mg/kg (n=20)	Mid 0.01/0.002 mg/kg (n=20)	High 0.02/0.004 mg/kg (n=15)	Total (n=55)
Sustained polymorphic VT	0	1 [#216]	**1 [#224]**	2
Nonsustained polymorphic VT	0	0	1 [#224]	1
Sustained monomorphic VT	**1 [#204]**	1 [#402]	1 [#1504]	3
Nonsustained monomorphic VT	0	1 [#209]	0	1

[a] Patient identification numbers are given in brackets [].
[b] Serious adverse events are indicated by bold type.
[c] Some patients experienced more than one adverse event.

2.5.4 Patient Narratives

This section summarizes the clinical course of selected patients who experienced medical events. Many of these patients experienced several medical events, so the events noted in the sections above are highlighted. The narratives are listed in the order of the patient number and are in the words of the sponsor.

Patient #204, *Sustained Monomorphic Ventricular Tachycardia*: The patient was a 75-year-old black male with a history of CAD, anterior MI, and CHF. One week prior to the study the patient had a cardiac arrest and was successfully defibrillated. The monitor showed ventricular fibrillation/VT. His LVEF was 25-30%. Monomorphic VT was induced at baseline and required DCC. The patient received the 0.005 mg/kg loading dose, followed by the maintenance infusion of 0.001 mg/kg. His QTc at Minute -10 was 0.442 sec*, and following the loading dose (Minute 10) was 0.509 sec*. The maintenance infusion was stopped after 22 minutes due to sustained monomorphic VT with loss of consciousness. His QTc was 0.446 sec*. Approximately 13 minutes after the end of the infusion sustained monomorphic VT was induced with a single extrastimulus during determination of ventricular ERP. Five minutes later there was a spontaneous onset of sustained monomorphic VT. The investigator felt these events were possibly related to the administration of ibutilide fumarate.

Patient #209, *Nonsustained Monomorphic Ventricular Tachycardia*: This was a 52-year-old white male with a history of an inferior wall MI complicated by heart block, elevated cholesterol, HTN, and nonischemic cardiomyopathy. He also had three syncopal episodes in the prior 6 months. His LVEF was 40%. He received a loading dose of 0.010 mg/kg ibutilide fumarate, followed by a maintenance infusion of 0.002 mg/kg. At baseline VT was induced at both the RVA and RVOT requiring DCC. His QTc at Minute -10 was 0.457 sec*, followed by 0.496, 0.580, and 0.494 sec* at Minutes 10, 25, and 40, respectively. Seven hours following the infusion the patient had seven beats of monomorphic VT. The investigator did not feel this was due to treatment with ibutilide fumarate.

Patient #216, *Sustained Polymorphic Ventricular Tachycardia*: This patient was a 71-year-old white female with a history of CAD, CABG, CHF, HTN, and intermittent atrial fibrillation. She also had a history of documented monomorphic VT and was taking Quinidex. Her LVEF was 35%\-40%. She received a loading dose of 0.010 mg/dl ibutilide fumarate and 17 minutes of the 0.002 mg/kg maintenance infusion. At that time ventricular extrastimulus testing was performed at a pacing cycle length of 600 msec. At coupling intervals of 600/270/220, polymorphic VT was induced, resulting in rapid loss of consciousness. A 200 joule shock was required and the resulting rhythm was atrial flutter/fibrillation. Subsequent measurements could not be obtained due to the atrial arrhythmia, which spontaneously converted to NSR approximately 4 hours after the infusion. The patient's QTc at Minute -10 was 0.441 sec*, and rose to 0.478, 0.546, and 0.515 sec* at Minutes 10, 25, and 40, respectively. This event was considered by the investigator to be possibly due to the ibutilide fumarate infusion.

Patient #220, *Hypotension*: This patient was a 65-year-old white male with a history of CAD, diabetes mellitus, PVD, and sustained monomorphic VT. He had symptoms of increasing SOB, chest tightness, and palpitations at the time of the medical history. His EF was 70%. In addition, he had a history of bladder cancer 14 years prior, which ultimately led to a left nephroureterectomy 9 years later, as well as an esophageal ulcer with gastritis and severe antral erosions. He was entered into this study following routine EP study. He received 0.020 mg/kg ibutilide fumarate over 10 minutes. He complained of chest tightness at the midpoint of the infusion and was given

sublingual nitroglycerine. At the end of the loading infusion and beginning of programmed stimulation, the patient complained of worsening chest tightness and pain radiating to his neck with associated SOB. His blood pressure decreased from 131/76 mmHg at Time 0 to 72/43 mmHg at Minute 10 and 80/58 mmHg at Minute 15. The maintenance infusion (0.004 mg/kg) was discontinued after 9 minutes. He was placed in Trendelenburg and an IV bolus of normal saline was given. His blood pressure returned to 105/63 mmHg. Reinduction of VT was not attempted, and most of the EP measurements were not done. The patient had a screen hemoglobin and hematocrit of 9.1 g/dl and 30%, respectively. At Hour 24 his hemoglobin had dropped to 8.5 g/dl and his hematocrit to 28%. The patient was on a heparin drip, but had heme positive stools and the heparin was discontinued. The chest tightness and dyspnea were considered by the investigator to be possibly related to the ibutilide fumarate infusion, but the hypotension was not considered related.

Patient #223, *QT Segment Prolonged*: This 56-year-old white male had a history of CAD, MI, CABG, HTN, and NIDDM. He also had an episode of VT. His LVEF was 34%. His Minute -10 QTc was 0.442 sec$^{\frac{1}{2}}$, which rose to >0.600 sec$^{\frac{1}{2}}$ at the midpoint of the loading dose, at which time the infusion was stopped and 1 g magnesium sulfate was given IV push. The patient remained in NSR and hemodynamically stable. His QTc was 0.561 sec$^{\frac{1}{2}}$, 0.514 sec$^{\frac{1}{2}}$, and 0.488 sec$^{\frac{1}{2}}$ at Minute 10, Minute 25, and Minute 40, respectively. This event was considered by the investigator to be possibly due to the ibutilide fumarate infusion.

Patient #224, *Sustained Polymorphic Ventricular Tachycardia*: This patient was a 59-year-old white female with a history of CAD, CABG, CHF, anterior MI, HTN, and PVD. Four days prior to the study she was found unresponsive at home and was DC cardioverted. Her LVEF was 20-25%. She underwent EP study for syncope with sustained wide complex tachycardia. At baseline sustained monomorphic VT was induced twice, both episodes requiring DC cardioversion to terminate. The patient received the 10-minute 0.020 mg/kg loading dose of ibutilide. During the determination of atrial pacing threshold at the end of the 10-minute infusion, the patient experienced the spontaneous onset of bizarre wide complex polymorphic ventricular tachycardia requiring immediate cardioversion to terminate due to loss of consciousness. The infusion was stopped immediately and the maintenance infusion was not given. Her QTc at Minute -10 was 0.454 sec$^{\frac{1}{2}}$, then increased to 0.669 sec$^{\frac{1}{2}}$, 0.511 sec$^{\frac{1}{2}}$, and 0.536 sec$^{\frac{1}{2}}$ at Minutes 10, 25, and 40 respectively. The patient experienced a second episode of spontaneous wide bizarre polymorphic VT shortly thereafter during the institution of atrial pacing and while magnesium sulfate was prepared for administration. The second induction followed a long-short interval, apparently due to transient loss of atrial capture. Two grams of magnesium sulfate were administered immediately and atrial pacing at 100 bpm suppressed the recurrence of polymorphic VT. A third gram of magnesium sulfate was administered and over the next 45 minutes the atrial pacing rate was decreased from 100 to 70 bpm with no further ventricular arrhythmias. Pacing was discontinued and while in sinus rhythm at 60 bpm, the patient had a third recurrence of spontaneous wide complex polymorphic VT, again requiring DC cardioversion. Atrial pacing at 90 bpm was reinitiated and two more grams of magnesium sulfate were administered intravenously. A temporary pacing wire was placed through the right internal jugular vein into the right atrial appendage for continued atrial pacing on discharge from the EP lab. The patient had no further ventricular arrhythmias during continuous atrial pacing while monitored in the coronary intensive care unit over the next 36 hours. She was scheduled for automatic implantable cardiac defibrillator placement. The investigator felt this represented a proarrhythmic event which was probably related to the ibutilide fumarate infusion.

Patient #402, *Sustained Monomorphic Ventricular Tachycardia*: This was a 66-year-old white male with a history of CABG, frequent PVCs, anemia, and insulin-dependent diabetes mellitus. His LVEF was 25%. Eight days prior to the study he had a run of sustained VT requiring cardioversion with 200 and 400 joules. He was started on bretylium 2 mg/min and the VT recurred 40 minutes later. During the baseline period of this study, VT was induced twice at the RVA, per protocol. The patient received a loading dose of 0.010 mg/kg ibutilide fumarate, and a maintenance dose of 0.002 mg/kg. During the end of the maintenance infusion VT was reinduced. The patient's QTc at Minute -10 was 0.395 $sec^{\frac{1}{2}}$, and increased to 0.506 $sec^{\frac{1}{2}}$, 0.400 $sec^{\frac{1}{2}}$, and 0.406 $sec^{\frac{1}{2}}$ at Minutes 10, 25, and 40, respectively. Testing following completion of the infusion was stopped due to sustained monomorphic VT induced with a single extrastimulus during refractory period recordings. The investigator felt there was a possibility that this event was caused by the investigational drug.

Patient #1504, *Sustained Monomorphic Ventricular Tachycardia*: This patient was a 52-year-old white male with a history of an anterolateral MI, left atrial enlargement, mitral regurgitation, septal wall hypokinesis, and a subendocardial MI. Three years prior to the study the patient had VT and was started on tocainide. A week prior to the study he had sustained VT, was cardioverted, and was started on lidocaine. The patient had VT induced multiple times at baseline at the RVA. He received a loading dose of 0.020 mg/kg ibutilide fumarate and a maintenance infusion of 0.004 mg/kg. Distal heart block occurred during the maintenance infusion. Sustained monomorphic VT at a rate of 173 bpm occurred at Minute 20, and was pace-terminated. Another episode of sustained monomorphic VT occurred 5 minutes after the end of the infusion, and required DCC with 200, 200, 300, and 360 joules. This was followed by a third episode of sustained monomorphic VT 15 minutes after the end of the infusion due to catheter manipulation, which was pace-terminated. The QTc values were 0.426 $sec^{\frac{1}{2}}$, 0.532 $sec^{\frac{1}{2}}$, 0.600 $sec^{\frac{1}{2}}$, and 0.546 $sec^{\frac{1}{2}}$ at Minutes -10, 10,25, and 40, respectively. The investigator felt all the episodes could have been due to the investigational medication.

3. REVIEWER'S COMMENTS

This was an open-label study of the effects of escalating doses of intravenous ibutilide fumarate in patients with hemodynamically stable ventricular tachycardia on the following: (a) the ability to induce ventricular tachycardia by programmed electrical stimulation; (b) the length of the ventricular effective refractory period (VERP) and the duration of monophasic action potentials (MAPs); (c) the relation of these first two parameters to the QT interval, and; (d) the relationship of the MAP duration/ERP ratio to cycle length. The study was not randomized, not blinded, and not placebo controlled.

The effects of increasing doses of intravenous ibutilide on the ability to induce ventricular tachycardia by programmed electrical stimulation (PES) and the effects on electrophysiologic measurements were to be evaluated in three sequential dosing groups of twenty patients. Within each of the dosing groups, the dosing regimen consisted of a 10-minute infusion (i.e., a "loading" dose), followed by a 30-minute infusion (i.e., a "maintenance" infusion). As summarized in the table below, 55 patients enrolled in the study:

Distribution of Patients by Treatment Group

	n	Loading[a] (mg/kg)	Maintenance[b] (mg/kg)
Group 1	20	0.005	0.001
Group 2	20	0.01	0.002
Group 3	15	0.02	0.004

[a] infused over 10 minutes
[b] infused over 30 minutes

General: The design of this study (non-randomized, open-label, no placebo control, sequential enrollment of the treatment groups) limit the definite conclusions that can be drawn from the study. Of the 55 patients enrolled in the study, 52 (94.5%) were white and 3 (5.6%) were black. Forty-seven (85.5%) of the patients were men, and eight (14.5%) were women. Thirty-four (61.8%) of the patients were at least 65 years of age, and the most elderly patient was 83 years old. Pediatric patients were excluded from the trial; the youngest patient was 40 years old. Patients were required to have a baseline QTc of less than 0.440 sec[½], and to have normal baseline serum electrolytes. Patients with hypertension, congestive heart failure, angina pectoris, or a history of torsades de pointes were excluded from the trial. The use of class I or class III antiarrhythmic medications was prohibited within five half-lives prior to enrollment.

Hence, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to patients with different demographic characteristics (e.g., subjects with age, sex, or racial differences), cardiovascular disease, cardiac abnormalities (e.g., structural or mechanical abnormalities), baseline QTc intervals that exceed 0.440 sec[½], or with electrolyte abnormalities such as hypokalemia. This study does not contribute any information about possible interactions of ibutilide with class I or class III antiarrhythmic agents.

As noted, the different doses of ibutilide were evaluated sequentially, rather than concurrently. Thus, effects of the drug may be confounded with the effects of time (i.e., "period effects").

The sponsor is not seeking an indication for the prolonged administration of ibutilide fumarate. Nonetheless, it should be noted that in this study the pharmacodynamics, efficacy (in preventing reinduction of VT), and safety of ibutilide were not evaluated at steady state. That is, the study was not performed at steady-state blood levels, nor at steady-state tissue levels of the drug.

Dose exploration: As planned, the sponsor studied only the three regimens outlined above. The effects of higher doses were not evaluated. Thus, the effects and tolerability of dose regimens with a bolus dose of greater than 0.02 mg/kg and a maintenance infusion of greater than 0.004 mg/kg for thirty minutes remain unknown. The failure to explore the effects of these higher doses has at least two consequences:

- possible associations of QTc prolongation with arrhythmogenesis were not assessed;
- at these higher doses, *other* possible electrophysiological effects, hemodynamic effects, pharmacodynamic effects, or *other* adverse effects of ibutilide were not evaluated.

The sponsor seeks to obtain approval for 10-minute infusions of ibutilide fumarate that are not adjusted for body weight. For reference, then, the following table provides the absolute doses administered to subjects of varying weights in the different treatment groups. In this trial, the lightest patient was 42.7 kg (94 lbs), and the heaviest was 119.1 kg (262 lbs).

Absolute Dose of Ibutilide Fumarate (mg) by Treatment Group and Body Weight[a]

	Treatment group								
Body weight	0.005→0.001 mg/kg			0.01→0.002 mg/kg			0.02→0.004 mg/kg		
	Bolus	Maint[b]	Total	Bolus	Maint[b]	Total	Bolus	Maint[b]	Total
40 kg							0.80	0.16	0.96
50 kg									
60 kg									
70 kg									
80 kg									
90 kg									
100 kg									
110 kg	0.55	0.11	0.66						
120 kg	0.60	0.12	0.72						
130 kg	0.65	0.13	0.78	1.30	0.26	1.56	2.60	0.52	3.12

[a] Shaded cells encompass the range of body weights for patients included in this trial.
[b] Maint = Maintenance

Pharmacokinetics: As stated by the sponsor, post-infusion concentrations rapidly declined in a multi-exponential fashion, and concentrations were typically around or below 1 ng/ml within 1 hour after the maintenance infusion. However, a high degree of interpatient variability was observed in all dose groups, and the presence of extreme outliers resulted in atypically high measures of variability. In addition, many concentration-time profiles were atypical: some were erratic, and some showed maximum concentrations later than the end of the first infusion. In general, maximum ibutilide plasma concentrations and area under the concentration versus time profile values increased in a dose-related manner. Pharmacodynamic data were also atypical in regards to previous studies. Although studies in healthy volunteers have shown that infusion of ibutilide fumarate results in prolongation of the QTC interval and this prolongation is directly correlated with ibutilide fumarate dose and ibutilide plasma concentrations, no such correlation was found in this study.

Pharmacodynamics: Invasive hemodynamic measurements were not recorded for this study.

Ibutilide appeared to depress sinus node function somewhat, but these effects generally were not marked. Ibutilide appeared to prolong the corrected sinus node recovery time to some extent. Ibutilide prolonged the maximal sinus node recovery time. These effects may be of greater significance in patients with intrinsically abnormal sinus node function, a group that was not systematically evaluated during the development of the drug. However, ibutilide did not appear to affect the basic cycle length consistently in this study.

Similarly, ibutilide appeared to depress AV nodal function to some extent, but these effects also generally were not marked. Ibutilide appears to prolong both the AV and VA Wenckebach cycle lengths to some degree. These apparent effects may be of greater significance in patients with intrinsically abnormal AV nodal function, another group that was not syatematically evaluated during the development of the drug. However, ibutilide did not appear to prolong the AH interval to any great degree in this study.

As expected of a Class III antiarrhythmic agent, ibutilide prolonged the duration of the ventricular monophasic action potentials,[9] and it increased the atrial and ventricular effective refractory periods. In general, these effects were greater at the higher doses of ibutilide. Similarly, consistent with its characterization as a Class III antiarrhythmic agent, ibutilide prolonged the QT and QTc intervals (as assessed with 12-lead ECGs). Prolongation of the QT and QTc intervals appeared to be dose-related. That is, (a) at the higher doses, prolongations were generally greater than prolongations at the lower doses; (b) at the higher doses, significant prolongations generally began earlier than the prolongations at the lower doses, and; (c) at the higher doses, significant prolongations generally lasted longer than prolongations at the lower doses.

Ibutilide did not appear to alter HV conduction. The drug did not appear to alter atrial or ventricular thresholds.

Correlation analyses were performed on electrophysiological data obtained at a paced cycle length of 600 msec. At the end of the loading dose (Minute 10), the prolongation of the QTc interval was somewhat related to changes in the duration of the ventricular monophasic action potential (VMAP). Although less correlated, at the end of the loading dose the prolongation of the QTc interval was weakly related to changes in the ventricular effective refractory period (VERP).

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[9] The effects of ibutilide on the duration of atrial monophasic action potentials was not assessed in this study.

Prolongation of the QTc interval did not generally appear to be correlated with changes in the atrial effective refractory period (AERP).

The changes from baseline of the MAP/ERP ratio at a given paced cycle length were often significantly and positively correlated with the changes from baseline of the MAP/ERP ratio at the other paced cycle lengths.

Efficacy: Overall, sustained monomorphic ventricular tachycardia could not be induced during the infusion in 44% (21 of 48) of the evaluable patients. However, this result is difficult to interpret in the absence of a concurrent placebo control group or, in fact, *of any* concurrent control group. Moreover, any putative effect of ibutilide to prevent the reinduction of sustained monomorphic tachycardia did not show a dose response. That is, the difference in the "success" rate across the dose groups was not statistically significant (p=0.8324).

Safety: No patients enrolled in the study died. Of the 55 patients enrolled in the trial, three experienced serious medical events, all of the cardiovascular system, and all of whom required discontinuation of the infusion. These serious events included hypotension (associated with angina and dyspnea), sustained monomorphic VT, and sustained polymorphic VT (associated with nonsustained polymorphic VT).

Of the 55 patients enrolled in the trial, 50 completed the study as planned. Three of the five patients in whom the infusion was discontinued had experienced serious medical events (noted above), and two had experienced non-serious medical events (including sustained polymorphic VT and prolongation of the QT segment).

This trial confirms that ibutilide may induce arrhythmias, some of which may have hemodynamic consequences. Overall, six patients exposed to ibutilide experienced a total of seven ventricular arrhythmias classified as adverse events. As noted above, in two of these patients the ventricular arrhythmias were serious (sustained polymorphic VT in one case and sustained monomorphic VT in another) and led to discontinuation of the infusion. Of the seven ventricular arrhythmias, the five remaining included sustained polymorphic VT (1 additional case), nonsustained polymorphic VT (1 case), sustained monomorphic VT (2 additional cases), and nonsustained monomorphic VT (1 case). The two patients that experienced sustained polymorphic ventricular tachycardia were successfully DC cardioverted.

Among the 55 patients exposed to ibutilide, the most frequent treatment-emergent medical events were back pain (9.1%, n=5), atrial flutter (5.5%, n=3), chest pain (5.5%, n=3), headache (5.5%, n=3), and sustained monomorphic ventricular tachycardia (5.5%, n=3).

APPENDIX E

TABLE OF CONTENTS

Comparative Pharmacokinetics and Pharmacodynamics of Ibutilide Fumarate and Its Enantiomers, U-92,206E and U-92,209E, Following Single 10-Minute Intravenous Infusions in Healthy Male Volunteers (Protocol P-7550-0008).

1. DESCRIPTION OF THE STUDY

1.1 Title

Comparative Pharmacokinetics and Pharmacodynamics of Ibutilide Fumarate and its Enantiomers, U-82,208E and U-82,209E, Following Single 10-Minute Intravenous Infusions in Healthy Male Volunteers (Protocol P-7550-0008).

1.2 Objectives

As specified in the protocol, the objectives of this study were as follows:

- to define and compare the pharmacokinetics and pharmacodynamics of ibutilide fumarate, a racemic mixture, and its separate enantiomers, U-82,208E and U-82,209E, following a single 10-minute intravenous infusion of each drug.
- to determine if racemization occurs *in vivo* using chiral-specific assay methodology.
- to determine if the presence of one enantiomer affects the disposition of the other.

1.3 Experimental Design

This was a randomized, double-blind, three-way crossover study performed at the Upjohn Research Clinics.[1] The study had three periods, each with a different treatment, and with each treatment separated by seven days:

Treatment A: ibutilide fumarate; 0.01 mg/kg i.v. over ten minutes for one dose
Treatment B: U-82,208E; 0.01 mg/kg i.v. over ten minutes for one dose
Treatment C: U-82,209E; 0.01 mg/kg i.v. over ten minutes for one dose

Six healthy men were randomly allocated to unique treatment sequences, and each treatment was administered after an overnight fast. Serial blood and urine samples were obtained for pharmacokinetic analysis, and serial signal-averaged electrocardiograms were obtained for the assessment of QT intervals.

To be included in the study, subjects were required to be men between 18 and 50 years of age, and to have a body weight between 150 and 200 pounds and within 15% of the ideal weight. Subjects who smoked or who used concomitant medications were excluded from the study.

1.4 Drug Administration

Ibutilide fumarate, U-82,208E, and U-82,209E were supplied in 10 ml clear glass ampules, each at a concentration of 2.5 mg/ml. The formulations were isotonic and buffered with acetate to a pH of 4.6. A standardized diluent for preparation of the intravenous injections was not specified in the protocol.

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[1] The study was not placebo-controlled.

1.5 Evaluations

Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- supine blood pressure, pulse, respirations, and body temperature
- 12-lead electrocardiograms
- signal-averaged electrocardiograms
- safety laboratories: blood for safety laboratories (hematology, chemistry) and urine for complete urinalysis
- blood and urine samples for drug levels (concentrations of the enantiomers were determined in plasma and urine by a chiral-specific HPLC method).
- medical events

The subjects were also monitored by cardiac telemetry for 24 hours before and after each dose of study medication.

2. RESULTS

2.1 Disposition of Subjects

Six men enrolled in the trial and completed the evaluations. None withdrew.

2.2 Demographic and Baseline Characteristics

Six men enrolled in the trial. Of these six men, four were white, one was black, and one was of an "other" race. The subjects had a mean age of 32 years (, a mean weight of 82.6 kg (, and a mean height of 71.1 in (

2.3 PHARMACOKINETIC RESULTS[2]

The results of pharmacokinetic analyses are summarized in the table on the next page.

As stated by the sponsor, the enantiomers of ibutilide have a high clearance, which approximates liver blood flow, and a large volume of distribution. The pharmacokinetics of each enantiomer are similar regardless of the compound administered. There was no evidence of in-vivo racemization as only the administered enantiomer was detected in plasma following treatment with either U-82,208E or U-82,209E.

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[2] For a complete discussion of pharmacokinetic issues, see the review by the biopharmaceutical reviewer.

Compound Doses	Bistilide Fumarate			[illegible]	[illegible]
Parameter Estimates For:	[illegible]	[illegible]	Bistilide	[illegible]	[illegible]
AUC$_{0-\infty}$ (ng × hr/mL)	3.26 ± 0.79	3.06 ± 0.64	6.27 ± 1.35	6.30 ± 1.63	5.77 ± 1.45
C_{max} (ng/mL)	5.61 ± 2.05	5.30 ± 1.94	11.0 ± 3.99	11.1 ± 7.0	7.91 ± 4.85
CL (mL/min/kg)	26.8 ± 6.8	28.3 ± 5.7	27.6 ± 5.8	27.8 ± 7.0	30.7 ± 9.0
V_{ss} (L/kg)	11.8 ± 4.1	12.8 ± 5.1	11.6 ± 4.9	13.2 ± 6.9	12.9 ± 4.3
λ_z (hr^{-1})	0.107 ± 0.033	0.110 ± 0.0[illegible]	0.113 ± 0.037	0.095 ± 0.019	0.100 ± 0.032
t½ (hrs)*	6.5	6.3	6.1	7.3	6.4
% of dose in urine	9.1 ± 2.3	9.4 ± 2.4	9.8 ± 2.5	8.5 ± 2.2	9.2 ± 2.7

* Harmonic mean

2.4 PHARMACODYNAMIC RESULTS

2.4.1 Signal-averaged electrocardiogram[3]

The QT interval lengthened after infusions of ibutilide fumarate, U-82,208E, and U-82,209E. The maximal change in the QT interval was at the end of the infusion. On average, the QT interval was prolonged for four hours after administration of ibutilide or U-82,208E. By comparison, the maximal QT prolongation was less and the QT interval was prolonged for a shorter time after infusion of U-82,209E. Blood pressure, pulse, PR intervals, and QRS intervals,[4] did not change following any of the treatments. The table on the next page shows the lengthening of the QT interval with each of the three treatments.

Using the NLIN procedure in SAS, ΔQT versus plasma concentration for the first six hours was fitted to the sigmoidal Emax model:

$$\Delta QTc=(Emax \times C^s)+(EC_{50}{}^s + C^s)$$

where C is the plasma concentration. As shown in the table below, estimates for Emax (the maximum change in QTc interval), EC_{50} (the plasma concentration at which ΔQTc is 50% of Emax), and s (the slope factor) were obtained. The figures on page 6 show changes in QT interval for a "representative" subject a) with respect to time, and b) with respect to plasma concentration.

Estimates of Pharmacodynamic Parameters (mean ± s.d.)
Obtained by Fitting the Sigmoidal Emax Model with NLIN

	Ibutilide Fumarate (n=6)	U-82,208E (n=6)	U-82,209E (n=3)
EC_{50} (ng/ml)	0.58±0.18	0.55±0.14	0.98±0.69
S	5.0±3.0	4.7±2.7	3.9±2.8
Emax (msec)	120±37	172±34	44±10

[3] Signal-averaged electrocardiograms were obtained at the times of blood sampling for determination of drug concentrations in plasma. Heart rate, and PR, QRS, and QT intervals were measured and averaged from 25 beats. Prolongation of the QT interval (ΔQT) was calculated as the difference between the measured QT interval and the average of the predose values.

[4] PR intervals and QRS intervals were measured with 12-lead electrocardiograms, not signal-averaged electrocardiograms.

QT Interval (msec) - Time Data Following Infusion of Ibutilide Fumarate, U-[illegible], or U-[illegible] (Mean ± SD)

Time (hr)	Compound Dosed		
	Ibutilide Fumarate	U-[illegible]	U-[illegible]
-0.5	401 ± 31	407 ± 26	399 ± 19
-0.25	403 ± 23	395 ± 17	401 ± 22
0.167	529 ± 62	530 ± 55	437 ± 31
0.25	520 ± 59	506 ± 48	430 ± 27
0.5	493 ± 41	535 ± 45	420 ± 24
0.75	470 ± 32	518 ± 27	411 ± 23
1.0	467 ± 42	488 ± 28	408 ± 23
1.5	454 ± 35	467 ± 37	405 ± 30
2.0	433 ± 29	445 ± 29	403 ± 27
3.0	417 ± 29	432 ± 28	398 ± 18
4.0	403 ± 33	425 ± 22	390 ± 22
6.0	384 ± 37	381 ± 24	358 ± 17
8.0	369 ± 24	380 ± 35	367 ± 20
10.0	377 ± 35	386 ± 18	377 ± 26
12.0	372 ± 25	366 ± 22	361 ± 26
24.0	373 ± 25	391 ± 24	386 ± 28

Figure 2. Representative subject ΔQT inter

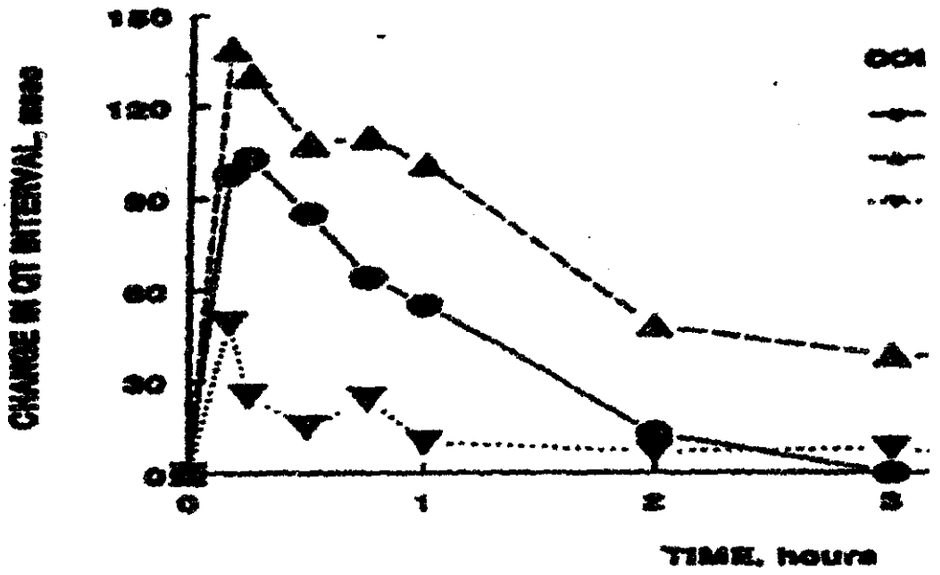
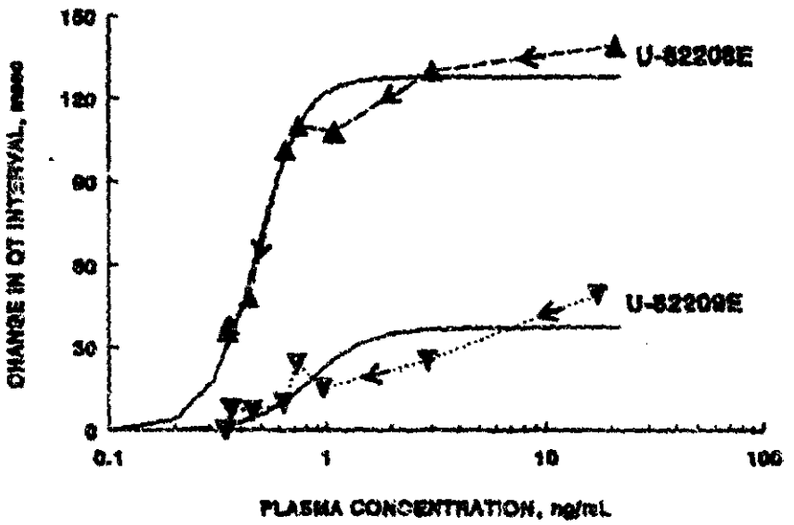


Figure 3. Representative subject ΔQT interval versus plasma concentration (observed points are connected by broken lines and arrows indicating the time course of observations; the solid lines are the predicted values from the E_{max} model)



2.5 SAFETY RESULTS[5]

No subject withdrew from the trial because of an adverse event; no serious or severe adverse events were reported. Thirteen non-serious medical events of mild-to-moderate severity were reported by five of the six subjects who were enrolled and completed the study. Of these adverse events, several were possibly related to the cardiovascular system including the following: chest pressure (n=1), mid-sternal pressure (n=1), dizziness (n=1), and lightheadedness (n=1).

3. REVIEWER'S COMMENTS

The objectives of this study were (a) to define and compare the pharmacokinetics and pharmacodynamics of ibutilide fumarate, a racemic mixture, and its separate enantiomers, U-82,208E and U-82,209E, following a single 10-minute intravenous infusion of each drug; (b) to determine if racemization occurs *in vivo* using chiral-specific assay methodology, and; (c) to determine if the presence of one enantiomer affects the disposition of the other.

This was a randomized, double-blind, three-way crossover study. The study was not placebo controlled. The study had three periods, each with a different treatment, and with each treatment separated by seven days. For each treatment, a single dose of the study agent was administered intravenously over 10 minutes: (a) ibutilide fumarate; 0.01 mg/kg; (b) U-82,208E; 0.01 mg/kg, or (c) U-82,209E; 0.01 mg/kg. Six healthy men participated in the study. QT intervals were assessed with signal-averaged electrocardiograms.

General: Features of this study (i.e., the randomized, double-blind, crossover design) increase the likelihood that reliable data were obtained for the studied population. However, the lack of a placebo control and the lack of dose exploration limit the definite conclusions that can be drawn from the study, particularly with regard to pharmacodynamics. Furthermore, as this was a single-dose study (within each period), pharmacodynamic and safety data were not obtained at steady-state.

All six of the subjects were men. The youngest subject was 22 years of age, and the oldest was 55 years of age. Thus, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to subjects with different demographic characteristics (e.g., to pediatric subjects, elderly subjects, or women), or to non-healthy individuals.

Dose exploration: Only one dose of each study drug (0.01 mg/kg) was evaluated. Thus, this study does not provide any information about the linearity of the pharmacokinetics of ibutilide or of its enantiomers (U-92,208E and U-82,209E). Similarly, beyond the limited data obtained with this one dose, the study does not otherwise provide any pharmacodynamic or safety information.

Pharmacokinetics: As summarized by the sponsor, the enantiomers of ibutilide had a high clearance, which approximated liver blood flow, and a large volume of distribution. The pharmacokinetics of each enantiomer were similar regardless of the compound administered. There was no evidence of in vivo racemization as only the administered enantiomer was detected in plasma following treatment with either U-82,208E or U-82,209E.

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[5] Safety issues are discussed comprehensively in Dr. Gordon's review.

Pharmacodynamics: The QT interval lengthened after infusions of ibutilide fumarate, U-82,208E, and U-82,209E. The maximal change in the QT interval was at the end of the infusion. On average, the QT interval was prolonged for four hours after administration of ibutilide or U-82,208E. By comparison, the maximal QT prolongation was less and the QT interval was prolonged for a shorter time after infusion of U-82,209E. Blood pressure, pulse, PR intervals, and QRS intervals did not change following any of the treatments.

Safety: The safety data from this trial are of limited use given the characteristics of the trial design (e.g., single dose) and the characteristics of the subjects (e.g., healthy men). Nonetheless, no subject withdrew from the trial because of an adverse event; no serious or severe adverse events were reported. Thirteen non-serious medical events of mild-to-moderate severity were reported by five of the six subjects who were enrolled and completed the study.

APPENDIX F

TABLE OF CONTENTS

Evaluation of the Metabolism and Excretion of Ibutilide Following an Intravenous Infusion of ^{14}C-Ibutilide Fumarate in Healthy Male Volunteers (Protocol P-7550-0016).

1. DESCRIPTION OF THE STUDY

1.1 Title

Evaluation of the Metabolism and Excretion of Ibutilide Following an Intravenous Infusion of ^{14}C-Ibutilide Fumarate in Healthy Male Volunteers (Protocol P-7550-0016).

1.2 Objectives

As stated in the protocol, the objective of this study was to quantify the disposition (metabolism and excretion) of ^{14}C-ibutilide in man after intravenous administration in a manner similar to that recommended for antiarrhythmic therapy. The goals included the following:

- to evaluate the distribution and clearance of ibutilide and possible metabolites from plasma and blood (from the quantitative analysis of blood and plasma)
- to obtain information on the rates and routes of excretion of the ibutilide-related materials, as well as information on the chemical structures of the excreted metabolites (from the analysis of urine and fecal specimens)
- to compare metabolite profiles in man with metabolic pathways that have been established in animal models.

1.3 Experimental Design

This was an open-label study in which a single dose of 1 mg containing 30 µCi ^{14}C-ibutilide was to be given as a ten minute intravenous infusion to six healthy male volunteers after a fast of ten hours. Quantitative urine and fecal samples were to be collected until the excretion of the drug-related radioactivity in the urine and feces for the subject reached a level less than three times background. Metabolites of ibutilide were to be identified and quantified in blood, plasma, and urine when possible.

To be included in the study, subjects were required to be between 35 and 55 years of age, to weigh at least 70 kg, to be within 10% of ideal body weight, and to have a corrected QT interval of ≤0.440 sec[a]. Subjects were excluded if they were smokers or had a history of torsades de pointes or long-QT syndrome. Ingestion of caffeine, alcohol, or use of other medications prior to enrollment were prohibited.

1.4 Drug Administration

^{14}C-ibutilide (Lot 26,657) was supplied in 1 ml vials in a concentration of 2.5 mg/ml. The solution was isotonic and buffered with acetate to a pH of 4.6. Subjects were to receive an intravenous infusion of 1 mg containing 30 µCi ^{14}C-ibutilide. The ^{14}C-ibutilide solution was to be diluted in 5% dextrose in water (D_5W) and infused over 10 minutes.

1.5 Evaluations

Pharmacokinetics and safety were evaluated by serial monitoring of the following:

- blood, urine, and fecal specimens for drug and metabolite levels (by HPLC)

- expired air (to monitor for radioactivity)
- vital signs (heart rate, supine blood pressure, respiratory rate, temperature)
- 12-lead electrocardiograms
- continuous electrocardiographic recording (Holter) for the 24 hours before and after drug administration
- safety laboratories: blood for safety laboratories (hematology, chemistry, coagulation) and urine for urinalysis and microscopic evaluation

The subjects were also monitored by cardiac telemetry.

2. RESULTS

2.1 Disposition of Subjects and Amount of Drug Administered

Six male subjects enrolled in the study and completed the evaluations. The mean (±s.d.) dose of ibutilide fumarate received by the six subjects was 0.83 ± 0.04 mg. When adjusted for body weight, the mean dose of ibutilide fumarate was 0.010 ± 0.001 mg/kg. The mean dose of radioactivity delivered was 24.95 ± 1.16 µCi.

2.2 Demographic and Baseline Characteristics

All six of the subjects were white men. The subjects had a mean age of 45 years (
, a mean weight of 83.5 kg (
, and a mean height of 179 cm (

2.3 PHARMACOKINETIC RESULTS[1] (Refer to the table on page 3 and the figures on pages 4-6)

As summarized by the sponsor, the pharmacokinetics of unchanged ibutilide and its enantiomers were consistent with previous reports of high clearance and extensive distribution. Within seven days of dosing, all of the radiolabeled dose was accounted for after excretion in urine and feces. On average, 82% ± 2% and 19% ± 1% of the dose was recovered in urine and feces respectively. No radioactivity was detected in expired air samples. Eight ibutilide-related metabolites (previously identified in rat, dog, and monkey) as well as unchanged ibutilide were detected in urine and accounted for 89% ± 4% of the radioactivity present in urine. Six metabolites and unchanged ibutilide were detected in fecal samples from the two subjects evaluated, and accounted for 97% of the radioactivity present in the fecal samples. Low levels of radioactivity were measured in blood an plasma. Unchanged ibutilide accounted for the radioactivity in plasma at early time points, and four metabolites were detected in later samples. The metabolism of ibutilide in humans appears to proceed primarily through a pathway consisting of ϖ-oxidation of the heptyl side-chain followed by β-oxidation of the heptyl side-chain of ibutilide. Initial (ϖ-1)-oxidation of the heptyl side-chain and the associated one-carbon-loss pathway is a less significant metabolism pathway in humans. Metabolites resulting from these degradative oxidation processes and unchanged ibutilide are then eliminated principally through urinary excretion (about 82% of the dose).

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[1] For a complete discussion of pharmacokinetic issues, see the review by the biopharmaceutical reviewer.

Table 8
Pharmacokinetic parameters estimates for ibutilide fumarate and its (+)- and (-)-enantiomers (U-82208E and U-82209E) following intravenous infusion of approximately 0.8 mg [^{14}C]ibutilide fumarate (25 µCi) to healthy male volunteers (mean ± sd)

Parameter	Ibutilide	U-82208E	U-82209E
$AUC_{0-\infty}$ (ng × hr/mL)	6.44 ± 1.42	3.48 ± 0.79	3.00 ± 0.65
C_{max} (ng/mL)	9.79 ± 3.49	5.03 ± 1.79	4.75 ± 1.70
CL (ml / min/kg)	27.2 ± 6.7	25.2 ± 6.5	29.1 ± 7.0
V_{ss} (L/kg)	9.18 ± 2.43	9.22 ± 2.27	9.82 ± 2.65
λ_z (hr^{-1})	0.129 ± 0.024	0.120 ± 0.029	0.128 ± 0.024
$t_{1/2}$ (hr)*	5.4	5.8	5.4

*harmonic mean

Figure 2 Excretion of radioactivity following intravenous infusion of about 0.8 mg [^{14}C]ibutilide fumarate (~25 µCi) to healthy male volunteers (mean ± sd)

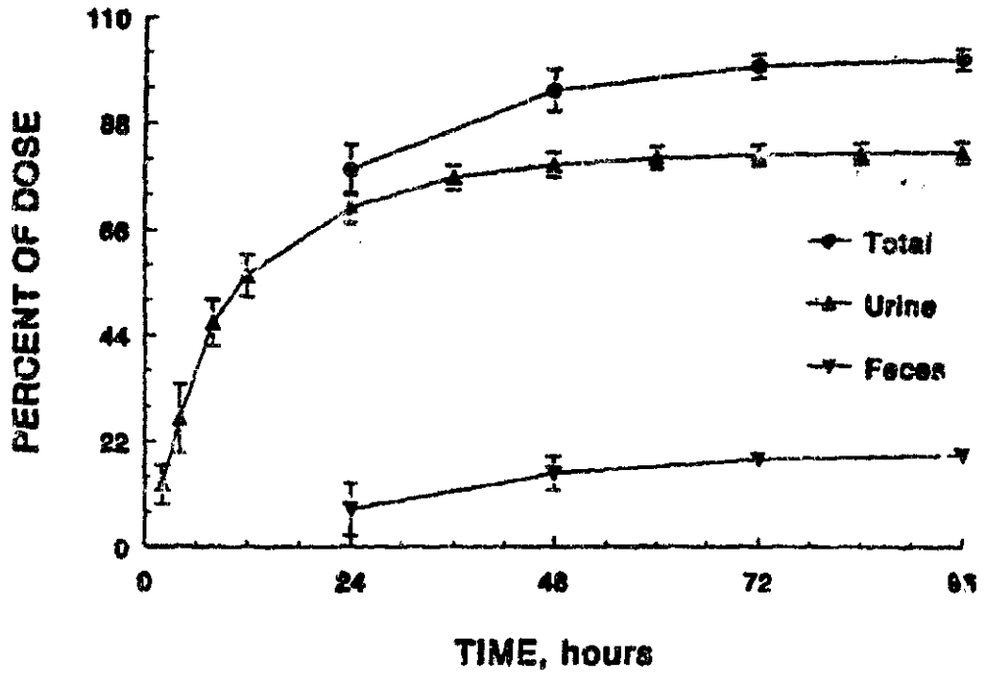


Figure 5 Plasma concentration profiles of U-82208E and U-82209E after intravenous infusion of about 0.8 mg [^{14}C]ibutilide fumarate (~25 µCi) to healthy male volunteers (mean ± sd)

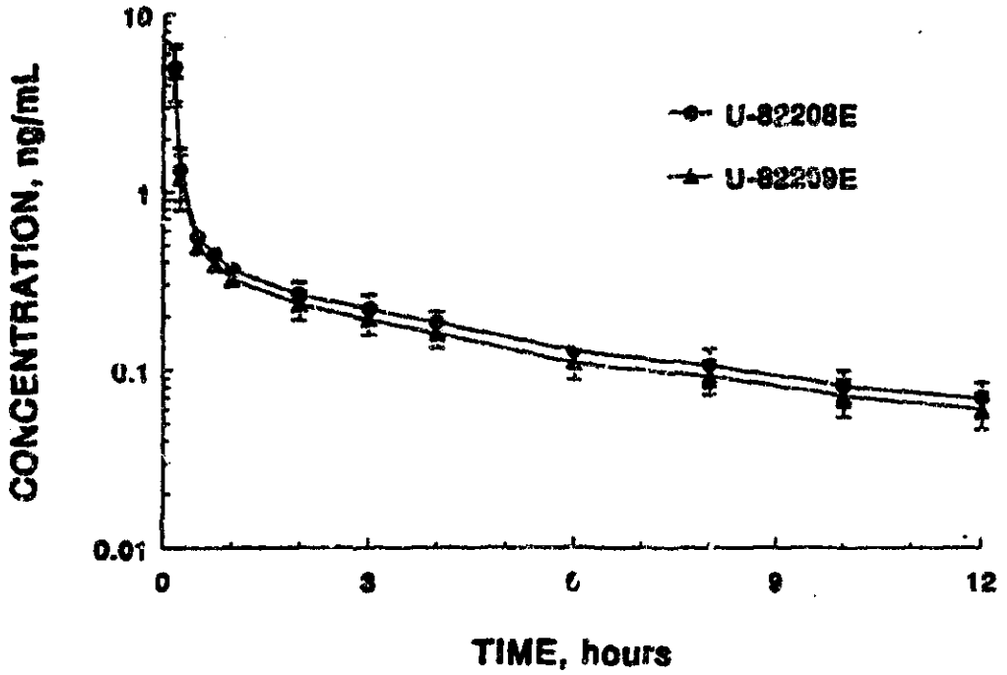
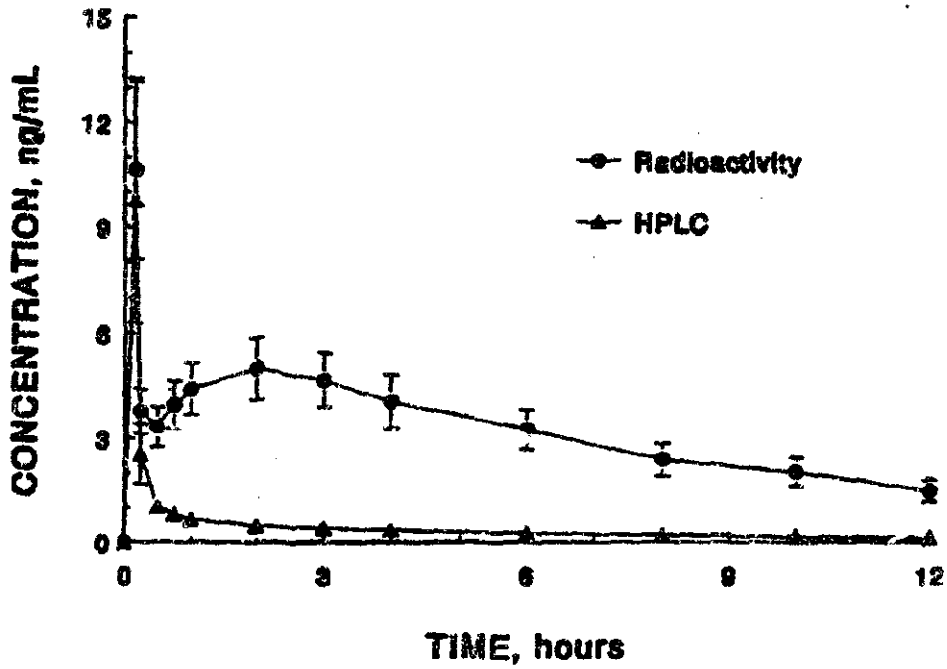


Figure 6 Plasma concentration profiles of total radioactivity and unchanged ibutilide fumarate measured by HPLC methodology after intravenous infusion of about 0.6 mg [^{14}C]ibutilide fumarate (~25 µCi) to healthy male volunteers (mean ± sd)



2.4 PHARMACODYNAMIC RESULTS

The QT interval was prolonged in each subject after the infusion of ibutilide. Maximal prolongation occurred at the end of the infusion in each subject, and the prolongation dissipated by 12 hours.

QTc Intervals (mean ± s.d.)
before and after an intravenous infusion of ibutilide fumarate
in six healthy men

	Predose	10 minutes*	1 hour	12 hours	24 hours
QTc	381.7 ±26.5	451.2 ±34.0	420.3 ±22.3	387.3 ±27.4	380.8 ±26.6

* End of the infusion

2.5 SAFETY RESULTS[2]

No subject withdrew from the trial because of an adverse event. No serious or severe adverse events were reported. Of the six subjects who enrolled and completed the study, three subjects reported a total of seven medical events which were all of mild-to-moderate intensity. None of these events were related to the cardiovascular system.

3. REVIEWER'S COMMENTS

The objective of this study was to quantify the disposition (metabolism and excretion) of ^{14}C-ibutilide in man after intravenous administration in a manner similar to that recommended for antiarrhythmic therapy.

This was an open-label study in which a single dose of 1 mg containing 30 µCi ^{14}C-ibutilide was given as a ten minute intravenous infusion to six healthy male volunteers after a fast of ten hours. The study was not blinded and not placebo controlled. Only one dose of ibutilide was evaluated, and therefore the study also was not randomized.

General: The design of this study (open-label, no placebo control, no concurrent control group, single dose, no randomization) limit the definite conclusions that can be drawn from the study, particularly with regard to pharmacodynamics. Furthermore, as this was a single-dose study, pharmacodynamic and safety data were not obtained at steady-state.

All of the subjects were white men. The youngest was 37 years of age and the oldest was 49 years of age. To enroll, subjects were required to have a corrected QT interval of ≤0.440 sec^{½}. Subjects were excluded if they had a history of torsades de pointes or long-QT syndrome. Ingestion of other medications prior to enrollment was prohibited.

Thus, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to subjects with different demographic characteristics (e.g., pediatric or elderly subjects, to

[2] Safety issues are discussed comprehensively in Dr. Gordon's review

women, or to subjects of different races). Similarly, the results should be extrapolated with caution to subjects with a baseline QTc interval that exceeds 0.[illegible]10 sec*, or to subjects with long-QT syndrome. The study does not contribute any information about drug interactions between ibutilide and other medications.

Dose exploration: Only one dose of drug (0.01 mg/kg) was evaluated. Thus, this study does not provide any information about the linearity of the pharmacokinetics of ibutilide. Similarly, beyond the limited information obtained with this one dose, the study does not otherwise provide any pharmacodynamic information or safety information.

Pharmacokinetics: As summarized by the sponsor, the pharmacokinetics of unchanged ibutilide and its enantiomers were consistent with previous reports of high clearance and extensive distribution. Within seven days of dosing, all of the radiolabeled dose was accounted for after excretion in urine and feces. On average, 82% ± 2% and 19% ± 1% of the dose was recovered in urine and feces respectively. No radioactivity was detected in expired air samples. Eight ibutilide-related metabolites (previously identified in rat, dog, and monkey) as well as unchanged ibutilide were detected in urine and accounted for 89% ± 4% of the radioactivity present in urine. Six metabolites and unchanged ibutilide were detected in fecal samples from the two subjects evaluated, and accounted for 97% of the radioactivity present in the fecal samples. Low levels of radioactivity were measured in blood an plasma. Unchanged ibutilide accounted for the radioactivity in plasma at early time points, and four metabolites were detected in later samples. The metabolism of ibutilide in humans appears to proceed primarily through a pathway consisting of ω oxidation of the heptyl side-chain followed by β-oxidation of the heptyl side-chain of ibutilide. Initial (ω-1)-oxidation of the heptyl side-chain and the associated one-carbon-loss pathway is a less significant metabolism pathway in humans. Metabolites resulting from these degradative oxidation processes and unchanged ibutilide are then eliminated principally through urinary excretion (about 82% of the dose).

Pharmacodynamics: The QT interval was prolonged in each subject after the infusion of ibutilide. Maximal prolongation occurred at the end of the infusion in each subject, and the prolongation dissipated by 12 hours.

Safety: The safety data from this trial are of limited use given the characteristics of the trial design (e.g., single dose) and the characteristics of the subjects (e.g., healthy white men). Nonetheless, no subject withdrew from the trial because of an adverse event. No serious or severe adverse events were reported. Of the six subjects who enrolled and completed the study, three subjects reported a total of seven medical events which were all of mild-to-moderate intensity.

APPENDIX G

TABLE OF CONTENTS

Pharmacokinetics and Pharmacodynamics of Ibutilide Fumarate in Healthy Male and Female Volunteers (Protocol P-7550-0022 [BC 1054]).

1. DESCRIPTION OF THE STUDY

1.1 Title

Pharmacokinetics and Pharmacodynamics of Ibutilide Fumarate in Healthy Male and Female Volunteers (Protocol P-7550-0022 [SC 1054]).

1.2 Objectives

As stated in the protocol, the primary objective of this study was to evaluate potential sex-related differences in the pharmacokinetics of ibutilide fumarate. Another objective was to evaluate potential sex-related differences in pharmacodynamic responses, as measured by prolongation of the QT interval.

1.3 Experimental Design

This was an open-label study in which a single dose of 0.01 mg/kg of ibutilide fumarate was to be given after an overnight fast as a ten minute intravenous infusion to 6-10 healthy men and to 6-10 healthy women. Male and female subjects were to be matched by age (±2 years).

Subjects were required to be between 45 and 80 years of age, to weigh between 50 and 100 kg (inclusive), and to be within 20% of ideal body weight. At least three of the women were to be at least 60 years of age. The subjects were required to have a corrected QT interval of ≤0.440 sec[a] and a resting heart rate greater than 60 beats/minute. Women were required to be post-menopausal (or surgically sterile) and to have a negative pregnancy test. Hormone-replacement therapy and smoking were permitted. Subjects were excluded from the study if they had a history of torsades de pointes, long-QT syndrome, were treated with medications known to prolong the QT interval, or had ingested alcohol in the 48 hours prior to drug administration. Informed consent and review by an Institutional Review Board were stipulated.

1.4 Drug Administration

Ibutilide fumarate (0.1 mg/ml in a total of 10 ml infusate) was supplied in single-dose vials (Lot 27,127).

1.5 Evaluations

Pharmacokinetics, pharmacodynamics, and safety were evaluated by serial monitoring of the following:

- vital signs (supine blood pressure, heart rate, respiratory rate
- signal-averaged electrocardiograms for measurement of the QTc interval (heart rate, QT, and QTc intervals were measured and averaged from 25 beats)
- blood specimens for drug levels (as measured by chiral-specific HPLC)
- safety laboratories: blood for safety laboratories (hematology, chemistry, coagulation) and urine for urinalysis and microscopic evaluation

The subjects were also monitored by cardiac telemetry and 2-lead Holter monitors for the 24 hours before and after administration of the study drug.

2. RESULTS

2.1 Disposition of Subjects and Amount of Drug Administered

Eight men and eight women enrolled and completed the study. Six of the eight pairs of subjects were matched for age within ±2 years; the seventh and eighth pairs were matched within 3 and 5 years, respectively. The men had a mean age of 64.8 years (the women had a mean age of 64.2 years (

2.2 Demographic and Baseline Characteristics

All of the men and women were white. The men had a mean weight of 79.1 kg (, and a mean height of 68.9 inches (. The women had a mean weight of 67.4 kg (, and a mean height of 63.7 inches (. The combined mean, age, weight, and height variables for both men and women were 64.5 years, 73.2 kg, and 66.3 in, respectively.

2.3 PHARMACOKINETIC RESULTS[1]

As summarized by the sponsor, postinfusion plasma concentrations of the (+)- and (-)-enantiomers as well as total racemic ibutilide decreased rapidly with at least two rapid distribution phases. Nearly identical concentrations of U-82,208E and U-82,209E were achieved after dosing in both male and female subjects. Racemic ibutilide and its enantiomers exhibited similar pharmacokinetic properties; all components demonstrated a high systemic clearance, approximating liver blood flow, and a large volume of distribution. No differences in pharmacokinetic parameter estimates were found between male and female subjects, as illustrated in the tables on the next page. The time course of plasma concentrations in representative men and women are shown in the figure on page 4.

[1] For a complete discussion of pharmacokinetic issues, see the review by the biopharmaceutical reviewer.

Pharmacokinetic Parameter Estimates* for Ibutilide (Racemate) Following a Single 10 Minute Intravenous Infusion of Ibutilide Fumarate

Parameter	Males	Females	p-value
$AUC_{0-\infty}$ (ng × hr/mL)	7.58 ± 1.04	7.11 ± 0.85	0.3358
C_{max} (ng/mL)	7.67 ± 4.35	7.56 ± 2.19	0.9477
CL (mL/min/kg)	22.2 ± 3.2	23.5 ± 2.5	0.4027
V_{ss} (L/kg)	13.4 ± 3.4	11.8 ± 2.3	0.2698
λ_z (hr^{-1})	0.080 ± 0.016	0.097 ± 0.017	0.0595
$t_{1/2}$‡	8.7	7.1	-

* Data expressed as the mean ± standard deviation.
‡ Harmonic mean.

Pharmacokinetic Parameter Estimates* for U-82309E Following a Single 10 Minute Intravenous Infusion of Ibutilide Fumarate

Parameter	Males	Females	p-value
$AUC_{0-\infty}$ (ng × hr/mL)	3.97 ± 0.62	3.80 ± 0.46	0.5073
C_{max} (ng/mL)	3.93 ± 2.24	3.90 ± 1.15	0.9723
CL (mL/min/kg)	21.3 ± 3.4	22.0 ± 2.3	0.6646
V_{ss} (L/kg)	13.1 ± 2.7	12.0 ± 2.1	0.3779
λ_z (l/hr)	0.077 ± 0.015	0.069 ± 0.015	0.1510
$t_{1/2}$‡	9.0	7.8	-

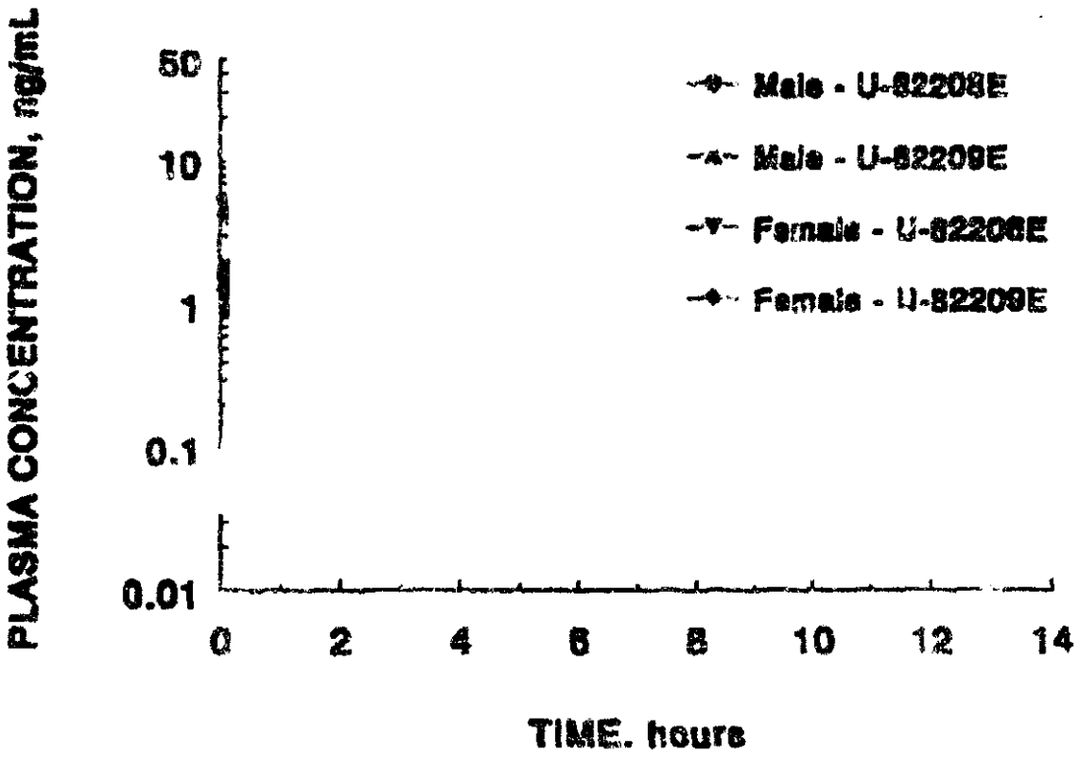
* Data expressed as the mean ± standard deviation.
‡ Harmonic mean.

Pharmacokinetic Parameter Estimates* for U-82309E Following a Single 10 Minute Intravenous Infusion of Ibutilide Fumarate

Parameter	Males	Females	p-value
$AUC_{0-\infty}$ (ng × hr/mL)	3.93 ± [illegible]	3.51 ± 0.45	0.2143
C_{max} (ng/mL)	3.75 ± 2.11	3.66 ± 1.06	0.9216
CL (mL/min/kg)	21.9 ± 4.5	23.9 ± 3.1	0.3228
V_{ss}	15.6 ± 3.7	13.5 ± 2.3	0.1873
λ_z (l/hr)	0.070 ± 0.024	0.086 ± 0.017	0.1378
$t_{1/2}$‡	9.9	8.1	-

* Data expressed as the mean ± standard deviation.
‡ Harmonic mean.

Figure 1. Representative subjects: Plasma concentration versus time profiles



2.4 PHARMACODYNAMIC RESULTS

Compared to baseline measurements in both men and women, infusions of ibutilide fumarate resulted in prolongation of the QTc intervals. See the table below. The prolongations wee generally measurable for three hours after drug administration. The maximal QTc prolongation was 0.066 sec* for men and 0.065 sec* for women; both maxima were observed five minutes after the end of the infusion, and recresented a 16% and 15% prolongation in the QTc interval for men and women, respectively.

QTc Interval (msec) - Time Data Following A Single 10 Minute Infusion of Ibutilide Fumarate

Time (hr)	Male	Female
-1.0	409 ± 22	429 ± 21
-0.5	406 ± 9	422 ± 20
0.167	473 ± 16	480 ± 24
0.25	475 ± 14	491 ± 8
0.5	465 ± 17	472 ± 21
0.75	456 ± 23	470 ± 14
1.0	456 ± 17	465 ± 17
2.0	439 ± 17	460 ± 17
3.0	427 ± 13	435 ± 10
4.0	413 ± 16	434 ± 18
6.0	417 ± 14	428 ± 21
8.0	400 ± 14	422 ± 24
10.0	413 ± 20	426 ± 16
12.0	416 ± 13	425 ± 23
24.0	411 ± 16	421 ± 29

*Mean (±) standard deviation.

Using the NLIN procedure in SAS, ΔQT versus plasma concentration for the first six hours was fitted to the sigmoidal Emax model:

$$\Delta QTc=(Emax \times C^{s})+(EC_{50}^{s} + C^{s})$$

where C is the plasma concentration. As shown in the table below, estimates for Emax (The maximum change in QTc interval), EC_{50} (the plasma concentration at which ΔQTc is 50% of Emax), and s (the slope factor) were obtained for men and women. The figures on the next page show changes in QT interval for "representative" subjects a) with respect to time, and b) with respect to plasma concentration.

Similar estimates were obtained in men and women in the study. However, the predose QTc intervals were slightly longer in women than in men (0.426 sec[½] vs. 0.408 sec[½]).

Estimates of Pharmacodynamic Parameters (mean ± s.d.)
Obtained by Fitting the Sigmoidal Emax Model with NLIN

	Men (n=8)	Women* (n=7)
EC_{50}	0.52±0.13	0.58±0.21
S	4.31±2.01	4.71±2.99
Emax	67±16	65±15

* Data from one woman could not be fitted to the Emax model

Figure 2. Representative subjects: ΔQTc interval versus time profiles

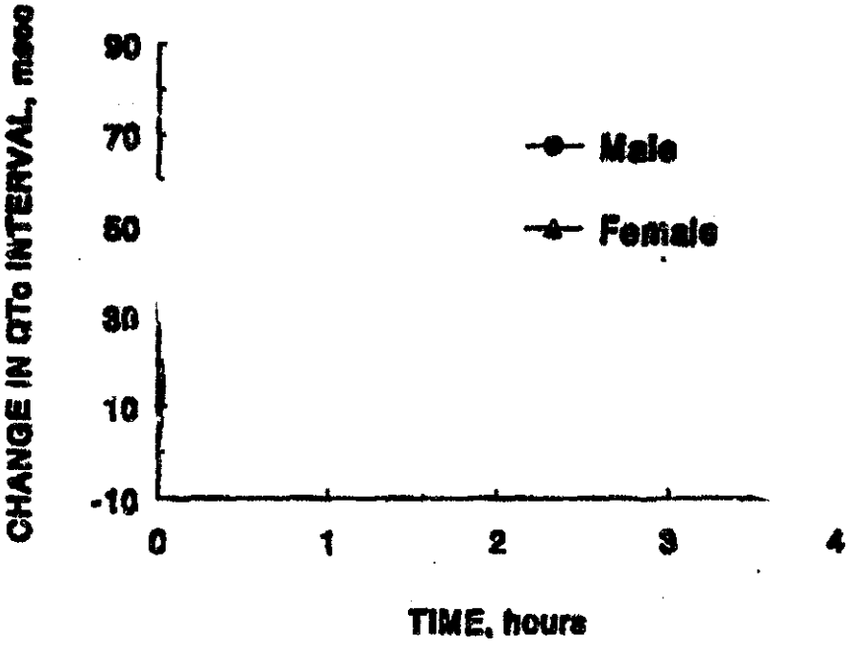
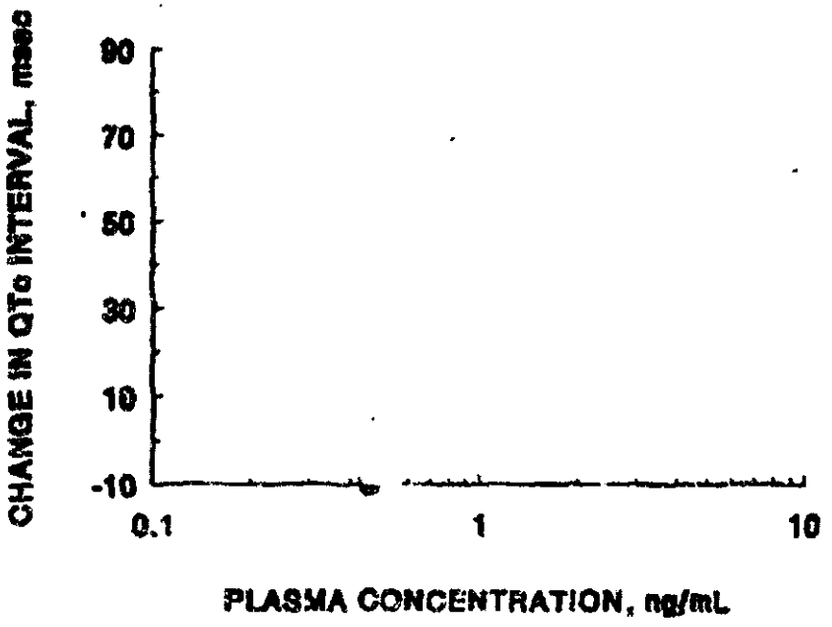


Figure 3. Representative subjects: ΔQTc interval versus plasma concentration (observed points are connected by broken lines and arrows indicating the time course of observations; the solid lines are the predicted values from the Emax model; male = ● ; female = ▲).



2.5 SAFETY RESULTS[2]

No subject withdrew from the trial because of an adverse event. No serious or severe adverse events were reported. Of the sixteen subjects who enrolled and completed the study, two subjects reported a total of three medical events which were all of mild intensity. None of these events were related to the cardiovascular system.

3. REVIEWER'S COMMENTS

The primary objective of this study was to evaluate potential sex-related differences in the pharmacokinetics of ibutilide fumarate. Another objective was to evaluate potential sex-related differences in pharmacodynamic responses, as measured by prolongation of the QT interval.

This was an open-label study in which a single dose of 0.01 mg/kg of ibutilide fumarate was to be given as a ten minute intravenous infusion to 6-10 healthy men and to 6-10 healthy women. Male and female subjects were to be matched by age. The study was not blinded and not placebo controlled. Only one dose was evaluated, and therefore the study also was not randomized. Eight men and eight women enrolled in and completed the study.

General: The design of this study (open-label, no placebo control, no concurrent control group, single dose, no randomization) limit the definite conclusions that can be drawn from the study, particularly with regard to pharmacodynamics. Furthermore, as this was a single-dose study, pharmacodynamic and safety data were not obtained at steady-state.

All of the men and women were white. To enroll, the subjects were required to be between 45 and 80 years of age and to have a corrected QT interval of ≤0.440 sec[½]. Subjects were excluded from the study if they had a history of torsades de pointes, long-Q[T] syndrome, or were treated with medications known to prolong the QT interval.

Thus, the pharmacokinetic, pharmacodynamic, and safety results should be extrapolated with caution to subjects with different demographic characteristics (e.g., pediatric subjects or subjects of different races), to subjects with a baseline QTc interval that exceeds 0.440 sec[½], or to subjects with long-QT syndrome. The study does not contribute any information about drug interactions between ibutilide and other medications known to prolong the QT interval.

Dose exploration: Only one dose of drug (0.01 mg/kg) was evaluated. Thus, this study does not provide any information about the linearity of the pharmacokinetics of ibutilide. Similarly, beyond the limited information obtained with this one dose, the study does not otherwise provide any pharmacodynamic or safety data.

Pharmacokinetics: As summarized by the sponsor, postinfusion plasma concentrations of the (+)- and (-)-enantiomers as well as total racemic ibutilide decreased rapidly with at least two rapid distribution phases. Nearly identical concentrations of U-82,208E and U-82,209E were achieved after dosing in both male and female subjects. Racemic ibutilide and its enantiomers exhibited similar pharmacokinetic properties; all components demonstrated a high systemic clearance,

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[2] Safety issues are discussed comprehensively in Dr. Gordon's review.

approximating liver blood flow, and a large volume of distribution. No differences in pharmacokinetic parameter estimates were found between male and female subjects.

Pharmacodynamics: Compared to baseline measurements in both men and women, infusions of ibutilide fumarate prolonged the QTc interval. The prolongations were generally measurable for three hours after drug administration. The maximal QTc prolongation was 0.066 sec[*] for men and 0.065 sec[*] for women; both maxima were observed five minutes after the end of the infusion, and represented a 16% and 15% prolongation in the QTc interval for men and women, respectively.

Safety: The safety data from this trial are of limited use given the characteristics of the trial design (e.g., single dose) and the characteristics of the subjects (e.g., healthy men and women). Nonetheless, no subject withdrew from the trial because of an adverse event. No serious or severe adverse events were reported.

APPENDIX H

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An Open-Label, Dose-Ranging Study in Patients Undergoing Electrophysiologic Study (P-7550-0004).

1. TITLE OF TERMINATED STUDY

An Open-Label, Dose-Ranging Study in Patients Undergoing Electrophysiologic Study (P-7550-0004).

2. DESCRIPTION AND RESULTS OF THE STUDY

This study, conducted by Dr. Glen Kabell, was closed after one patient was treated under the protocol. The sponsor's summary of this patient's course follows:

Subject #101 was a 56 year old white male undergoing electrophysiologic study. He was given three ten-minute infusions of 0.005, 0.01, and 0.02 mg/kg ibutilide with 7-8 minutes between each infusion. There were no clinically significant safety lab abnormalities. Medical events reported were shoulder pain, palpitations, abdominal muscle pain, groin pain, back pain, and headache. None were felt to be related to the ibutilide infusion. Corrected QT intervals increased as follows: 0.410 sec* at baseline, 0.460 sec* following the 0.005 mg/kg infusion, 0.520 sec* following the 0.01 mg/kg infusion, and 0.530 sec* following the 0.02 mg/kg infusion. Sinus node recovery times were normal both at baseline and following the infusions. Atrial and ventricular effective refractory periods (ERPs) increased following ibutilide infusions. Ventricular ERP increased from a baseline of 250 msec to 300 msec at a cycle length of 600 msec at the end of the 0.02 mg/kg infusion.

3. REVIEWER'S COMMENTS

No reliable conclusions can be drawn from an isolated case report. The electrophysiological findings in this patient that occurred with ibutilide infusion (i.e., prolongation of atrial and ventricular effective refractory periods and prolongation of the QTc interval) are consistent with findings in other studies and the expected actions of ibutilide.

APPENDIX I

TABLE OF CONTENTS

An Open-Label, Single-Dose, Pilot Study in Patients with Paroxysmal Atrial Flutter/Fibrillation (P-7550-0018).

1. TITLE OF TERMINATED STUDY

An Open-Label, Single-Dose, Pilot Study in Patients with Paroxysmal Atrial Flutter/Fibrillation (P-7550-0018).

2. DESCRIPTION AND RESULTS OF THE STUDY

This study, conducted by Professor HJJ Wellens of The Netherlands, was closed after two patients were treated under the protocol. The sponsor's summary of these cases follows:

2.1 Subject number 202

This was an eighty-one year-old female patient with paroxysmal atrial fibrillation (AF) of less than 24 hours duration. Her QTc interval from the electrocardiogram on enrollment was 0.420 sec[½]. She was given 1 mg of ibutilide infused over a period of 10 minutes in a volume of 20 ml. She did not convert to sinus rhythm in the first hour after infusion, and 24 hours after the infusion she was electrocardioverted with a single shock of 200 joules. There were no effects of ibutilide on blood pressures or laboratory tests. Her QTc was 0.475 sec[½] thirty minutes after the infusion. There were no reported medical events during the infusion and up to three days after the infusion.

2.2 Subject number 203

This patient was a 70 year-old male with paroxysmal atrial fibrillation of a duration less than 24 hours. His electrocardiogram showed evidence of right bundle branch block (RBBB) and a QTc of 0.473 sec[½]. He was given 1 mg of ibutilide infused in 20 ml over a 10 minute period.

At the end of the infusion his blood pressure was reported to be 90/60 mmHg from a previous recording of 125/65 mmHg made five minutes earlier. No action was taken and the next recorded blood pressure was 140/75 five minutes later. At this time (i.e., five minutes after the end of the infusion) the patient converted to sinus rhythm. He remained in sinus rhythm until the end of the study which was 31 hours after the infusion. His QTc was reported to be 0.460 sec[½] at the time of the conversion. There were no reported medical events during the study period and there were no effects of ibutilide on laboratory tests performed before and five hours after the infusion.

3. REVIEWER'S COMMENTS

No reliable conclusions can be drawn from isolated case reports. Although the course of subject #203 provides minimal anecdotal support of the efficacy of ibutilide in terminating atrial fibrillation, the clinical course of subject #202 provides none. The hypotension that occurred in subject #203 is notable.

NDA # 20,491

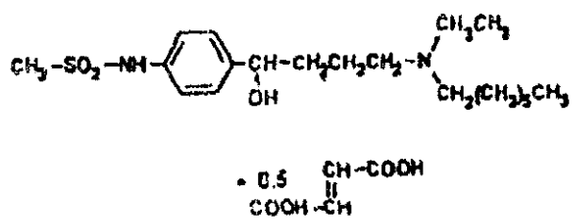
OCT 19 1995

REVIEW & EVALUATION OF PHARMACOLOGY/TOXICOLOGY

Reviewer:	P.Gill-Kumar, M.D.
Review Completion dt.:	Sept 18, 1995
Editorial Changes:	Sept 28, 1995

CDER receipt dt.:	Oct. 31, 1994
Reviewer receipt dt.:	Nov 2, 1994
Sponsor:	The Upjohn Co, 7000 Portage Rd Kalamazoo, Michigan, 49001-0199
Drug:	Ibutilide Fumarate
Trade Name:	Corvert Injection
Molecular Formula:	$C_{22}H_{36}N_2O_5S$
Molecular wt.:	442.62
Formulation:	Aqueous solution for i/v use containing 0.1 mg/ml ibutilide fumarate.
Pharmacological Class:	Class III Antiarrhythmic agent.
Proposed Therapeutic use:	Treatment of atrial fibrillation & flutter

Structural Formula:



Note: Ibutilide fumarate is a racemate that contains equal amounts of two enantiomers.

Proposed Dosing Regimen:

In patients weighing ≥ 60 kg, 1 mg; in patients weighing < 60 kg, .01 mg/kg. The dose should be administered by i/v infusion over a 10 minute period. If the arrhythmia does not terminate, a second dose equal to the first may be administered 10 minutes after the first dose. Note: Doses are of the salt, and not of ibutilide. Comments: The maximum clinically proposed dose is 0.033 mg/kg in a patient who requires two doses and weighs approximately 60 kg.

Related INDs:

Submissions Reviewed:

NDA 20,491, original submission dt Oct 27, 1994
Amendment #99 dt Jan 19, '95 to IND 33,562
Amendment dt March 27, '95 to NDA 20,491
Amendment #103 dt June 14, '95 to IND 33,562

NDA # 20,491

Original Pharmacology/Toxicology Review

Table of Contents

Summary, Conclusions & Recommendations

Note: Page numbers referred to below are those of the Full review, which follows this section of the review.

Pharmacodynamics:
In-vitro studies:

- Action potential duration (APD) in isolated guinea pig atria was dose relatedly increased in the dose range 10^{-7}-10^{-5} M; increases in APD at 3 Hz and 1 Hz stimulation rates were similar (Study #1, p8). In another study, ibutilide was shown to dose relatedly increase atrial effective refractory period (AERP) 8-25% at doses of 10^{-6} and 10^{-5} M; force of contraction was not affected; spontaneous rate of contraction was slowed (Study #5, p11).
- In isolated guinea pig ventricular cells, using voltage clamp techniques, ibutilide was shown to increase the amplitude of the slow inward current (elicited by application of depolarization steps); increase in the slow inward current was maximum at 10^{-5} M ibutilide concentration. Using different external and internal perfusing solutions, it was shown that the inward current that is increased by the application of ibutilide is carried by Ca^{++} at about 5 msec into the depolarization step, and by Na^{+} at about 600 msec into the voltage step. Ibutilide increases the late inward current even when the holding potential is -40 mv, which inactivates the fast Na^{+} channel. This indicates that the late inward current which is increased by ibutilide is carried by a slow Na channel. Ibutilide does not seem to affect the activation/inactivation kinetics of this slow Na channel. (Study #2, pp9-10)

  Tetrodotoxin (TTX) 10^{-7}M abolished the effect of ibutilide on the APD of ventricular myocytes. In cells depolarized by increasing external K^{+} concentration, neither ibutilide not TTX affected the upstroke of action potentials which under these conditions is produced by Ca^{++}, but the prolongation of action potential was abolished by TTX (Study #3, p10).

  The late outward current carried by K^{+} was shown to be increased by ibutilide in the dose range 10^{-7}-10^{-5} M, under conditions in which the inward currents were abolished by using appropriate external solutions. (Study #4, p11)

- U-107246 (a metabolite of ibutilide in man and dog; its AUC in man was < 8% of the AUC of ibutilide, p21) dose relatedly increased AERP 18-30% in the dose range 10^{-6}-10^{-5} M.

In-vivo studies:

- In a dog model of atrial flutter, reproducibly inducible flutter was terminated by ibutilide in the dose range of 0.001-0.01 mg/kg i/v in all 8 dogs tested. At dose levels at which flutter was terminated, AERPs and monophasic action potential durations (MAP_{90}) were increased (Study #1, pp11-12).

- *Cardiovascular Effects:* In chronically instrumented conscious dogs, ibutilide in the dose range 0.01-1 mg/kg had no effect on mean arterial pressure and heart rate. At doses ≥0.1 mg/kg QT_c was increased, which is the expected effect of a drug that increases ventricular APD (Study #4, p15).

Conclusion: The studies summarized above show that: Ibutilide increases the APD of ventricular cells by increasing the magnitude of a slow inward current, which is carried in the early part of the AP by Ca^{++} and in the later part by Na^+ passing through a slow channel. This slow Na^+ channel is not inactivated by prolonged depolarization, but is blocked by TTX. Ibutilide also increases the late outward K^+ current. The mechanism by which ibutilide increases APD is thus an increase in slow inward currents, and not a decrease in the late outward K^+ current. Ibutilide also increases the APD of atrial cells, and AERP of atria. In a dog model of atrial flutter, flutter was terminated by administration of ibutilide. Ibutilide thus has the cardiac effects of a class III antiarrhythmic agent.

Toxicology:

Note: When a drug related change in any parameter is described, unless specified otherwise, the change is from the value in the control group; s-s stand for statistically significant and s-ns stands for statistically not significant; NAED stands for 'No Adverse Effect Dose'.

Rat:

Acute: *Ibutilide:* LD_{50}, 85.1 (80.1-90.8) mg/kg; there were no deaths in the 50 mg/kg group. *Ibutilide* · LD_{50}, 64.1 (58.3-69.7) mg/kg; 1/20 animals in the 50 mg/kg group died. is a degradation product formed during heat sterilization of ibutilide (Ibutilide (HS)); and may also form during shelf storage. *Note:* The 95% CIs for two LD_{50}s do not overlap. The sponsor has stated that at the most of ibutilide is degraded to during heat sterilization of ibutilide.

Subchronic:

14 day study: *12.5 mg/kg/day* was the NAED. *25 mg/kg/day:* clinical effect was only post dose salivation for a few minutes in 1/30 rats on one day; some females in this group had mucification of vagina, and proliferation of mammary glands; 2/15 males had atrophy of the seminiferous tubules of the testes; ≈5% reduction in body wts of males. *50 mg/kg/day:* Clinically, post dose salivation occurred in several animals in the last week of the study, and some animals exhibited depression, generalized shaking, hyperpnea/dyspnea during the first week. There was ≈5% reduction in body wts of males, ≈9% increase in body wts of females. *Liver wt* of females was increased by ≈ 13%, and *ALT* was increased by ≈20% in females (pp25-27).

7 day study with Ibutilide+ ; (3 mg ibutilide+ /kg/day had no adverse effects clinically, on body wts, or on the histopathology of heart, kidneys, liver, and male and female reproductive organs(p27).

Note: This submission also contains two week and three month oral toxicity studies in rat. These studies have not been reviewed since this NDA is only for at the most two i/v doses,

and these oral non clinical studies are therefore not at all relevant to either assessing possible risks during clinical use of the drug or indicating any precautions to be taken during clinical use.

Dog:

Acute: 6 mg/kg ibutilide (lowest dose tested) caused CNS signs like apprehension, head bobbing, body rocking, reduced motor activity... (p23); the signs lasted for a few hours. In 2/9 animals CPK was increased (in one after 8.5 mg/kg, in the other after 6 and 8.5 mg/kg); the increases ranged from 38%-72% over the highest value in the other 7 animals; on retesting 3 weeks later, CPK was normal.

Subchronic (14 day Study): 1.25 mg/kg/day (lowest dose used) was associated with slight apprehensive behavior for 1-2 days, and ≈18% increase in heart wts, in females. 2.5 mg/kg/day was associated with apprehensive behavior for 1-2 days in females; increase in heart wts in both sexes. 5 mg/kg/day was associated with CNS signs similar to those seen in the acute study; in the second week, the severity of the signs was less pronounced, and only 50% of the animals showed the signs; heart wts were increased in both sexes (more increase than at lower doses in females), thymus wts were increased in females, and there was testicular degeneration in 1/3 males (p 28).

Comments: 1.25 mg/kg/day, the lowest dose used in this study, was associated with increase in heart wts in females. Clinical signs which at this dose were present only in females were mild and transient, and therefore are not of toxicological significance.

Note: This submission also contains two week and three month oral toxicity studies in dog. These studies have not been reviewed for the reason given above for not reviewing the oral subchronic studies in the rat.

Reproduction Toxicology: (All studies oral; drug administration by gavage)

Rat:

- In a segment I study (pp30-32), ibutilide at a dose level of 20 mg/kg/day was embryocidal and teratogenic. Litter incidence of pup abnormalities at 10 mg/kg/day was s-ns (0/19 in control group and 2/17 in the 10 mg/kg/day dose group), but the sponsor thinks the abnormalities in this group may also be drug related.

- In a segment II study (pp32-p34) in which ibutilide doses of 20, 40, and 80 mg/kg/day were used, adverse effects were observed at all doses. There were no live fetuses in the high dose group; 20 and 40 mg/kg/day doses were associated with dose related embryocidal effects, and with teratogenic effects.

- In a repeat segment II study (p34) ibutilide doses of 5, 10, and 20 mg/kg/day were administered. 20 mg/kg/day ibutilide was associated with teratogenicity (no of live fetuses/dam were lower than in the control group, but difference was s-ns; table R6 after p29). The sponsor considers that the presence of fetuses with scoliosis in 2/24 litters in the 10 mg/kg/day group (versus 1/23 in the control group) may be indicative of teratogenicity at this dose level. 5 mg/kg/day was thus the NAED in this study.

Rabbit:

- In a segment II study, 2 mg/kg/day was the highest dose used; there were no adverse effects at any dose.

Genotoxicity studies:

The following tests were done and were all negative: Ames test in 5 strains of Salmonella typhimurium, Forward Gene Mutation Assay in mammalian cells, Unscheduled DNA Synthesis Assay in rat hepatocytes, and Micronucleus test in mouse bone marrow (pp36-39).

Discussion & Conclusions:

A mixture of Ibutilide + of the degradation product, had ≈ 25% lower LD_{50} in the rat than ibutilide alone. In the 7 day rat study, (had produced no adverse effects; in terms of body surface area (BSA), this dose is= . If the heat sterilized solution of ibutilide contains not more than ((the highest amount that the sponsor says is present in the heat sterilised solution of ibutilide), the maximum dose of this chemical that a patient weighing 60 kg could receive would be mg/M^2. Thus on a mg/M^2 basis, times the maximum proposed dose that a patient could receive had no adverse effects when administered to rats for 7 days. The amount of this degradation product (if it does not exceed of ibutilide) in the formulation therefore does not seem to pose a safety concern.

In both rat and dog, ibutilide produced CNS effects, the severity of which was dose related. The incidence and severity of these effects became less during continued dosing; thus adaptation seems to occur for these effects. From the point of view of help in assuring safety during clinical use of the drug, subchronic studies are mainly useful during drug development. Therefore the results of the 14 day studies are not discussed any further.

Reproduction Toxicity studies: The rabbit study is not helpful in assessing possible risk to pregnant women, since the study was an oral study, and there is no toxicokinetic information from the study that was done nor is the bioavailability of ibutilide in this species known. In the rat studies (which were also oral), 5 mg/kg/day was the NAED. Bioavailability of ibutilide in rat when given an oral dose of ~45 mg/kg was 4-11% (p12); in a second study (p12-p13), bioavailibility of ibutilide after 0.5 mg/kg oral dose was ~1.8%, and after 106 mg/kg oral dose, it was ~24%. Based on the results of these studies, one can estimate, that after an oral dose of 5 mg/kg, bioavailibility of ibutilide would be < 4%; this makes the 5 mg/kg oral dose the equivalent of a < 0.2 mg/kg i/v dose in terms of ibutilide AUC; this is < 1.45 mg/M^2. A patient who receives the maximum dose of the drug clinically, would receive 1.26 mg/M^2. Even though in the rat after an oral dose of 0.5 mg/kg, at least 60% of the drug is absorbed, there must be a very high rate of first pass metabolism to account for the low bioavailibility of ibutilide. Since one does not know the chemical entity/entities that cause teratogenicity after administration of ibutilide at doses > 5 mg/kg/day, the safe thing is to assume that ibutilide is the teratogenic agent; on this assumption, a patient receiving the maximum dose would receive a dose ≈ the NAED in the rat. This leads one to infer that there is hardly any safety margin from the point of view of fetal safety during the clinical use of this drug.

Safety Assessment of Inactive Ingredients:

Each ml of Corvert injection contains 0.1 mg ibutilide fumarate, 0.189 mg sodium acetate trihydrate, 8.90 mg NaCl, and HCl to adjust pH to approximately 4.6, and Water for Injection. The concentration of sodium acetate is < 0.2%. In the agency's list of inactive ingredients in marketed formulations, >1% concentrations of sodium acetate trihydrate are present in formulations for i/v injections. Therefore the amounts of inactive ingredients in this formulation are not a matter of concern from the point of view of patient safety.

Recommendations:

The results of the non clinical studies reviewed and discussed here do not contraindicate approval of this NDA. The approval would be decided on the basis of the clinical studies. However, since (the degradation product that is formed during heat sterilization and may also form during storage) is not inoccuous, if this drug is approved, the sponsor should be required to determine the rate of production of this product during storage to ensure that the amount of present in the drug solution does not exceed an amount that would have to be set by the division. As discussed above, of this material does not pose safety concerns.

Labelling:

Labelling proposed by the sponsor is attached (Attachment I).

- p2, para 1 of the 'Hemodynamic section' should be deleted. The statements in this section refer to the results of a study, the methodology of which was so poorly described that this study was not evaluable (p 10 of Full Review). Therefore the results of this study should not be included in labelling.
- p6, under the heading 'Pregnancy, Labour, and Delivery', 2nd line, after rats the present text should be deleted and the following substituted: The rat studies were done with oral dosing; using the lower part of the range of bioavailability observed in pharmacokinetic studies in the rat, and assuming that ibutilide itself is the teratogen, on a mg/M^2 basis, the 'No Adverse Effect Dose' in these studies is ≈ the maximum recommended human dose. Since the relative sensitivity of the human fetus with respect to the rat fetus is not known, there does not appear to be much of a safety margin. Therefore Corvert should not be administered to a pregnant woman, unless the clinical need of the patient outweighs the possibility of risk to the fetus.
- p10, under the heading 'Acute Experience in Animals', line 2: After 'convulsions.' the rest of the text should be deleted, and the following text substituted in its place: 'The i/v median lethal dose in the rat was more than 315 mg/M^2 (50 mg/kg); this dose, on a mg/M^2 basis, is at least 250 times the maximum recommended human dose.' The reasons for this recommendation are that the mouse study was a dose range finding study in which only 3 animals/sex/group were used, and the median lethal dose could not be determined. Moreover, the mouse study was done with ibutilide and not with ibutilide containing which is the amount of this degradation product in the i/v formulation for clinical use.

Full Review

Note: In the text of this review, b-s stands for biologically significant; s-s stands for statistically significant; s-ns for statistically not significant; used without a qualifier, s-s and s-ns refer to statistical tests done by the sponsor; s-rev stands for statistical tests done by this reviewer. Ibutl and ibutilide stands for ibutilide fumarate; the base comprises 86.9% of the weight of the salt. In the Pharmacodynamic section of the review, abbreviations have the following meanings: AP, action potential; APD_n, action potential duration measured at n% repolarization; MAP, monophasic action potential; PH, plateau height of the action potential; RMP, resting membrane potential; TFAP, threshold for firing action potential; I_x, current carried by ion x; V, voltage. Since this NDA is for treatment of atrial fibrillation and flutter, pharmacodynamic studies dealing with ventricular arrhythmias are not reviewed.

Pharmacodynamics:

§ 1: In vitro studies:

#1 Electrophysiological Effects of Ibutilide on guinea-Pig Atrial Cells:
Single atrial cells were isolated from guinea pig hearts by incubating the atria with tyrode solution containing 0.1% collagenase. Atrial action potentials, elicited by electrical stimulation, were recorded using glass microelectrodes; effects of different concentrations of the drug on APD_{90}, PH (measured at 1/3 of the AP duration above 0 mv membrane potential), and TFAP were measured:

Results:
APD was increased dose relatedly in the dose range 10^{-7}-10^{-5}M; magnitude of the effect at 3 Hz was similar to that at 1 Hz (Fig. 1 illustrates this effect). RMP, according to the sponsor's statement, was affected only at the high dose; there was some depolarization of RMP. TFAP was reduced at all doses. (According to the sponsor, since atrial cells do not have much of a plateau, TFAP measurement in these cells is not very useful.) Effects on APD, PH, and TFAP are summarized in Table 1 [1] Drug effects could not be reversed by wash out.

Comments: The sponsor states that comparison of dose effect relationships between atria and ventricles shows that atria are about 10 times less sensitive to the drug than the ventricles. In the ventricle, APD is prolonged by increase in the magnitude of I_{Na-s}, the slow Na current; the ionic mechanism of atrial APD prolongation by ibutilide has not been studied.

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[1] The values of various AP parameters after washout seem to indicate that washout was done after 10^{-5}M. Since this dose was tested only in 4 cells, n for washout should be 4, and not 7.

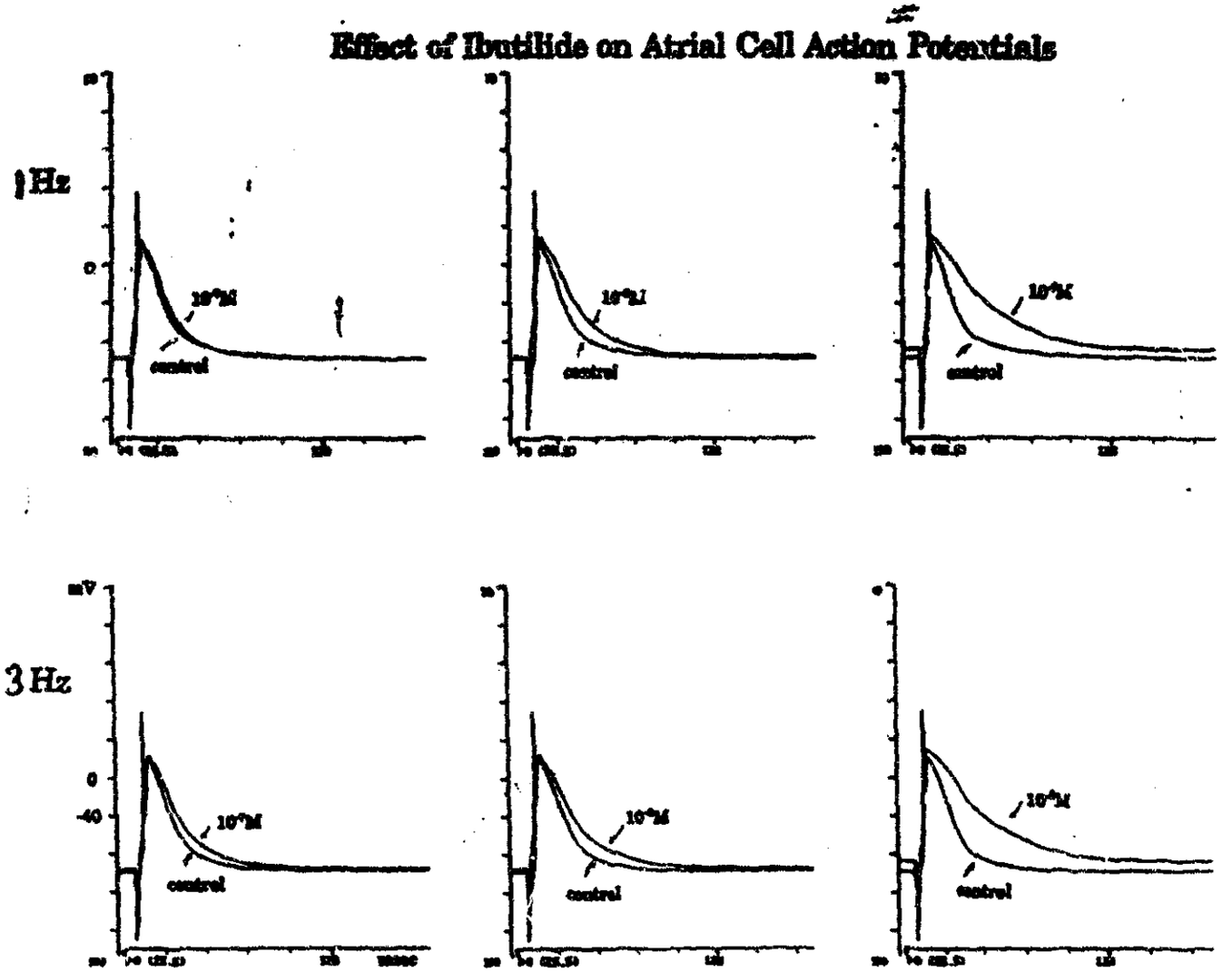


Figure 1. Effect of ibutilide on atrial cell action potentials. APD prolongation by ibutilide at 10^{-7}M to 10^{-6}M are shown. Results on upper panels were taken at 1 Hz stimulus frequency and those at lower panels, at 3 Hz.

TABLE 1

Raw mean values of experiments testing U70226E on the atrial cell

APD

Treatment		Pacing rate at 1 Hz Mean (ms)	SEM	n		Pacing rate at 3 Hz Mean (ms)	SEM	n
control	C	31.29	4.09	7	C	30.71	3.70	7
1E-07	D	38.00	4.46	7	D	38.79	4.82	7
control	C	30.10	5.80	5	C	29.60	5.23	5
1E-06	D	40.10	7.32	5	D	39.00	6.97	5
control	C	49.63	4.55	4	C	49.38	5.48	4
1E-05	D	61.38	6.86	4	D	63.00	8.00	4
wash	W	57.14	11.85	7	W	61.57	14.37	7

*: The mean value of APD that was pooled all control APDs together is 37.55±4.46 msec (n=10) at 1 Hz and 37.3±4.47 msec (n=10) at 3 Hz.

APH

Treatment		Pacing rate at 1 Hz Mean (mV)	SEM	n		Pacing rate at 3 Hz Mean (mV)	SEM	n
control	C	90.46	4.92	7	C	85.68	3.12	7
1E-07	D	89.48	4.31	7	D	89.12	3.58	7
control	C	86.38	5.29	5	C	83.76	3.69	5
1E-06	D	88.28	2.97	5	D	87.41	2.43	5
control	C	95.51	9.68	4	C	91.85	7.31	4
1E-05	D	93.06	5.63	4	D	89.61	6.25	4
wash	W	91.79	4.80	7	W	85.44	5.22	7

TFAP

Treatment		Pacing rate at 1 Hz Mean (nA)	SEM	N		Pacing rate at 3 Hz Mean (nA)	SEM	n
control	C	1.00	0.16	7	C	0.95	0.15	7
1E-07	D	0.81	0.14	7	D	0.80	0.15	7
control	C	1.05	0.22	5	C	1.02	0.21	5
1E-06	D	0.80	0.19	5	D	0.84	0.18	5
control	C	1.18	0.26	4	C	1.14	0.24	4
1E-05	D	0.75	0.11	4	D	0.61	0.06	3
wash	W	0.71	0.05	7	W	0.63	0.08	7

#2: Specific Activity of Ibutilide on a Novel Slow Inward Na^+ Current In Guinea Pig Ventricular Cells.

Single ventricular cells were isolated from guinea pig hearts by the following method: Perfusing the heart with oxygenated tyrode solution of a composition and pH used for studies on isolated perfused mammalian hearts (solution A) followed by perfusion with solution B (B = (A-Ca^{++} +0.1% hyaluronidase); incubating 1 mm thick slices of the ventricles in solution C (C = B+ 2% bovine serum albumin). Single ventricular cells were internally perfused and the effects of ibutilide on various currents were studied using whole cell voltage clamps with micropipettes used for internal cell perfusion. External and Internal solutions were:

External:

1: K^+ free, Na^+ and Ca^{++} solutions containing in mM: NaCl, 144; CsCl, 4; $CaCl_2$, 2; $MgCl_2$, 1; glucose, 5; pH adjusted to 7.6 with Tris buffer.

2: Na^+ free, K^+ free, solution in which NaCl of solution was replaced with equimolar CsCl or isotonic D-mannitol.

Internal:

3: K^+ free solution containing in mM: CsOH, 151; TEA, 20; 4-AP, 5; glucose, 5; ATP-Mg, 5; $MgCl_2$, 1; $CaCl_2$, 1; pH adjusted to 7.1.

5: Normal internal solution contains KCl instead of CsOH, and no TEA or 4-AP.

Note: solution #s are as assigned in the lab, and are not just sequential #s.

Results:

- With normal tyrode externally, switching from internal solution #5 to solution #3 abolished the late outward current I_k, without affecting the I-V relationships of inward currents (Fig. 2).
- With external solution #1, and internal solutions #5, 1 μM ibutilide increased the amplitude of the inward current measured at 60 msec into the voltage step, and that of the outward current measured at 600 msec; at +20 mV voltage step, the inward current seems increased up to 600 msec (Fig 3).
- With external solution #1, and internal solution #3, since there are no outward currents at any voltage, the full effect of ibutilide on inward currents could be studied. Fig. 4 shows the effect of 10^{-8} M ibutilide on inward currents. The effect on the fast inward current (I_{Na}) cannot be seen in the figure. According to the investigators, the increase in the inward current appeared at ≈ 5 msec into the voltage step, and inward current was present for a much longer period after ibutilide, than in the control drug free condition. In the lower part of fig 4, I-V relationship of current measured at 60 msec is plotted. The maximum increase in this slow inward current was ≈ 45%. Fig. 5 shows the dose response relationship of the inward currents, measured at 60 msec and 200 msec, at a +20 mV voltage step (where the effect on the inward current seems to be maximum, Fig 4). The investigators have given calculations for the magnitude of increase in the inward currents at 60 msec and 200 msec, and state that in the dose range 10^{-9} to 10^{-7} mM, the range of increase at 60 msec was 7%-47% (largest increase at 10^{-8}M) and at 200 msec, 47%-100% (largest increase again at 10^{-8}M).

FIGURE LEGENDS

Figure 1.2

Isolation of inward and outward currents. Currents obtained from the same cell, before (solid line) and after (dotted line) internal K^+ solution was replaced by Ca^+ solution that also contained 20 mM TEA and 5 mM 4-AP. Note that I_{in} was present due to the absence of external K^+; I_o was too brief to be seen on this time scale and I_K was small in comparison to the inward currents. I-V plot below, at left is control and at right, 15 minutes after switching to Ca^+ internal solution (solution 3, see method).

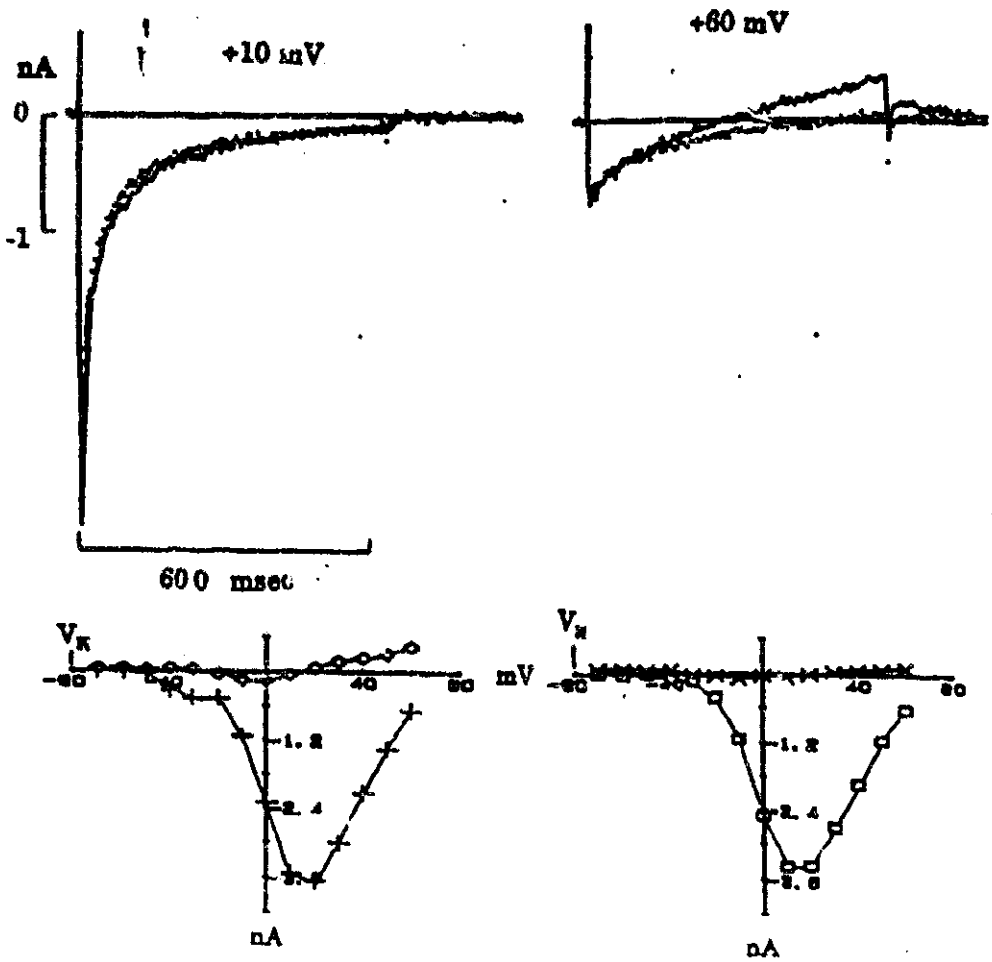


Fig 2.

Figure 3
Drug effects on inward and outward currents. Currents were recorded in internal solution 5 and normal Tyrode's external solution before (solid line,□,▲) and after (dotted line,■,△) drug treatment. With all the physiological ions present, current traces at +20 mV was comprised of a mixture of fast inward I_{Na}, L-type I_{Ca}, and the ibutilide sensitive late inward current. Outward currents are evident in current trace to +40 mV and on the I-V plot at right. Inward current amplitude (□,■) shown on the plot was measured at 60 msec into the steps while outward current amplitude (▲,△) was measured at 600 msec into the steps.

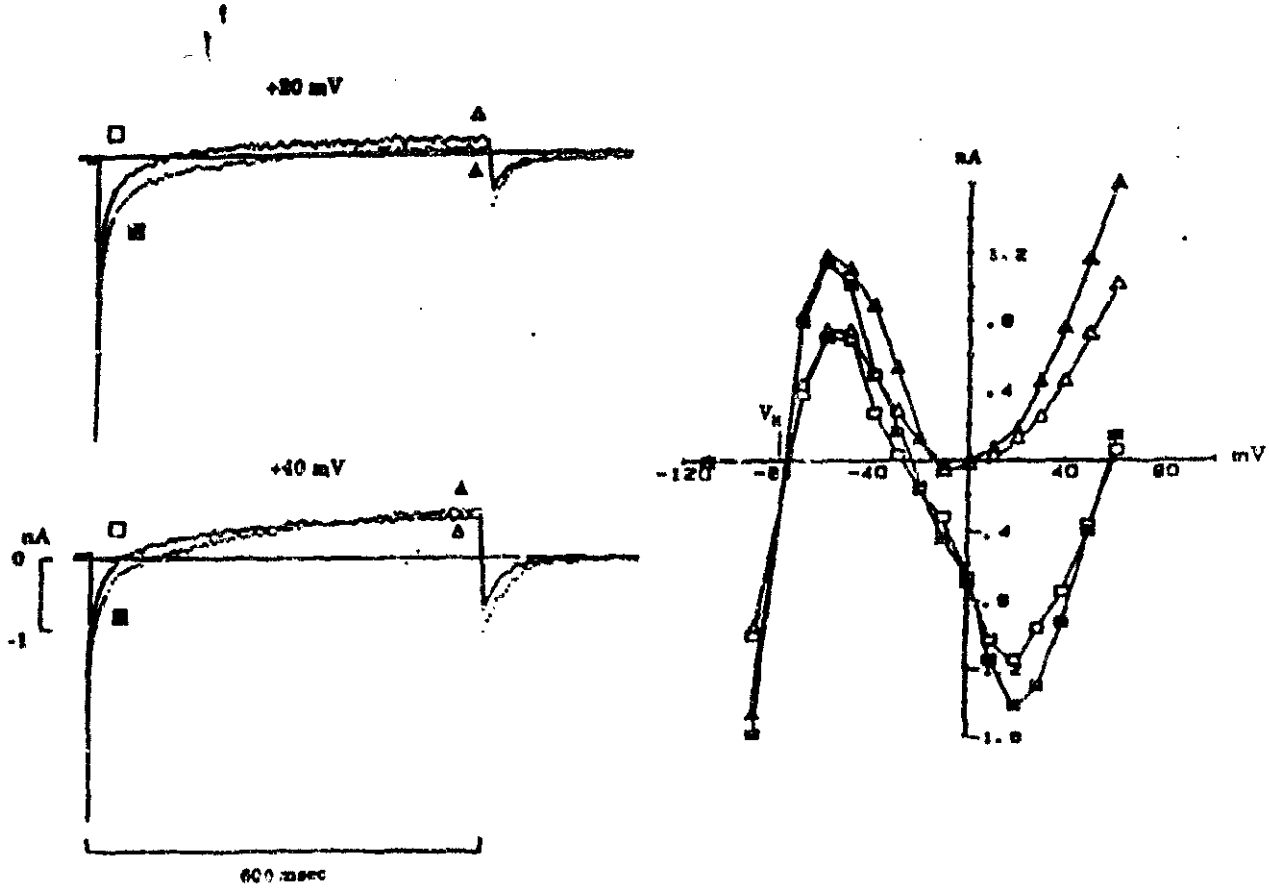


Fig. 3

Figure 4
Response of inward currents to 10^{-6} M ibutilide. In the absence of K^+_o and K^+_i and presence of Na^+_o and Ca^{2+}_o, all currents were inwardly directed. Superimposed current traces of control (solid line) and drug treated (dotted line) depict a subtle but long lasting effect of the drug on the inward currents. Voltage steps from V_H of -80 mV are shown above current traces. I-V plot below is compiled results from 14 cells and vertical bars are the s.e.m. Notice in this ionic conditions, a steady-state inward current which was partially removed by external Na^+ removal (Figure 8) existed.

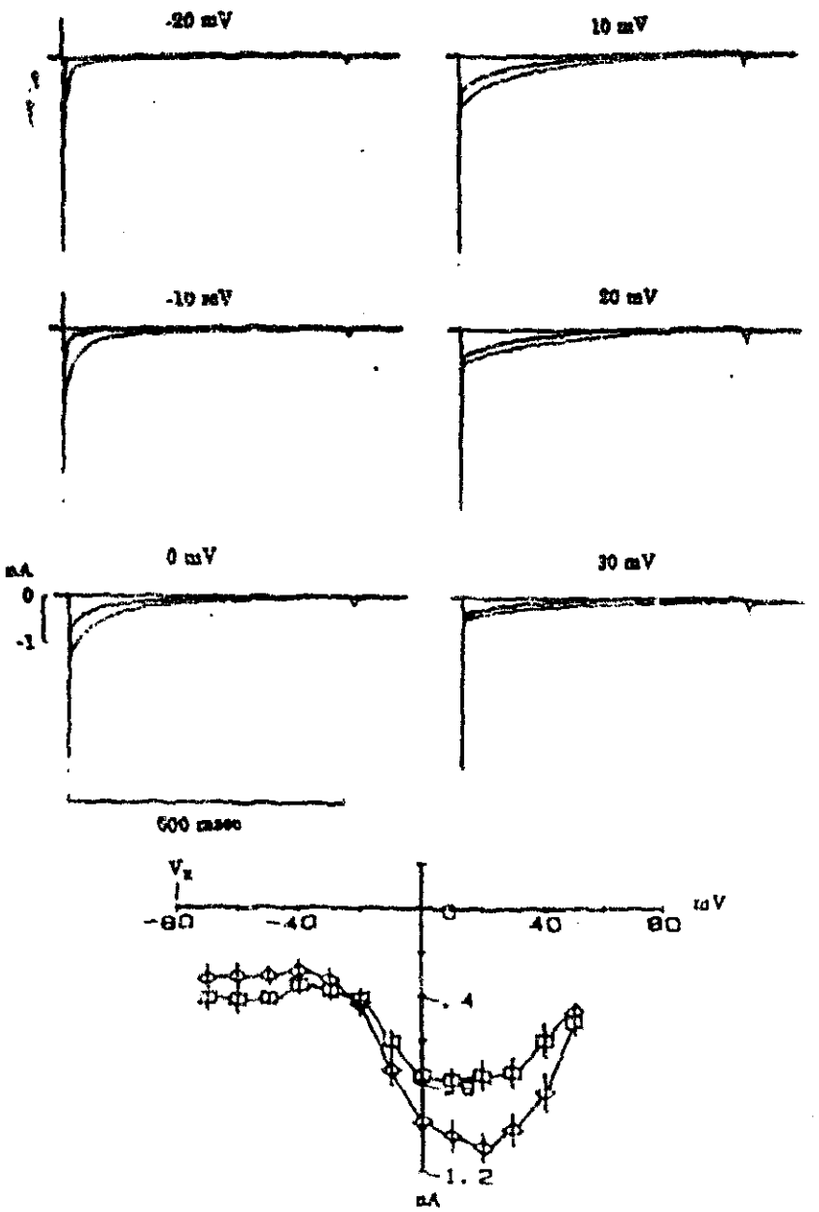
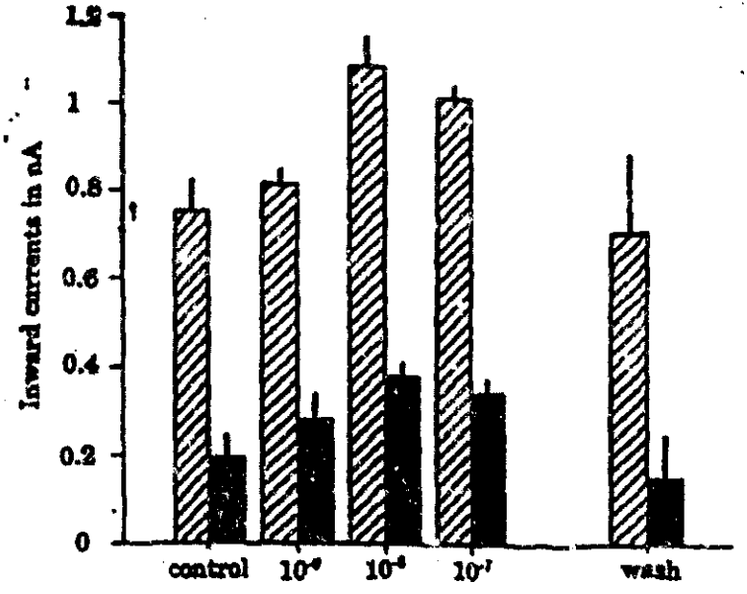
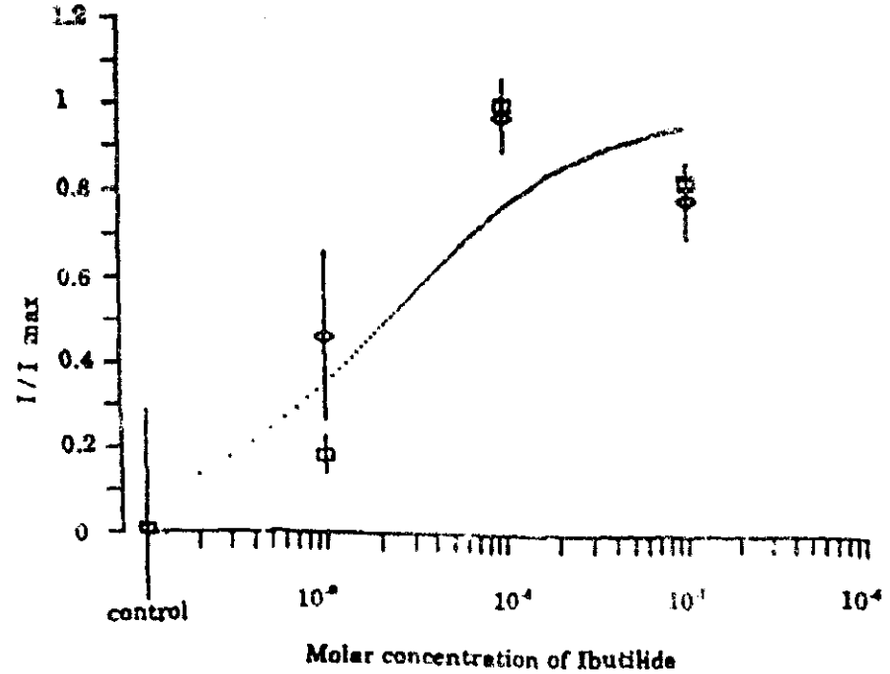


Fig. 4\ □ - □ Before drug ◊ - ◊ After drug

Figure 5
Dose response of inward current to increasing drug concentration. Upper panel shows inward current amplitudes measured at 60 msec (shaded bars) and 200 msec (solid bars) into a +20 mV step from V_H of -80 mV. Below is the same data normalised and fitted by the equation: $I/I_{max}=1-\{1/(1+[ln[drug],K_D)^n\}$. From the curve, K_D is found to be 2×10^{-6} M and n, the Hill coefficient is 0.78.





- When solution #2 (Na^+ free) was used as the external solution, and solution #3 as the internal solution, ibutilide 10^{-7}M increased the inward current; peak current amplitude measured at ≥5 msec into the voltage pulse was increased by 34%. This inward current was blocked by 1 μM nifedipine. These effects indicate that ibutilide has an effect on L-type Ca channels. The increase of this current was mostly at 5 msec; there was very little effect at 60 msec. With solution #1 as the external solution, the %increase in current in the presence of 10^{-6}M ibutilide was the largest at ≈ 600 msec (Fig 6). This result seems to indicate that ibutilide increases inward current mainly through a late, slow Na channel. Fig 7 shows that the increase in the late inward current at a holding potential of -40mV (which would inactivate the fast Na^+ channel) was reduced when Na^+ was removed from the external solution, and restored to ≈original amplitude, when NaCl in external solution was restored.
- Study of the effects of 10^{-6}M ibutilide on activation and inactivation kinetics of the slow inward current showed that the drug did not affect these kinetics; normalized curves with and without 10^{-6}M ibutilide, superimposed (Fig 8); 50% inactivation occurred at -27 mV in both cases, and 50% activation (after complete inactivation) occurred at +2 mV in both cases. *Note:* The time into the step pulse at which currents were measured for plotting activation and inactivation kinetics is not given in this report, but is stated to be 60 msec, in a paper (p 102 of J of Pharm and Exp Therapeutics, 1992, 262: 99-108).

Discussion: That the slow inward current is not due to slow inactivation of the fast Na^+ channel is indicated by the following results described above: The slow current is present at a holding potential of -40 mV, which inactivates the fast channel.

#3: Effect of Tetrodotoxin on Prolongation of APD by ibutilide:

In isolated guinea pig ventricular myocytes, effects of different concentrations of ibutilide on APDs were recorded, and at the dose level at which the APD increase was maximum, the effect of adding tetrodotoxin (TTX) on APD was studied. This experiment was repeated in cells depolarized to -45 mV by increasing the external K^+ concentration to 1 mM. These drug effects were also studied on inward currents in depolarized, voltage clamped cells.

Results:

Fig 9 shows the effects of 3 concentrations of ibutilide on APD; maximum prolongation of APD occurred at 10^{-7} M. Addition of 10^{-7} M TTX reduced APD to ≈ pre-ibutilide control value; washing reduced APD to below control level (Fig 10). Similar results (in terms of effects of ibutilide and TTX on Δ APD) were obtained in cells depolarized with 15 mM external K^+ (Fig 11). Ca^{++} mediated upstroke of the APs of depolarized cells was not affected by either drug. Fig 12 shows the I-V curves and the effects of ibutilide, and ibutilide + TTX (TTX added after ibutilide). TTX reduced the increase of inward current produced by ibutilide.

Comments: The investigators state this slow Na channel is much more sensitive to the blocking action of TTX than the fast Na channel that carries the current during the upstroke of cardiac APs.

Figure 6
Drug effect on early and late inward currents. Upper panels are current amplitudes measured at 5, 10, 60, 200, 620 msec into a +20 mV step from V_h of -80 mV. Shaded bars are control and solid bars are in the presence of 10^{-6} M flecainide. Lower panels are % change of drug treated current from control. Current amplitudes, left panels, were recorded in Na^+_o and Ca^{2+}_o containing solutions whereas panels at right were recorded in Na^+_o-free, 2 mM Ca^{2+}_o solution.

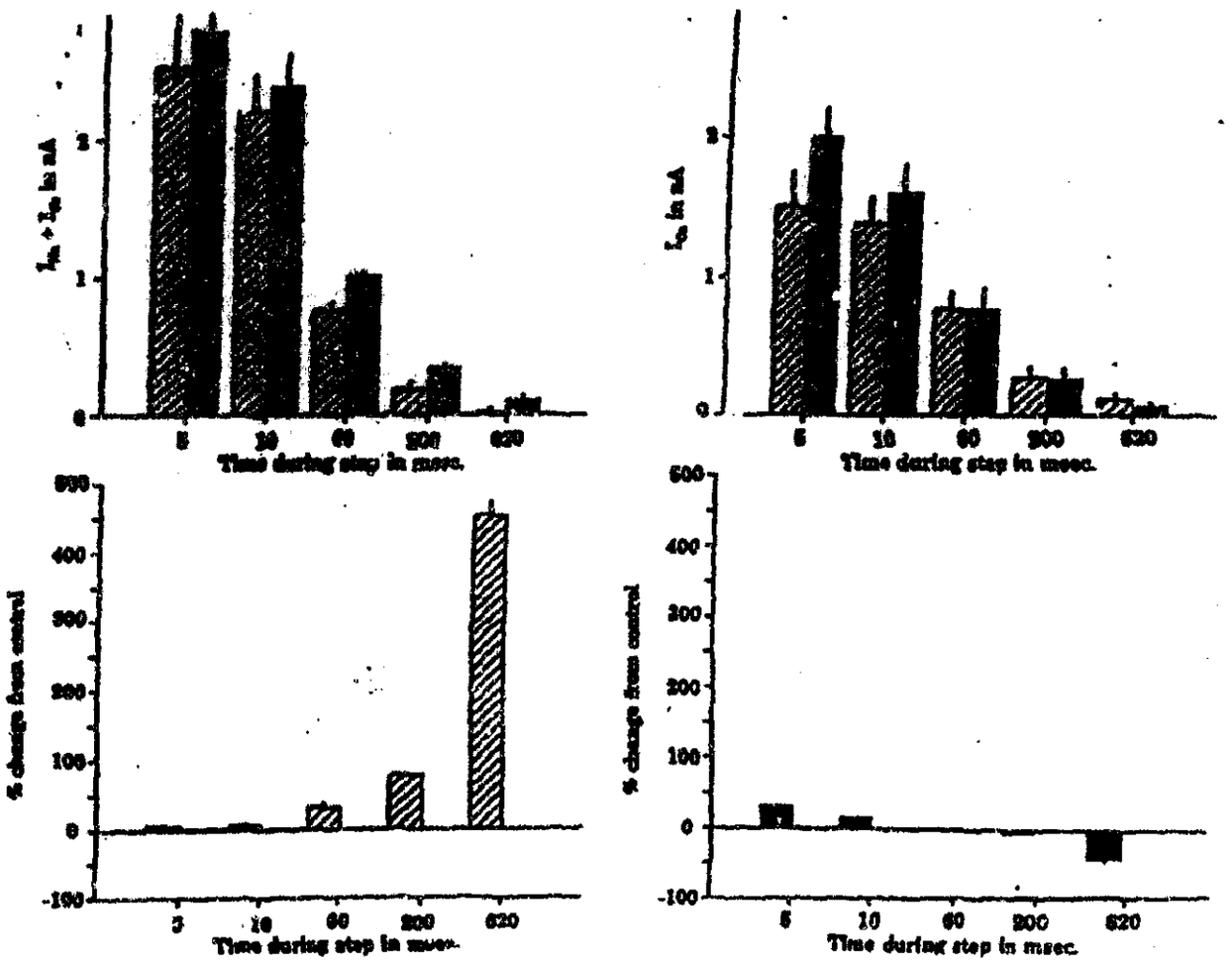


Fig. 6

Figure 7

Effect of external Na^+ removal on late inward current. Inward currents were recorded at holding potential of -40 mV in an external solution that contained Na^+, Cs^{2+}, (solution 1) and ibutilide (10^{-7} M) in order to maximize all inward currents at this holding potential (solid lines on left panel). Then, with the drug level unchanged, all external NaCl was replaced by CsCl (solution 2); the inward currents, especially the late component was significantly reduced (dotted line) and this reduction could be restored readily by restoring external Na^+ (as current from the same cell shown at right). Step potentials from a holding potential of -40 mV are indicated above the current traces. I-V curve below is peak inward currents in drug but measured before (◊) and after (♦) external Na^+ removal. V_R = -40 mV

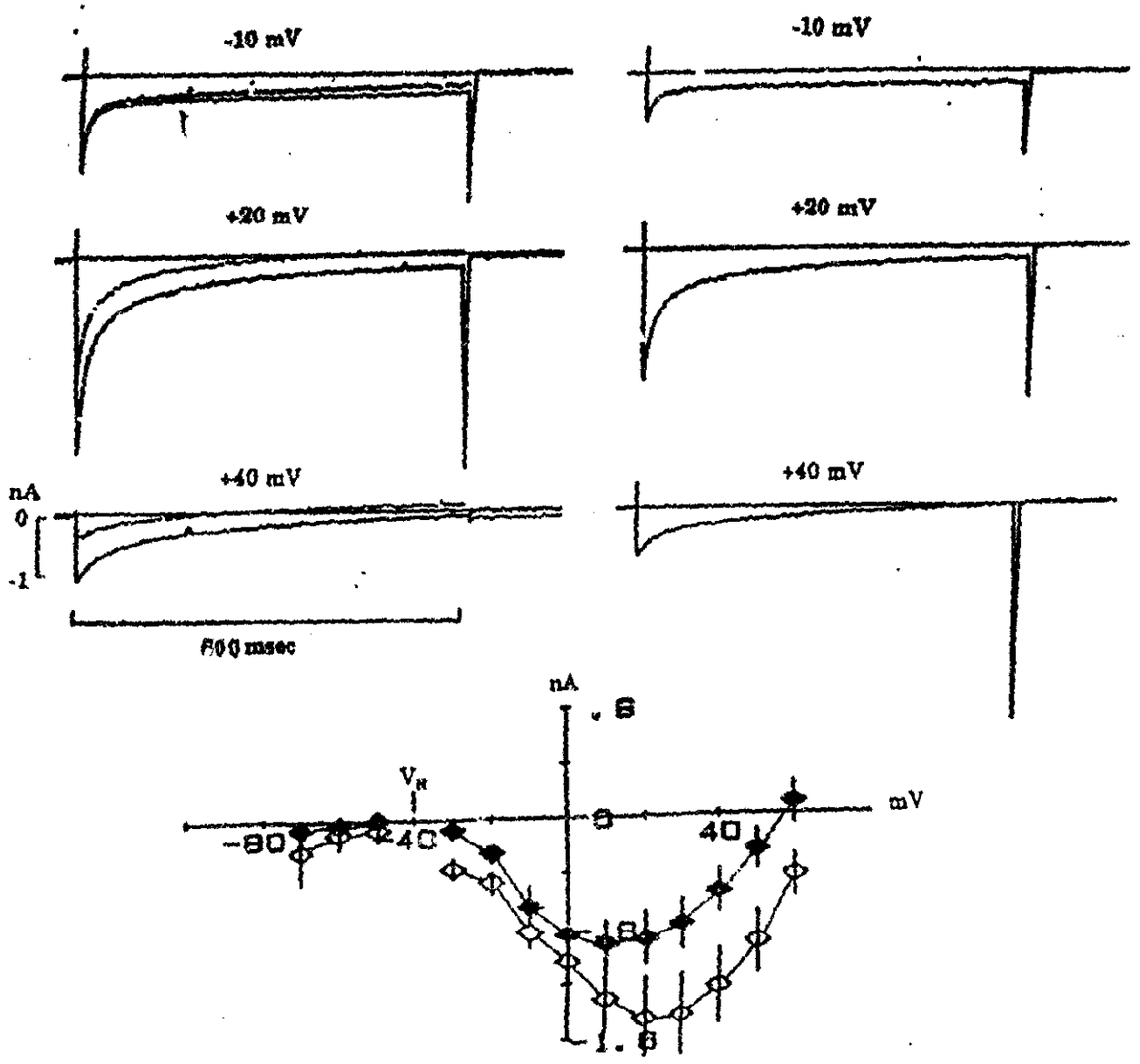


Fig. 7

Figure 8.
Steady-state kinetics of inward currents at step potential of +20 mV from V_H of -80 mV, in the absence (□,) and presence (◊,) of ibutilide. Upper panel at left is the h∞-V curve. The protocol was the following: at V_H of -80, the cell was step depolarized to +20 mV for 600 msec; then V_H was sequentially changed to -70, -60, -50, -40, -30, and -20 mV and after 5 seconds at each new V_H, the same +20 mV step was applied to assay the amount of inward current that remained. At the end of the run, V_H was immediately back to -80 mV for 10 seconds before the +20 mV step was applied again to measure amount of current recovery as indicated by the points at right of the curve. At right, is the M∞-V curve of the Hodgkin-Huxley g-V type to the power of 1. Below are normalized curves superimposed to show that the drug induced no shift on either curve.

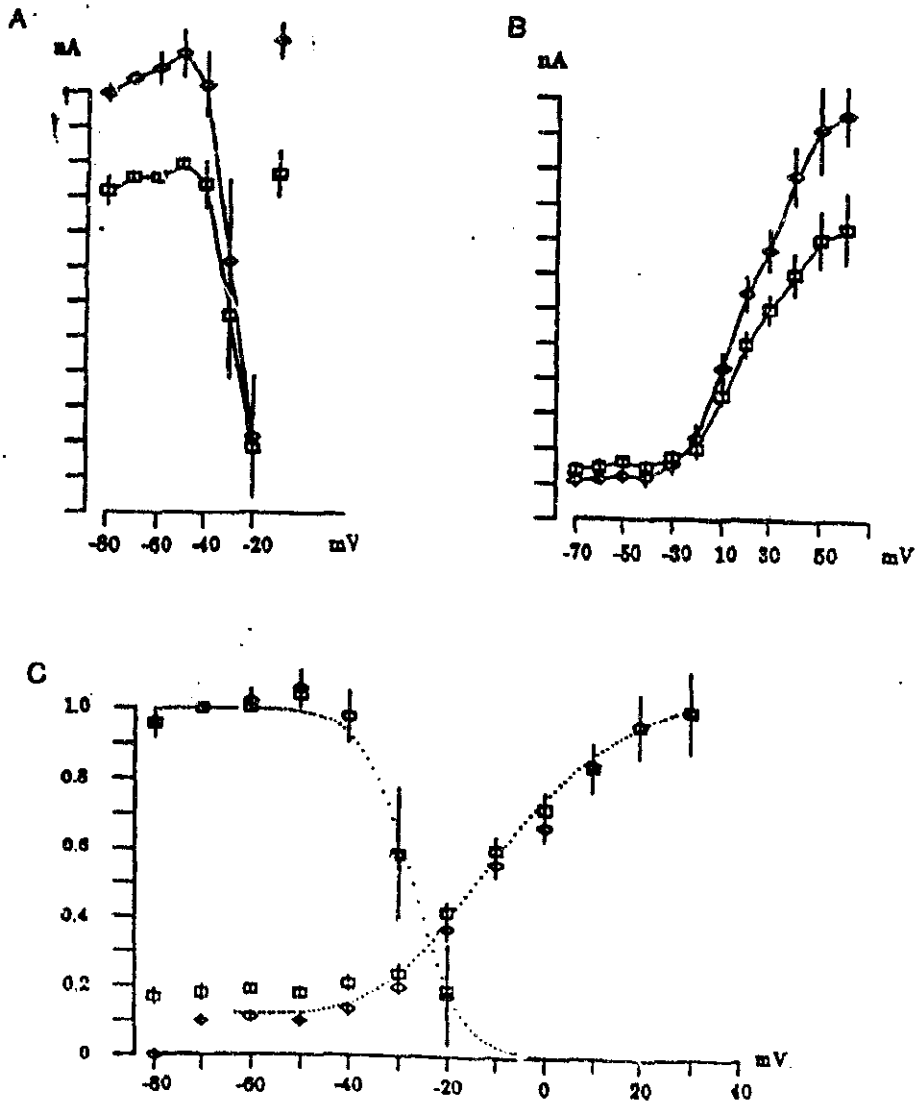


Fig. 8

Figure 9A Comparison of the percent change in APD for dose-response data obtained for U-70226E using either the suction pipette (whole-cell configuration) (A.) or conventional 3M KCl microelectrodes(B.). Although the microelectrode recordings show a larger percentage increase in APD than those obtained using suction pipettes the variation in the measurements is far greater. The most obvious difference between the two methods is the strong depression in APD at 10-5M U-70226E using the suction pipette method of recording.

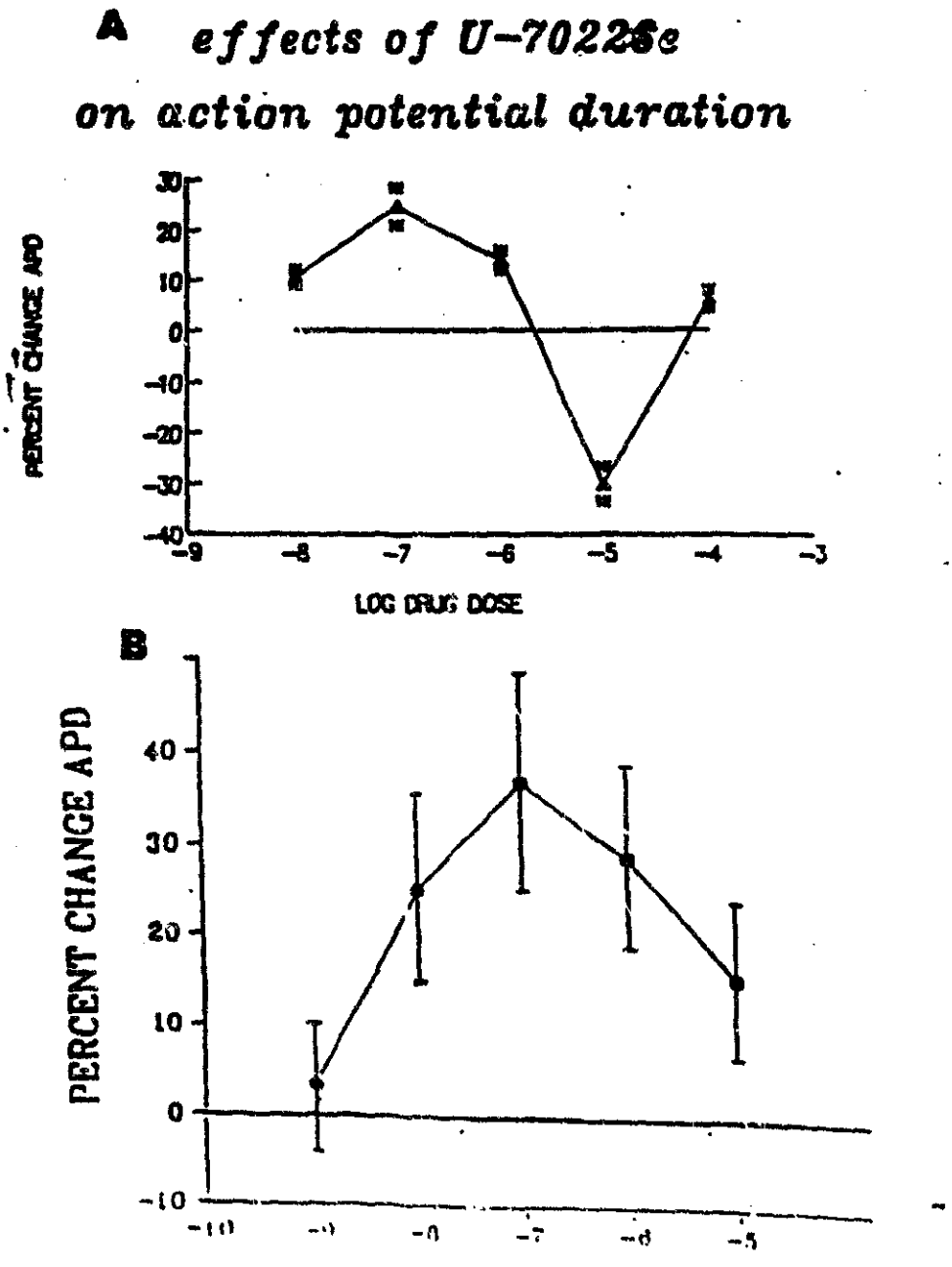
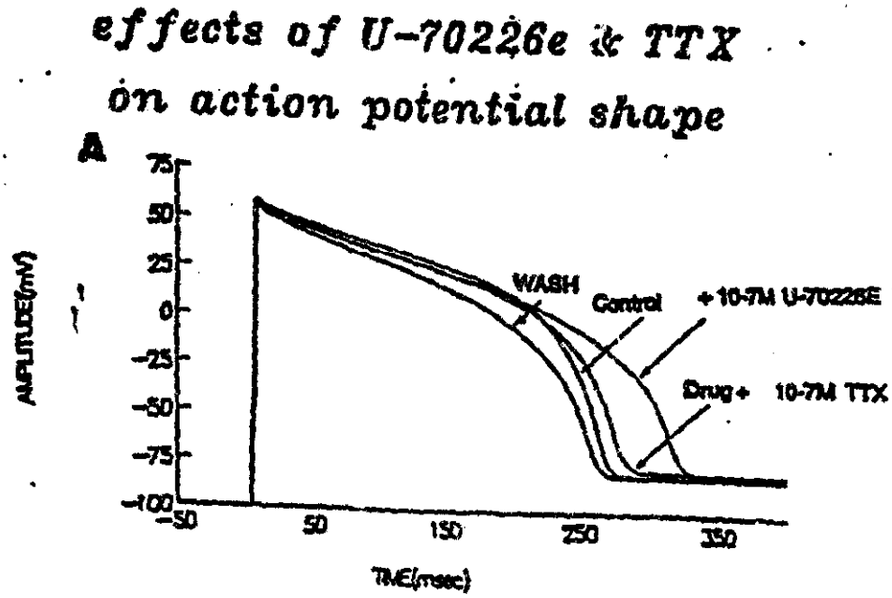


Fig. 9

Figure 10(A.) A Representative set of action potentials demonstrating the increase in APD when the cell is treated with 10-7M U-70226E and the subsequent reversal in APD when 10-7M TTX is added to the superfusing medium containing U-70226E. With washing APD never returns to pretreatment control levels. (B.) A graph of percent change in APD vs. control (N=4) for cells treated with 10-7M U-70226E followed with the addition of 10-7M TTX.



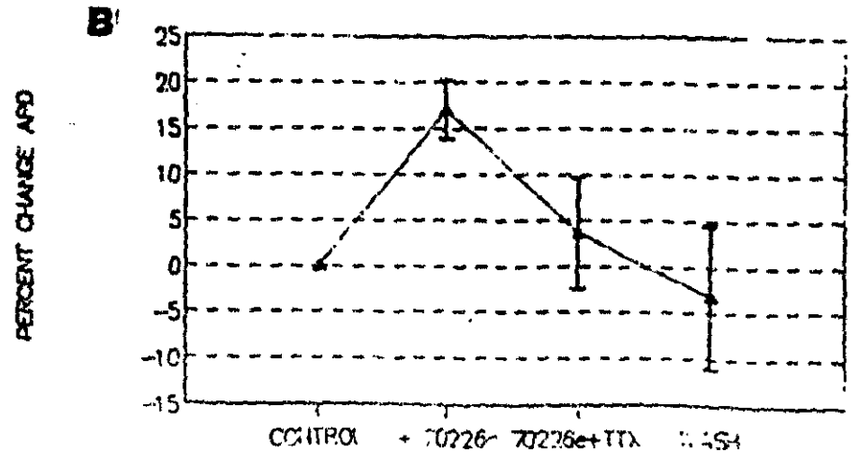


Fig. 10

Figure 11A representative set of action potentials showing the effects of 10-7M U-70226E and 10-7M TTX when a cell has been depolarised to approximately -45mV with high potassium KCl. This demonstrates that the effects of both U-70226E and TTX are not strongly dependent on resting membrane potential and that the fast inward sodium current is not involved as it is inactivated at membrane potentials positive to -55mV.

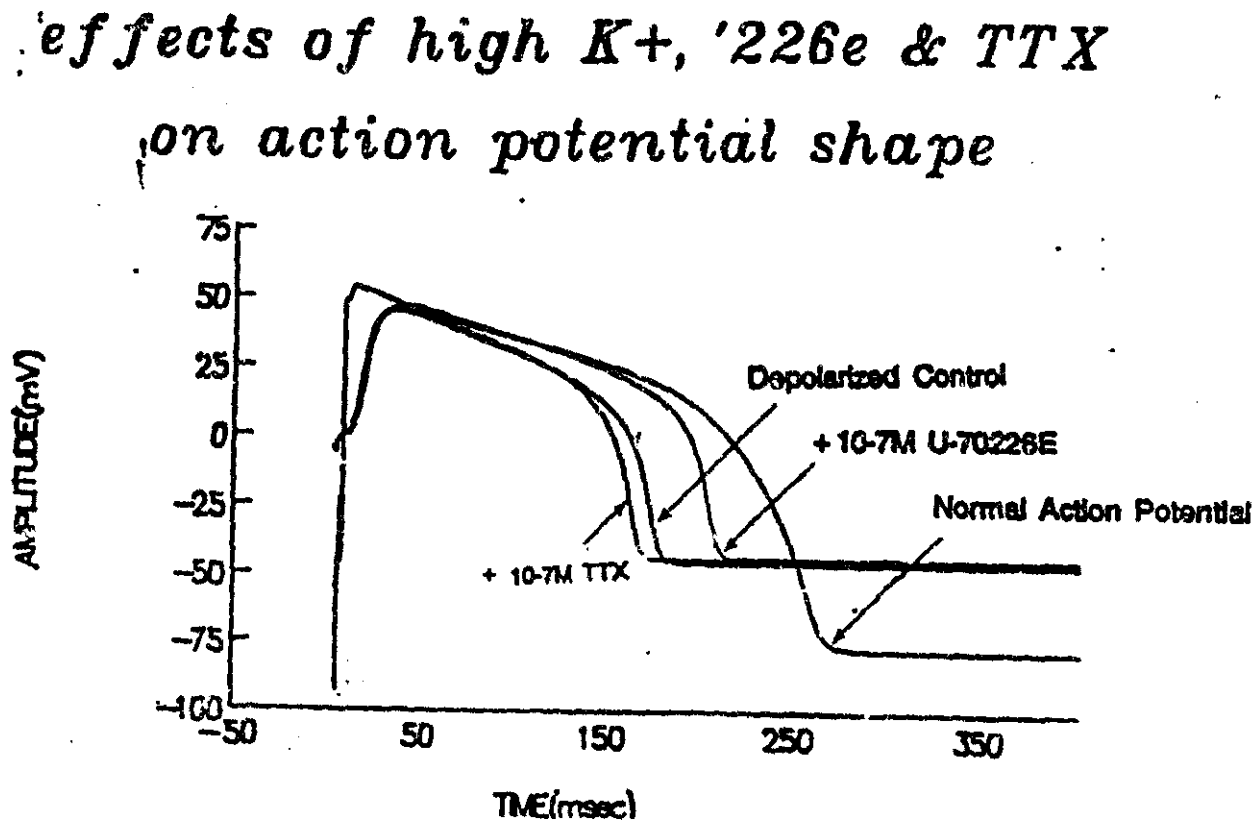


Fig. 11

Figure 12 A set of current records obtained in voltage-clamp comparing control, 10⁻⁷M U-70226E and 10-7M TTX. The addition of U-70226E increases the slow decay phase of the inward current, while the subsequent addition of TTX decreases the amount of inward current. The inset shows a family of currents obtained when the membrane potential is clamped at -40mV and step depolarized in 10mV increments to +70mV. The arrow shows the point at which the slow inward current were measured. (B.) A current-voltage relationship showing the effects of U-70226E and TTX on the slow inward current.

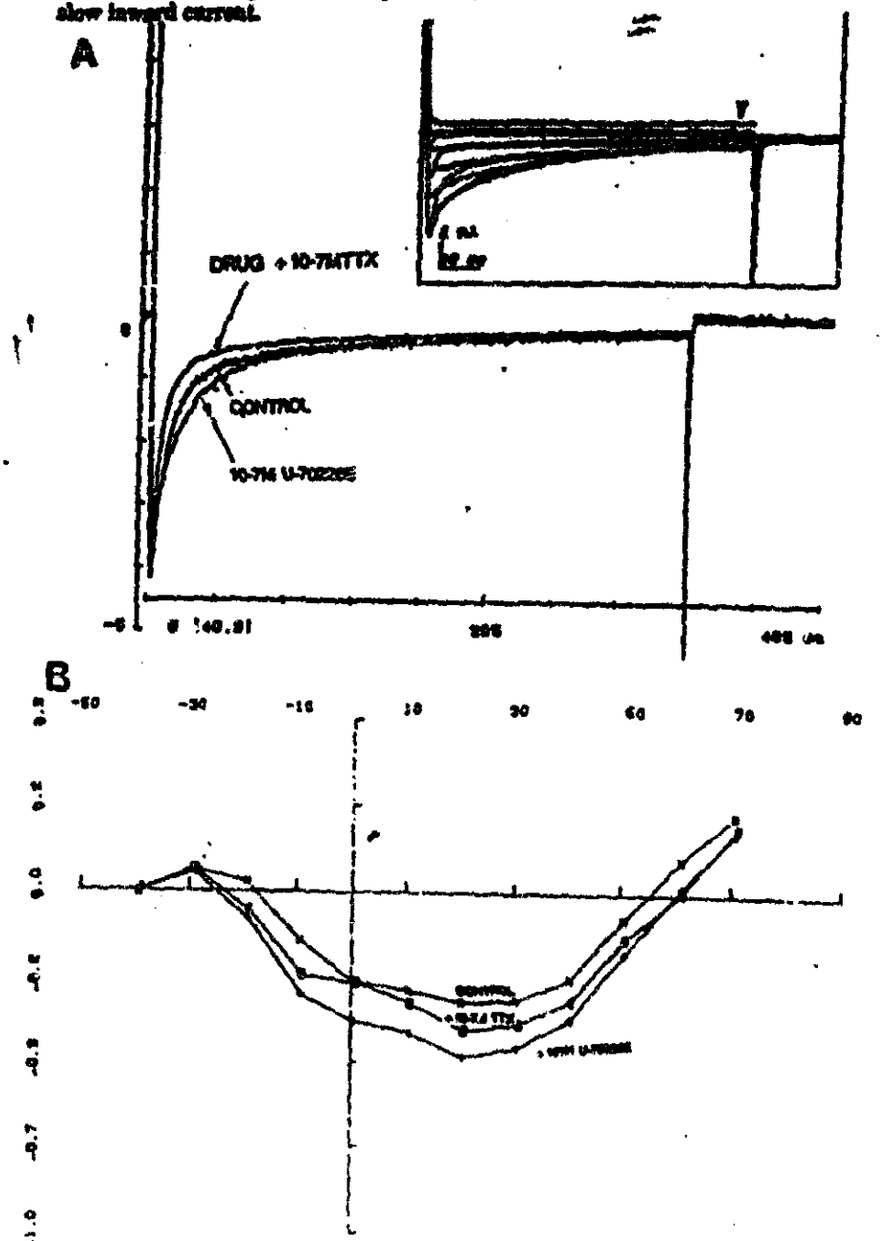


Fig. 12

#4:Effect of Ibutilide on I_k and the transient outward current, I_{to}:

Using whole cell voltage clamp technique, effect of ibutilide on I_Ks (There are more than one type of K channels in cardiac cells) of guinea pig isolated ventricular myocytes were studied. Internal solution was normal internal solution; external solution, at the start was Na^+ free, and K^+ free (Solution #1: CsCl 144 mM; $CaCl_2$, 2 mM; $MgCl_2$ 1 mM; normal amounts of glucose, and pH adjusted to 7.6 with Tris buffer). The inward current (carried by Ca^{++}) evoked by a 10 mV pulse was abolished by the addition of 2 mM Co^{++} added to the external solution; addition of Co had no effect on the Ik. After these initial observations, the external solution was 'Solution #1 + 2mM Co'.

Results:

- In the dose range 10^{-7}-10^{-5}, I_k was dose relatedly increased. Fig 13 shows the effects of (1-5)x10^{-5} M ibutl on I_k, and Fig 14 (solid bars) shows the dose response relationship of I_k. The resting (I_{k1}) and transient (I_{to}) outward currents (both carried by K^+) are inhibited by ibutl (Figs 15 and 16).

#5: Effect of Ibutilide on Rabbit Atria:

Effects of 10^{-6} and 10^{-5} M ibutl on ERP, force of contraction, spontaneous beating rate, and isoproterenol dose response relationships of isolated rabbit atria were studied.

Results: ('↑' indicates increase.)

- *AERP* (measured while pacing the left atria at 2 Hz) was increased by 14±3 msec (8±3 % ↑ over control), and 40±4 msec (25±2 % ↑ over control) at the two doses tested; the increase at the higher dose was s-s.
- *Force of contraction:* Ibutl at the doses tested had no effect on the force of contraction, or on the dose response relationship of isoproterenol for force of contraction.
- *Rate:* 10^{-5} M ibutl decreased the spontaneous rate of rt atria by approximately 25%; dose response relationship of isoproterenol was shifted downwards; -Δ HR was approximately the same at all doses of isoproterenol tested (dose range 10^{-9} to 3x10^{-7} M).

<u>§2: In-vivo Studies:</u>

#1: Effect of Ibutilide on Atrial Flutter in Anesthetized Dogs:

In anesthetized dogs, Y shaped incisions were made in the rt atria. After the incisions, atrial flutter could be induced in these animals by fast pacing of rt atria. Sustained flutter was terminated and induced by fast pacing several times to establish reproducibility of induction. AERPs were determined during periods of normal rhythm, and flutter cycle length was determined from recordings of MAP_{90}. Cumulative doses of ibutl (starting with 0.001 mg/kg) were given i/v at 5 min intervals till flutter was terminated. AERPs were again determined after flutter termination; and induction was tried at intervals for the 2-3 hours of observation. Effects of ibutl were tested in this manner in 8 dogs with reproducibly inducible flutter.

In six anesthetized dogs, no incisions were made in the rt atria, and effects of cumulative doses of ibutl on AERPs and MAP_{90} were studied.

Figure 13. Enhancement of I_{to} the delayed rectifier K^+ current by ibutilide. Current traces at left are control (solid) and in the presence of 5×10^{-5} M ibutilide (dotted). Those at right are from the same experiment but showing the drug effect (dotted line) could be washed off readily (solid line). (Step was to +60 mV.) Below is a compiled I-V curve before (□) and after (◊) 10^{-5} M drug treatment.

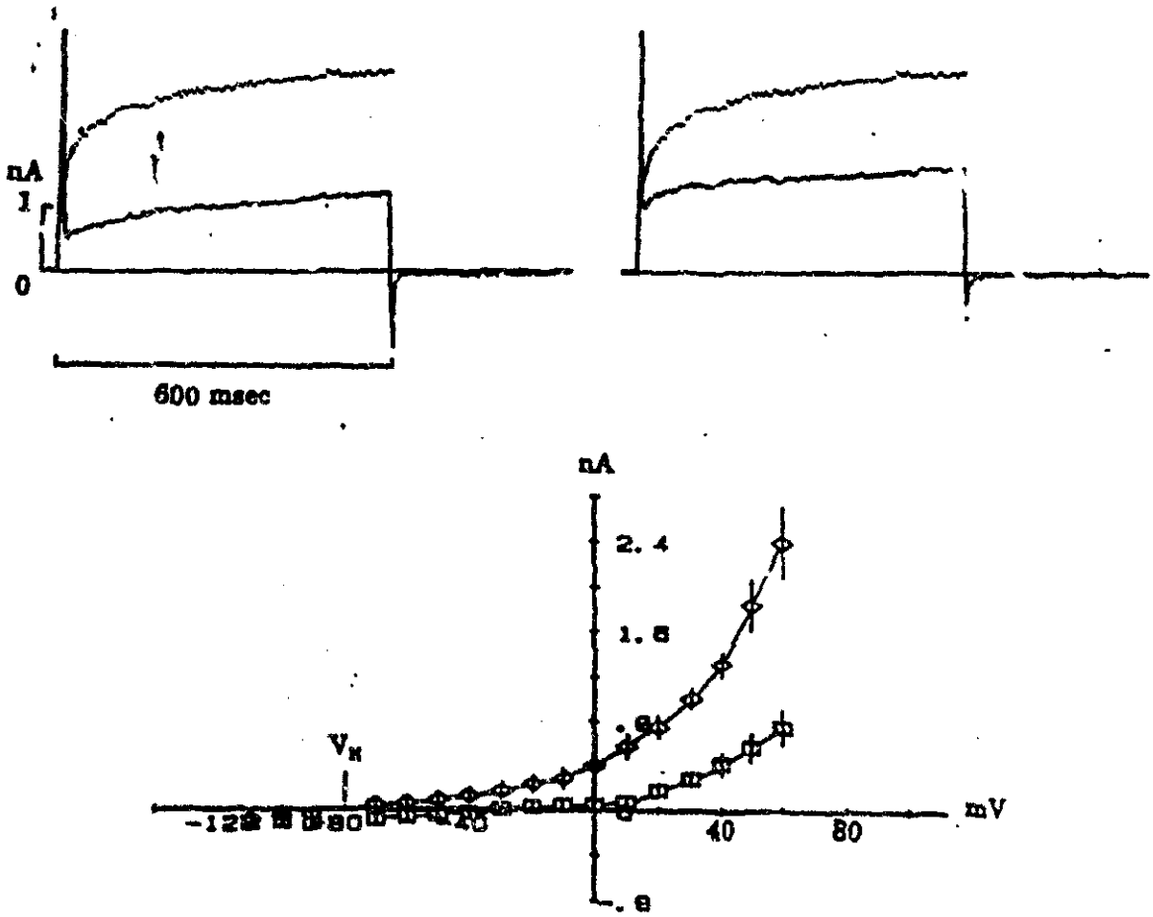


Fig. 13

Figure 14. Dose response of K^+ currents to increasing doses of ibutilide. Current amplitude of I_{to} (shaded bar), I_{K1} (dotted bar) and I_K (solid bar) at various drug concentrations. Current amplitudes at three step potentials of -50 mV, 0 mV and +40 mV were shown where I_{K1}, I_{to} and I_K were prominant. V_H were at -80 mV.

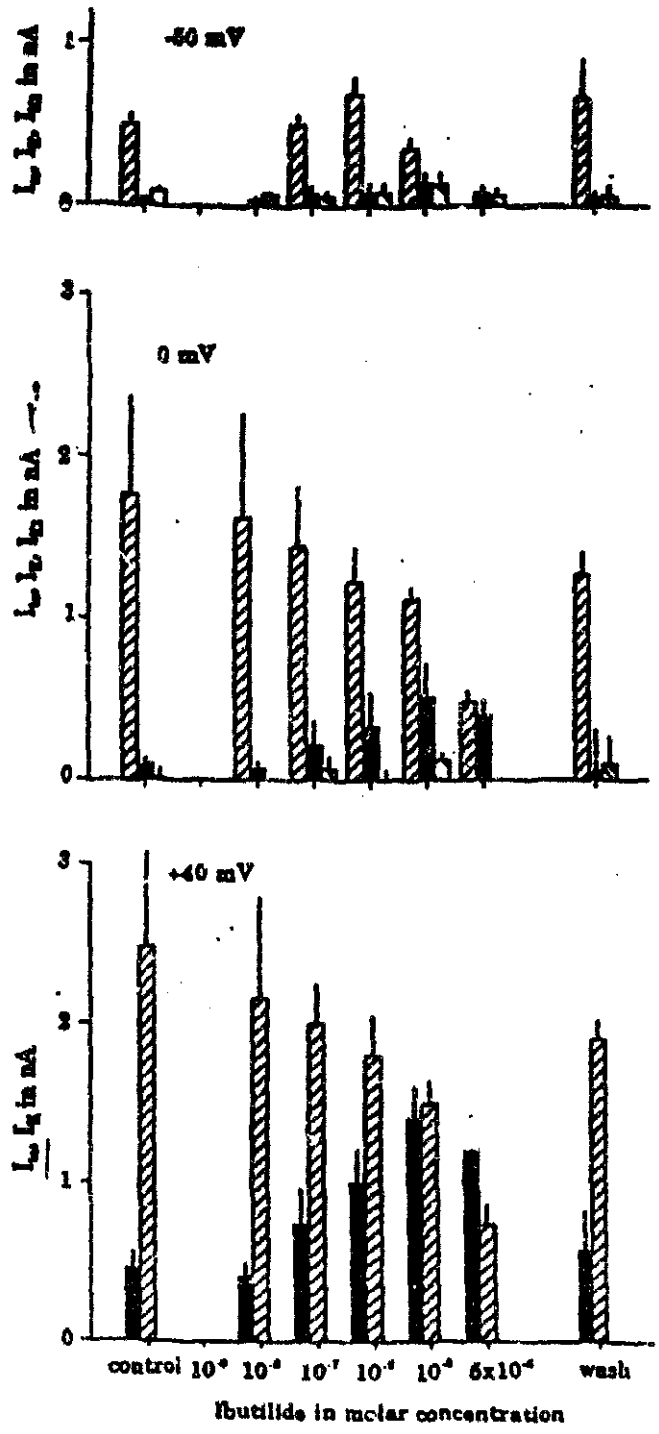
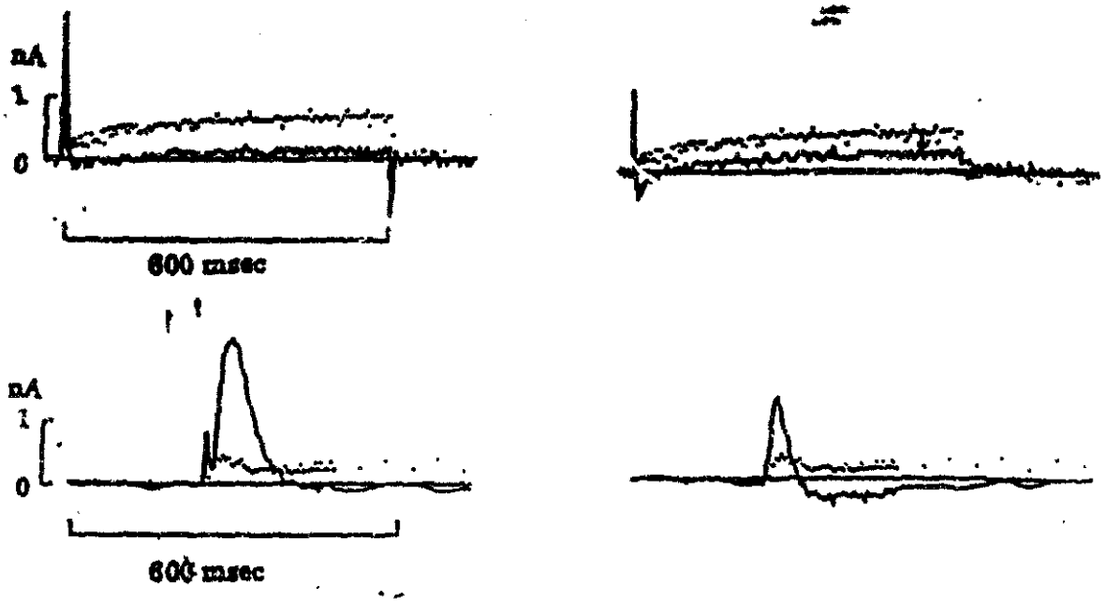


Fig. 14

Figure 15 Depression of I_{to}, the transient outward K^+ current by ibutilide.
Top and middle panels, left, are current traces before (solid line) and in 10^{-4} M ibutilide (dotted) showing opposite drug actions on I_{to} and I_K; notice the 10X difference in time scale. At right, traces show that in the same cell, the drug effect (dotted line) could be washed out (solid line) for either I_{to} or I_K. (Step was to +20 mV from a V_H of -80 mV.) Below is a compiled I-V curve of I_{to} before (□) and after (◊) 10^{-4} M ibutilide application.



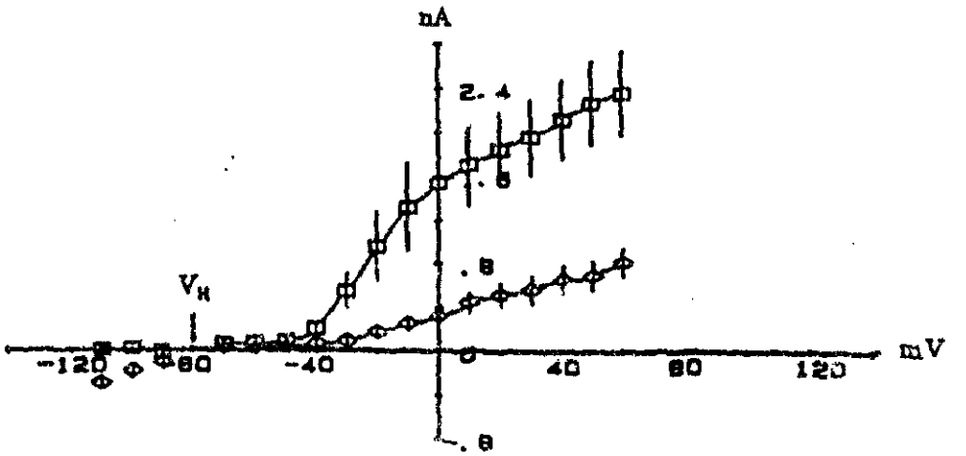


Fig 15

Note: The time scale of the left middle trace should be 60 msec, not 600 msec.

Figure 16. Depression of I_{K1} by ibutilide.
Current traces at left are control (solid line) and in 5×10^{-6} M of ibutilide (dotted line). Washout (solid trace) of drug effect (dotted line) is shown at right. Below is a compiled I-V taken before (□) and after (◊) drug treatment. Notice the "cross-over" at about -25 mV indicating the opposite effect of the drug on I_{K_1} and I_K. V_H = -80 mV.

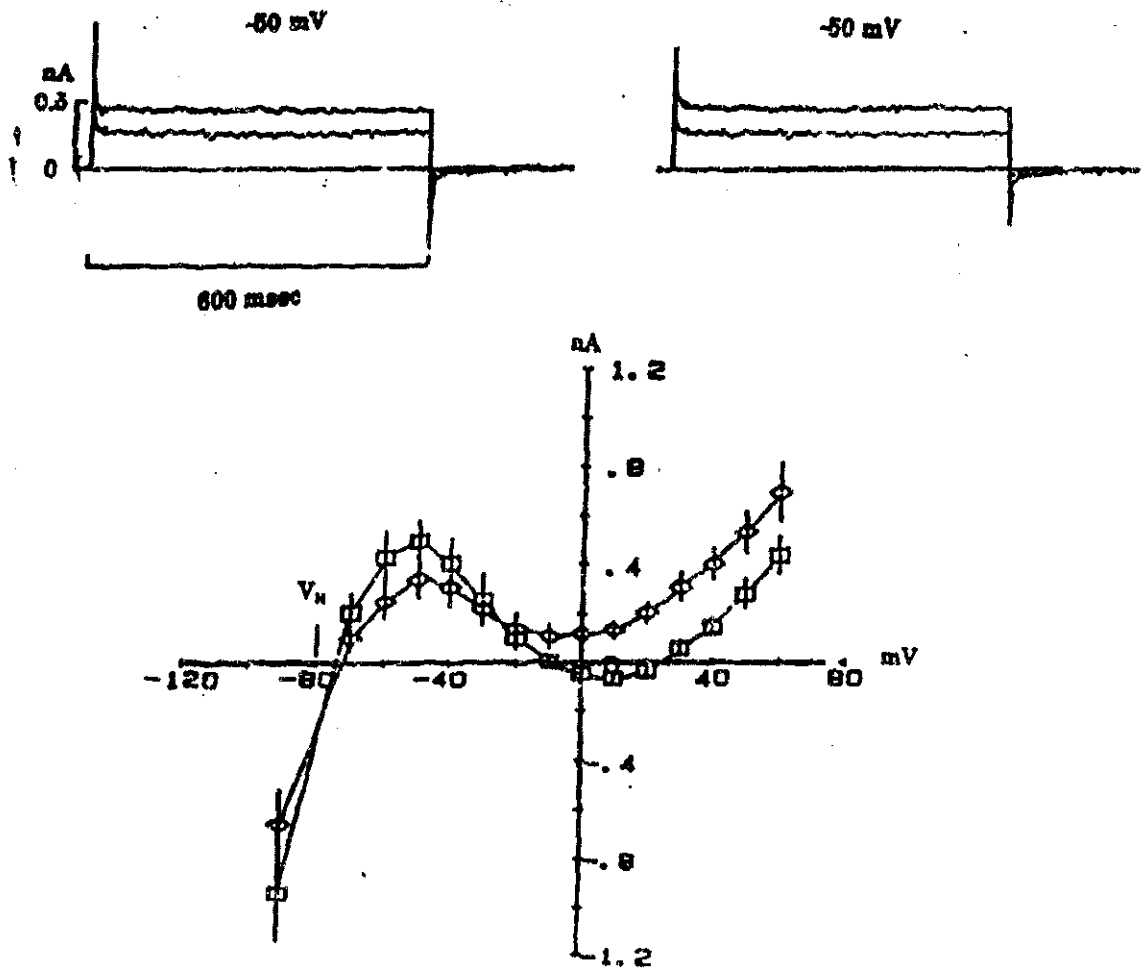


Fig. 16

Results:

- Cumulative doses of ibutl at which flutter was terminated were: 0.001 (2 dogs); 0.003 (2 dogs); and 0.01 (4 dogs) mg/kg. In 6 dogs, after flutter terminated, it could not be induced during the 2-3 hours of observation. In two dogs, in which flutter was terminated at 0.001 mg/kg, it could be induced again within one hour. These dogs were then given another dose of ibutl; flutter terminated at a cumulative dose of .003 mg/kg, and the dogs remained non inducible. Flutter cycle lengths before administration of ibutl (Control), and after the dose at which flutter terminated, and AERPs in the control condition and after flutter termination are given below.

	Control		Treated		
Dog #	AERP	Cycle-L	Cum Dose	AERP	Cycle-L
1	105	170	0.01	185	190
2	95	140	0.01	135	185
3	90	140	0.01	150	165
4	110	165	0.001		
			0.003	140	180
5	100	135	0.01	150	190
6	100	135	0.003	150	165
7	130	175	0.001		
			0.003	150	200
8	100	145	0.003	140	175

Note: Cycle-L is cycle length; Cum Dose is cumulative dose; ERP and Cycle-L are in msec; Cum Dose is in mg/kg. In dogs 4 and 7, AERP and Cycle-L after 0.001 mg/kg dose are not shown. It is not explicitly stated by the investigators, but presumably Cycle length during treatment must be the last cycle length before termination of flutter.

Comments: AERPs after a dose of ibutl that terminated flutter were increased v Control values in all cases, and flutter cycle length was increased before drug induced termination in 6/8 cases.

- In the six dogs in which the effects of cumulative doses on AERP and MAP_{90} were studied, both increased dose relatedly in the dose range tested; the increase at the highest dose (0.01 mg/kg) was 50 msec for AERP and 55 msec for MAP_{90}; difference from pre drug baseline values was s-s only at this dose ($p=0.0006$ and 0.01 respectively.)

#2: Comparative Assessment of Ibutilide, D-Sotalol, Clofilium, E-4031, and UK-68,798 in a Rabbit Model of Proarrhythmia. J of Cardiovascular Pharm 220: 540-590 (1993).

In rabbits, infusion of α-agonist methoxamine and administration of class III agent clofilium was found to induce polymorphic ventricular tachycardia (PVT). Based on this, the investigators (from sponsor's labs) tested the effects of compounds mentioned in the title of this paper in groups of 10-16 anesthetized rabbits receiving a continuous infusion of 10 μg/kg/min α-methoximine. The test drug infusion was started 15 minutes after the start of α-methoximine infusion, and the rate of test drug infusion was such that the maximum intended cumulative dose was administered in one hour; a group of 6 rabbits received

saline and served as control. In 4 rabbits from each group, monophasic action potentials (MAPs) were recorded from the rt ventricle several times during the experiment, and APD_{90} were determined. Lead II EKGs and arterial pressures were recorded throughout the experiment. Total cumulative doses of various drugs were 25 mg/kg for D-Sotalol, and 10 mg/kg for all others. The authors state that in the canine myocardial infarction model, therapeutically effective dose levels (TEDLs) of these drugs were: UK-68,798, 0.03 mg/kg; ibutl, 0.1 mg/kg; E-4031, 0.3 mg/kg; clofilium, 1 mg/kg; and D-Sotalol, 3 mg/kg. (*Note:* It is not clear whether 'therapeutically effective' indicates ED_{50} or the lowest dose showing a s-s effect compared to control.)

Results:

- Fig 17 shows the dose response of QT_c and $MAPD_{90}$ for the drugs tested in this study. QT_c intervals in all except D-sotalol group, were maximum at approximately 0.2 mg/kg dose, and remained at that level for higher doses. In the case of D-sotalol, QT_c interval increased with dose up to 10 mg/kg.
- Incidences of PVT and the 'Mean ± SE' cumulative dose at which PVTs occurred are shown below:

Group	Incidence	Cumulative Dose (mg/kg)
Ibutilide	2/16 (13%)	1.0 ± 0.9
D-Sotalol	6/10* (60%)	10.4 ± 2.1
E-4031	9/16* (56%)	0.4 ± 0.6
UK-68,798	11/16** (69%)	1.3 ± 0.4
Clofilium	8/10** (80%)	2.6 ± 0.7

*, ** indicate incidence significantly different compared to ibutl at $p \leq 0.05$ and $p \leq 0.01$ respectively (Fisher's exact test, s-rev).

- Amplitudes of 'Early After Depolarizations (EADs) as %s of MAP amplitudes in different groups were: 22.5±5.9, 84.7±18.4, 89.0±8.6, 87.0±9.5, and 62±8.7 respectively for the groups listed in the table above (n=4 in each case; these measurements could have been made only in rabbits in which MAPs were recorded.). EAD amplitudes in the ibutl group were s-s lower than all other groups. (*Note:* Development of EADs is considered to have a causal relationship to the proarrhythmic effects of class III antiarrhythmic agents.)

Comments: Doses at which PVTs were produced are probably not very useful for comparing the safety margins of the tested drugs. Drug administration was by continuous infusion, and the latencies for this effect may not necessarily be the same for all drugs. Since the maximum doses administered were 100, 8, 100, 300, and 10 times the 'Canine TEDLs' respectively of the drugs tested (in the order listed in the table above), the incidences of PVTs do indicate that with the possible exception of UK-68,798, ibutl has a higher safety margin than the other drugs. (*Note:* In terms of 'Canine TEDLs', the maximum dose of UK-68,798 was 3 times that of ibutl; the higher incidence of PVT in the UK-68,798 may not therefore necessarily imply a lower safety margin compared to ibutl.)

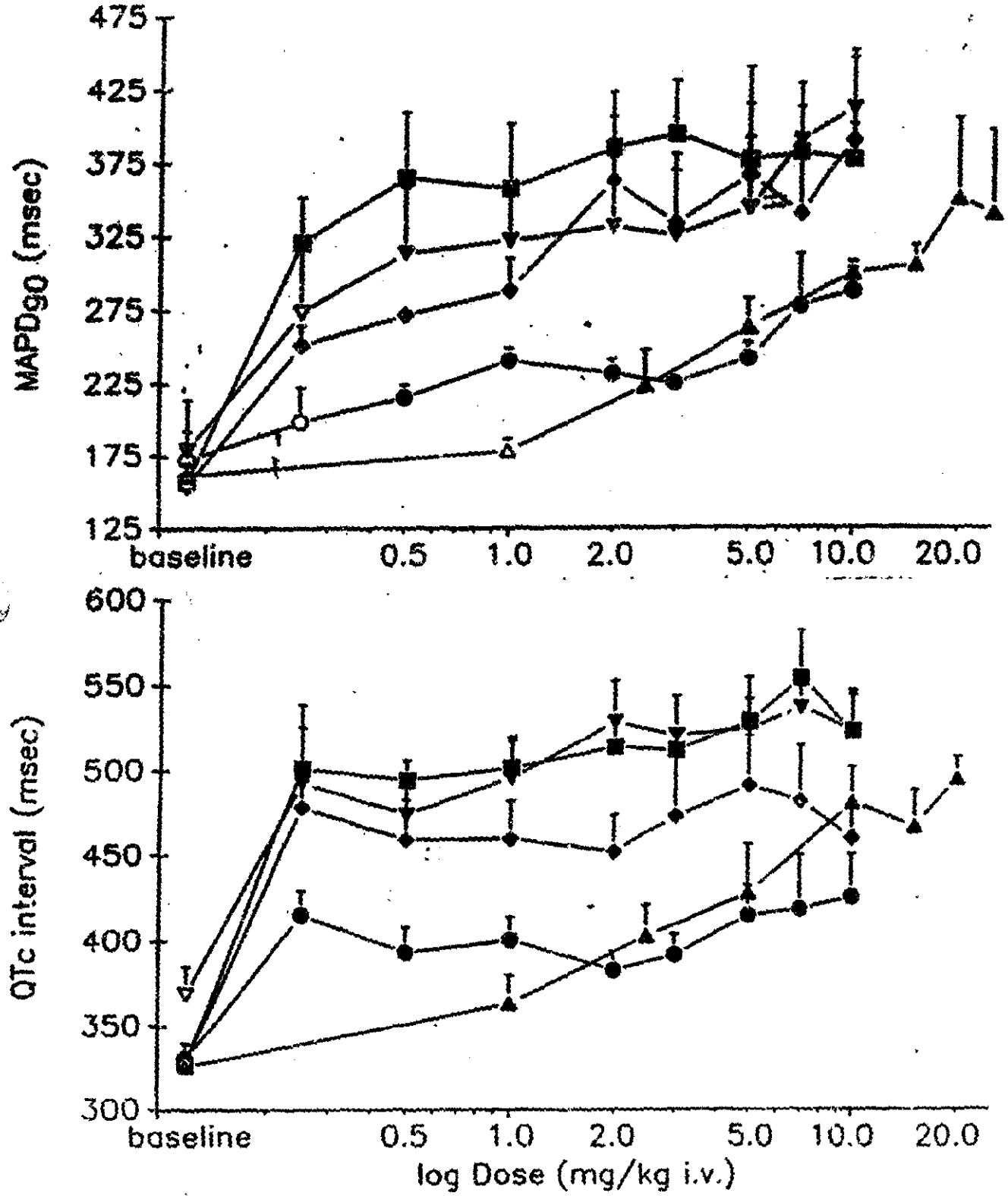


Figure 1) Effects of class III agents on QTc interval in anesthetized rabbits receiving continuous methoxamine infusion.

○ = ibutilide, △ = d-sotalol, □ = E4031, ▽ = UK-68,798, ◇ = clofilium. Filled symbols indicate $p \leq 0.05$ vs baseline.

#3: Comparative Assessment of Proarrhythmic Effects of Ibutilide, d-Soatalol, and Clofilium, in a Dog Model of Proarryhthmia.

In anesthetized dogs, complete AV block was achieved by electrically ablating AV node, and hearts were paced when necessary to maintain a minimum ventricular rate of 25 bpm; EKG and arterial pressure were monitored continuously; rt ventricular electrodes were positioned for recording MAPs. After baseline measurements of heart rate, aortic pressure, QT interval, and $MAPD_{90}$, methoximine was infused at the rate of 5 μg/kg/min; 20 minutes after the start of methoximine infusion i/v infusion of a class III agent or saline was begun (n=6 for each drug and the control group given saline). Doses of the drugs used were: d-Sotalol, 25 mg/kg; ibutilide and clofilium, 10 mg/kg each; the total dose was administered over a one hour period; cardiovascular parameters mentioned above were monitored before starting infusion of drug/saline and several times during drug/saline administration. (*Note:* Artilide and sematilide were also tested. However, artilide is not being developed as an antiarrhythmic any more, and there is no information about the 'Canine TEDL' of sematilide. The effects of these two drugs are therefore not reviewed here.)

Results:

Incidences of PVT and MVT in each group are given below (numbers within parentheses after the drug name are mean±SE of the cumulative dose at which VT appeared):

	PVT	MVT	PVT and/or MVT
Ibutilide (3.0±1.5)	1/6	3/6	4/6
d-Sotalol (12.4±3.1)	0/6	4/6	4/6
Clofilium (3.0±1.4)	5/6	3/6	5/6

Comments: This study is not adequate to determine the relative safety margins of the tested drugs. Total cumulative doses administered were: ibutilide, 100 times 'Canine TEDL' ; d-Sotalol, 8 times 'Canine TEDL'; and clofilium, 10 times 'Canine TEDL' (Canine TEDL values are taken from study #2). Because of the small sample size and a large difference between the total cumulative doses (in terms of 'Canine TEDLs') of ibutilide and the other two drugs, the relative safety margin of ibutilide vis a vis the other two drugs cannot be assessed from the results of this study.

#4: Cardiovascular Evaluation of Ibutilide and its enantiomers in the Conscious Dog:
In 8 chronically instrumented conscious beagle dogs, effects of ibutl and its two enantiomers on mean arterial pressure, HR and QT_c were studied. Each dog received saline, and the three drugs; on a particular day only one substance was administered, and 2-3 days' intervals were given between successive treatments; cardiovascular parameters were recorded at intervals for one hour before start of treatment; the drugs were administered as i/v boluses of 0.01, 0.1 and 1.0 mg/kg sequentially at two hour intervals; for each parameter average of 4-5 consecutive cardiac cycles was determined.

Results:

- Arterial Pressure: Table 2 shows the results. There was no significant (b-s or s-s) effect on mean arterial pressure at any dose level of any of the drugs (compared to baseline values as well as saline control).
- Heart Rate: Table 3 shows the results. Ibutl and the l-isomer had no s-s effects on Δ heart rate (presumably from baseline) at any dose level compared to saline control. At the highest dose of the d-isomer, Δ heart rate 30 minute post dose was s-s increased compared to saline control and ibutl. The increase was by 26-27 bpm. *Comments:* The mean baseline heart rate of this group was 23 bpm lower than that of the ibutl group. Therefore this does not seem to be a biologically significant effect.
- QT_c: Table 4 shows the results. According to the sponsor, statistical analysis has been done by adjusting for differences in pretreatment values. At dose levels ≥0.1 mg/kg, QT_c intervals in the Ibutl group were s-s increased compared to saline control at all time points , and in the case of the d-isomer, at all but one time point.
- PVCs: PVCs were looked for at 8 time points during the 2 hour post treatment period after each dose of each treatment. Results are shown in table 5. There were no differences amongst groups in terms of PVC frequencies at any dose level.

Comments:
At all doses tested (in the case of the racemate and the d-isomer, the highest dose tested was 10 times the dose at which QT_c was s-s increased (compared to saline control)) there were no significant effects on heart rate, arterial pressure and PVC frequencies in any treatment group.

#5: Cardiovascular evaluation of Ibutilide in the anesthetized dog:
Note: The methodology is described very poorly; a previous report is referred to which cannot be found anywhere in the submission. Therefore one does not know e.g.: what method was used for determination of cardiac output, and at what ventricular pressure dp/dt was determined. Ibutl is said to have been heated to dissolve; one does not know at what temperature, and what effect this heating had on its structure and activity.

In view of the above, this study is not evaluable.

TABLE 2. Absolute Changes in Mean Arterial Pressure (mmHg) in Conscious Beagle Dogs Treated with U-70226E and its Stereoisomers

Dose (mg/kg, i.v.)	Time (min)	Vehicle (saline)	Racemate (U-70226E)	d-isomer (U-[illegible]E)	l-isomer (U-[illegible]E)
Pretreatment	0	116 ± 4	109 ± 8	116 ± 3	112 ± 5
0.01	15	-1 ± 4	+2 ± 2	+2 ± 3	-2 ± 2
	30	+1 ± 3	-1 ± 2	-3 ± 1	0 ± 1
	60	0 ± 2	+1 ± 3	-2 ± 2	+3 ± 2
	120	-1 ± 4	-2 ± 4	+2 ± 1	0 ± 3
	Mean	0 ± 3	0 ± 2	0 ± 2	0 ± 1
0.10	15	-2 ± 2	0 ± 3	-2 ± 4	-6 ± 3
	30	-2 ± 3	+3 ± 3	-4 ± 1	0 ± 2
	60	+2 ± 3	+1 ± 3	-2 ± 2	0 ± 1
	120	-1 ± 3	0 ± 2	-5 ± 2	0 ± 2
	Mean	-1 ± 3	-1 ± 3	-3 ± 2	-2 ± 1
1.00	15	-2 ± 4	-3 ± 4	+3 ± 2	+2 ± 2
	30	-1 ± 2	-1 ± 3	+4 ± 3	+1 ± 2
	60	+3 ± 2	+1 ± 3	-1 ± 2	0 ± 1
	120	+5 ± 2	+1 ± 3	+1 ± 3	+2 ± 2
	Mean	+1 ± 2	-1 ± 3	+2 ± 2	+1 ± 1

n = 8 dogs/group

TABLE 3. Absolute Changes in Heart Rate (bpm) in Conscious Beagle Dogs Treated with U-70226E and its Stereoisomers

Dose (mg/kg, i.v.)	Time (min)	Vehicle (saline)	Racemate (U-70226E)	d-isomer (U-62266E)	l-isomer (U-62267E)
Pretreatment	0	100 ± 9	113 ± 11	90 ± 9	100 ± 10
0.01	15	-10 ± 6	-8 ± 6	+13 ± 7[a]	-7 ± 10
	30	-9 ± 8	-2 ± 6	+7 ± 7	-8 ± 8
	60	+3 ± 8	+5 ± 7	+15 ± 6	+12 ± 7
	120	-1 ± 6	-10 ± 8	+12 ± 7[b]	+6 ± 6
	Mean	-6 ± 5	-4 ± 4	+12 ± 3[ab]	+1 ± 6
0.10	15	+6 ± 13	-13 ± 10	+8 ± 5	-4 ± 8
	30	-5 ± 7	-14 ± 8	+6 ± 7	-5 ± 9
	60	+10 ± 8	-10 ± 7	+13 ± 8	+2 ± 8
	120	+7 ± 11	-13 ± 10	0 ± 10	+4 ± 11
	Mean	+4 ± 9	-12 ± 8	+7 ± 6	-1 ± 8
1.00	15	-1 ± 13	+6 ± 8	+24 ± 6	+3 ± 9
	30	0 ± 9	-1 ± 8	+26 ± 7[ab]	+12 ± 10
	60	+15 ± 13	0 ± 7	+13 ± 7	+12 ± 14
	120	+17 ± 7	-4 ± 9	+21 ± 5[b]	+7 ± 11
	Mean	+8 ± 9	0 ± 7	+21 ± 3	+9 ± 10
Posttreatment	ave:	+2 ± 7	-6 ± 5	+13 ± 3[b]	+3 ± 7

a = $p \leq .05$ from vehicle control; b = $p \leq .05$ from racemate
n = 8 dogs/group

TABLE 4 Covariant Corrected Lead II ECG QTc Interval Lengths in Conscious Beagle Dogs Treated with I.V. U-70226E or its Stereoisomers -

Dosage (mg/kg, i.v.)	Time (min)	Vehicle (saline)	Racemate (U-70226E)	d-isomer (U-62206E)	l-isomer (U-62209E)
(absolute mean pretreatment QTc values)					
Pretreatment	0	234 ± 9	255 ± 12	224 ± 6	247 ± 4
(estimated mean posttreatment QTc values corrected for PT x dog x block covariants)					
0.01	15	242 ± 10	258 ± 10	271 ± 10*▲	236 ± 10
	30	233 ± 11	259 ± 11	261 ± 11	233 ± 11
	60	234 ± 7	258 ± 7*	239 ± 7	253 ± 7
	120	236 ± 10	241 ± 10	246 ± 10	249 ± 10
	low dose ave:	236	254	254	243
0.10	15	231 ± 9	266 ± 9*	270 ± 9*	251 ± 9
	30	219 ± 10	267 ± 10*	276 ± 10*	257 ± 10*
	60	234 ± 10	264 ± 10*	271 ± 10*	261 ± 10
	120	229 ± 9	257 ± 9*	260 ± 9*	250 ± 9
	mid dose ave:	228	264	269	255
1.00	15	224 ± 8	273 ± 8*	271 ± 8*	290 ± 8*
	30	226 ± 10	277 ± 10*	284 ± 10*	276 ± 10*
	60	240 ± 11	273 ± 11*	271 ± 11	292 ± 11*
	120	232 ± 10	283 ± 10*	309 ± 10*▲	265 ± 10*
	high dose ave:	231	277	284	281
	3 hour post-treatment ave:	232	265	269	260

* = $p \leq .05$ from vehicle control

▲ = $p \leq .05$ from l-isomer

TABLE 5 Frequency of Premature Ventricular Contractions (PVC's) in Conscious Beagle Dogs Treated with U-70226E and its Stereoisomers

Dose & Time	Drug	Dog Number 1	2	3	4	5	6	7	8	Group Totals
0.01 mg/kg (0-2 hr)	Vehicle									4/64
	Racemate									6/64
	d-isomer									7/64
	l-isomer									8/64
0.10 mg/kg (2-4 hr)	Vehicle									8/64
	Racemate									4/64
	d-isomer									11/64
	l-isomer									5/64
1.00 mg/kg (4-6 hr)	Vehicle									14/64
	Racemate									15/64
	d-isomer									8/64
	l-isomer									11/64
Treatment Totals (0-6 hr)	Vehicle									26/192 (1.4%)
	Racemate									25/192 (1.3%)
	d-isomer									26/192 (1.4%)
	l-isomer									24/192 (1.3%)

§3: Effects of a Metabolite (U-107246) of Ibutilide in Isolated Rabbit Atria: (Report #7243/94/059; Amendment #025 dt March 27 to NDA 20,491)

Effects of U-107246, which differs from ibutilide in having an [OH] in place of an H in the end CH_3 group of the amino-haptyl chain, on isolated rabbit atria were studied. *Note:* According to the sponsor, this compound was first synthesized as it was thought that it may be a possible metabolite in rat, but it has now been shown to be a metabolite in man, rat, and dog. In the original method used to separate various metabolites, it co eluted with an other metabolite; using a different method this compound can be separated from others and its amount can be quantitated.

Results:

At 1 Hz ERP was increased dose relatedly; approximately 18% increase at 10^{-6} M and approximately 30% increase at 10^{-5} M; most of the increase was reversed at wash out (n=4). At 3 Hz, ERP increased to a lesser extent, and the increase was not reversed at wash out (n=4). Force of contraction was slightly increased at 1 Hz, and was unaffected at 3 Hz (n=4 in both cases).

Pharmacokinetics

Rat:

Bioavailability and pharmacokinetics of ibutilide in the rat: (Report # 7256/94/010)

2 female and 2 male rats were administered 7.5-7.7 mg (20.7-28.2 mg/kg) ibutl i/v; these 4 animals and 2 additional females were administered 14.3-15 mg (45.3-50 mg/kg) ibutl orally (by gavage); the i/v and oral doses were administered at a week's interval; blood for ibutl concentration was sampled at 10, 15, 30 minutes, and 1, 2, 4, 6, 8 and 24 hours post dose.

Results:

After i/v administration, measurable amounts of the drug (13.84 ng/ml) were detected in plasma for 6 hours in 3/4 rats and for 8 hours in 1/4; after oral dosing, measurable amounts were detected up to 8 hours in 5/6 rats and up to 4 hours in 1. Table below shows various pharmacokinetic parameters;

	i/v (n=4)		Oral (n=6)	
	Range	Mean±SD	Range	Mean±SD
C_{max} (μg/ml)		6.08±4.38		0.155±0.065
C_{max} (μg/ml)*		0.25±0.18		0.003±0.001
AUC (μg.hr/ml)				
$AUC_{t-\infty}$		3.66±1.25		0.521±0.183
$AUC_{0-\infty}$*		0.15±0.05		0.010±0.003
MRT (hr)		0.9±0.1		3.4±0.8
V_{ss} (L/kg)		6.63±2.4		
CL ($L.hr^{-1}/kg$)		7.1±1.8		
$t_{1/2}\beta$ (hr)		1.2±0.4		1.217±0.407
t_{max} (hr)				0.87±0.89
Bioavail (%)				7.2±2.3

Note: '*N*' indicates that this parameter value is normalized for dose on a mg/kg basis; 'Bioavail' stands for Bioavailability.

Metabolism of ibutilide: Plasma Concentration of Ibutilide and its Metabolites after i/v and Oral Dosing. (Report #7256/94/014)

i/v: 8 SD rats (male) were administered 1.05±0.05 mg/kg ^{14}C labelled ibutilide; blood samples were collected at 5, 10, 30 minutes, and 1, 2, 4, 8, and 24 hours (one rat/time point).
Oral: Two oral doses were used; Low (0.5 mg/kg) and high (106 mg/kg); blood was sampled at 5, 15, 30, 45 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours after the low dose (3 rats/time point); and 0.25, 1, 2, 4, 8, 12, and 24 hours after the high dose (one rat/time point).

Results:

i/v:

Ibutilide and/or its N-oxide : C_{max}: 277.5 ng eq/ml (100% of radioactivity) at 5 minutes; AUC 398 ng eq.hr/ml (84% of total radioactivity AUC); $t_{1/2}$ terminal, 10.7 hours.
Metabolites: Three metabolites identified as G, H, and L peaks, were present; G was present from 30 minutes to 2 hours, and comprised 5, 5, and 12% of total radioactivity at the time

points sampled; H was present at the same time points and comprised 6, 4, and 4% of radioactivity; L was present at 2 and 4 hours, and comprised 11 and 36% of total radioactivity at the time points sampled.

Oral:

Low Dose: Ibutilide and/or its N-oxide: C_{max} 5.7 ng eq /ml at 0.5 hours; AUC, 3.6 ng eq.hr/ml (< 2% of total radioactivity AUC); there was no measurable ibutl peak after one hour. Metabolites: There were several metabolites; metabolites that contributed to the total AUC in amounts ≈ or greater than ibutl were: G, 29%; H, 20%; F, 7%; E, 4%; J, 3%.

High dose: Ibutilide and/or its N-oxide: C_{max} 4845 ng eq/ml at 15 minutes; AUC, 9762 ng eq.hr/ml (16% of total radioactivity AUC); there was no measurable ibutilide peak at 8 hours. Metabolites: Metabolites that contributed up to 10% of the contribution of ibutl to the total AUC were: C, 22% (detectable up to 8 hours, the last time point up to which individual peaks are listed); B, 13%; F, ≈1.8%; I, ≈1.7%; G & H were only detectable at 2 hours and G comprised only 0.3% of total AUC; H was 1/10th of G.

Comments: E, F, G, and H peaks (which according to the sponsor correspond to metabolites resulting from ω-oxidation/β-oxidation and ω-1 oxidation/one carbon loss) represented 65.2-84.1% of radioactivity in the 0.25-4 hr time interval after low oral dose. The sponsor states that peaks B and C represent intermediate metabolites in the one carbon loss pathway, which seems to become saturated after the high oral dose resulting in the accumulation of these intermediate metabolites.

Dog:

Bioavailability and pharmacokinetics of ibutilide in the beagle dog: (Report # 7256/87/057)

Two dogs were given 5 mg/kg ibutl i/v and oral each at one week interval; blood was collected at 5, 10, 20, 40 minutes, and at 1, 1.5, 2, 3,4, 6, 8, 12, 24, 36, 48, and 56 hours post dose for determination of serum concentrations of ibutl.

Results: Figs k1 and k2 show the time profiles of serum concentrations in the two dogs. Pharmacokinetic parameters are shown below:

	Dog #1		Dog #2	
	I/v	Oral	I/v	Oral
C_{max} (μg/ml)	1.91	0.34	1.26	0.53
AUC (μg.hr/ml)	5.26	1.79	3.78	3.27
MRT (hr)	3.7	4.8	4.1	5.7
V_{ss} (L/kg)	3.1		4.7	
CL (L.hr^{-1}/kg)	0.837		1.157	
Bioavail (%)		33.0		83.5
$t_{1/2}$ (hr)	2.7	2.7	2.9	3.7
k_a (hr^{-1})		2.2		2.4

Note: 'Bioavail' stands for Bioavailability; MRT is the time for 63.2% of the drug to be eliminated. It is not stated whether AUC is for 12 hours, the time up to which detectable/quantifiable drug concentrations were present in the serum.

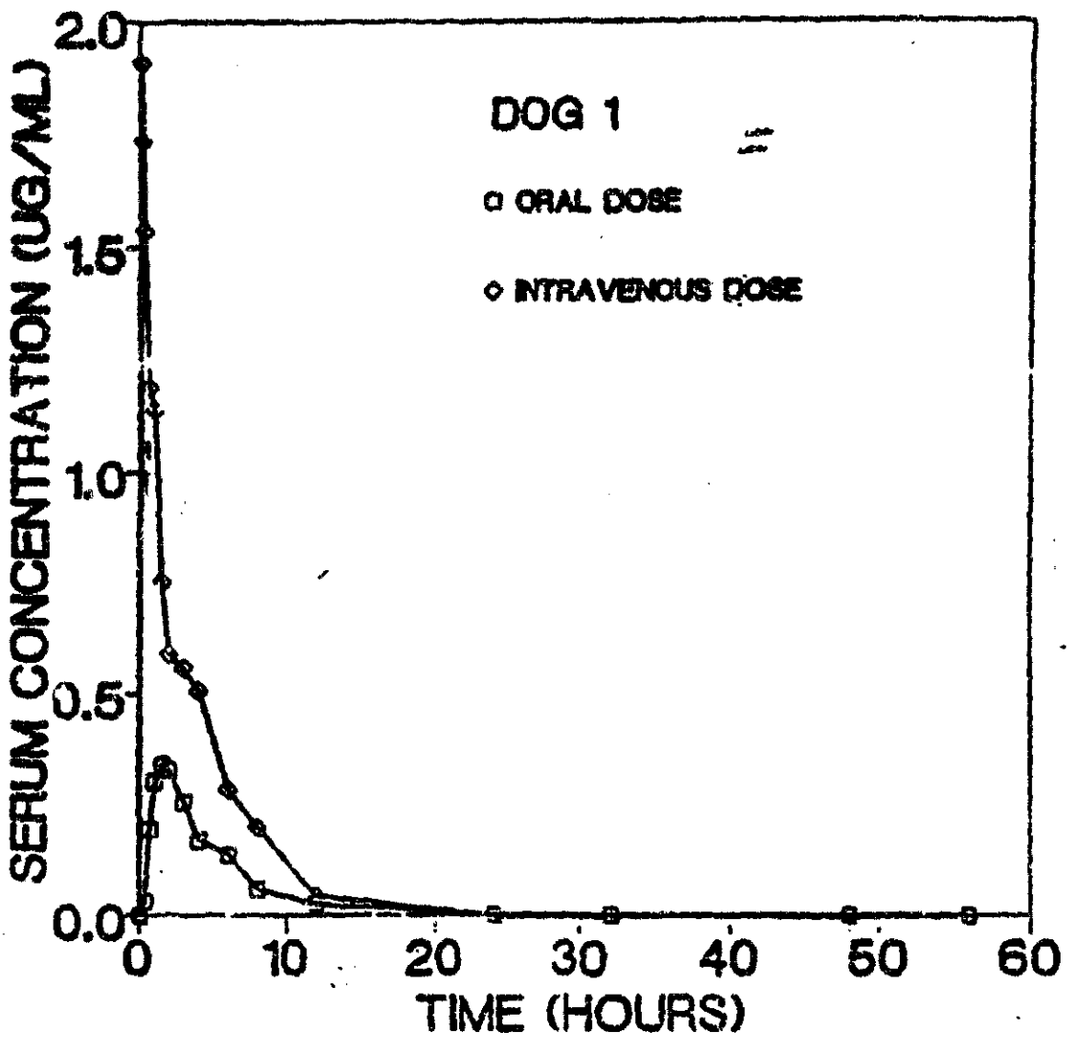

DOG 1
ORAL DOSE
INTRAVENOUS DOSE
SERUM CONCENTRATION (UG/ML)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
TIME (HOURS)

Fig. K1

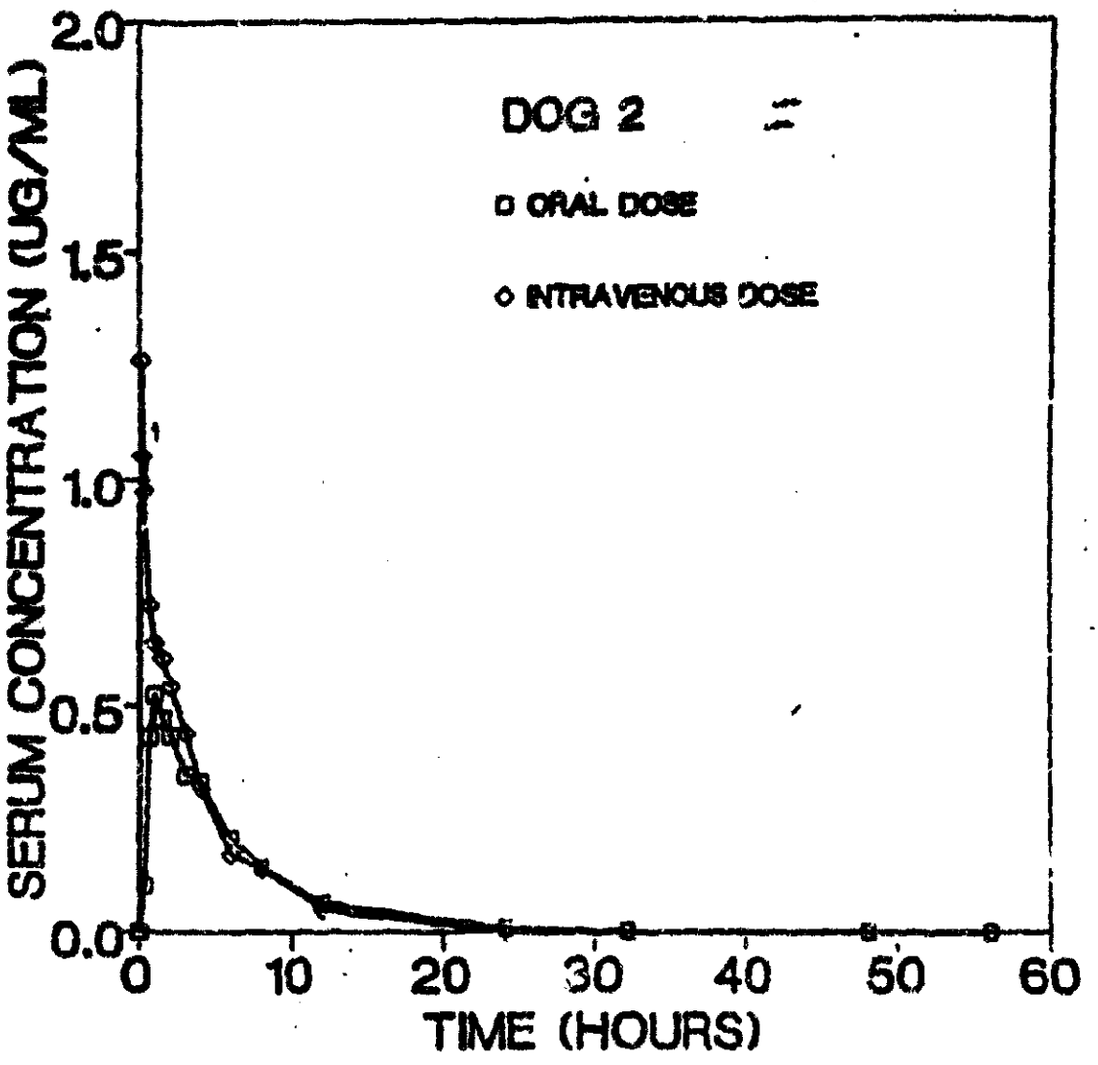

DOG 2
□ ORAL DOSE
◇ INTRAVENOUS DOSE
SERUM CONCENTRATION (UG/ML)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
TIME (HOURS)

Fig. K2

Bioavailability and pharmacokinetics of ibutilide in the beagle dog: (Report # 7256/87/058) 4 dogs were given 3 mg/kg ibutl i/v and oral each; same methodology as in the previous study.

Results:

	i/v		Oral	
	Range	Mean±SD	Range	Mean±SD
C_{max} (μg/ml)		0.91±0.312		0.14±0.074
AUC (μg.hr/ml)		1.27±0.79		0.507±.414
MRT (hr)		2.16±1.23		3.03±1.01
CL ($L.hr^{-1}/kg$)		2.97±1.23		
V_{ss} (L/kg)		4.57±1.43		
T_{max} (hr)				1.08±0.44
Biolavail (%)				31.8±12.36
$t_{1/2}\beta$ (hr)		1.84±0.76		1.74±0.59
k_a (hr^{-1})				2.55±0.53

Note: 'Bioavail' stands for bioavailability; all values for oral dosing are from 3 animals (one animal that coughed up some of the oral dose is excluded). As in the previous study, time over which AUC is calculated is not indicated.

Man:

From the sponsor's summary: In a number of studies in which i/v infusions of 0.01-0.1 mg/kg ibutl were infused in human volunteers over a 10 minute period, C_{max} was very variable (e.g. at a dose of 0.03 mg/kg, 2.0±0.5 ng/ml in one study and 28±10.8 ng/ml in another). According to the sponsor this was due to a rapid distribution phase and difficulty in precise recording of sampling times in the clinical setting. So this parameter in these studies is not reliable. The other pharmacokinetic parameters that show consistency across studies are shown below; values are mean±SD.

Dose (mg/kg)	0.01 (n=36)	0.03 (n=14)	0.06 (n=8)	0.1 (n=8)
AUC (ng.h/ml)	6.65±1.26	19.79±5.93	36.3±9.8	55.3±9.3
CL (ml.min^{-1}/kg))	25.91±5.32	27.47±2.21	29.1±6.4	30.9±5.1
V_{ss} (L/kg)	11.62±3.31	13.7±6.2	11.8±3.0	10.5±2.5
$t_{1/2}$ (hr)[1]	5.4-7.1	6.9	6.1	5.7

Note: [1] $t_{1/2}$ was determined as a harmonic mean (presumably by taking the mean value of K_es, and then taking the reciprocal of this mean, and multiplying by 0.693); 0.01 mg/kg was administered to 5 different groups, and the range of $t_{1/2}$s for this dose is the range of values in these groups.

Comments: Within the dose range tested, AUC is fairly dose proportional, and CL, and $t_{1/2}$ are fairly constant, indicating that elimination does not saturate within this dose range.

Species Comparison of metabolism and excretion of Ibutilide in Rat, Dog, and Man. (Report #7256/94/072 in Amendment #99 dt Jan 19, 95 to). *Note:* This comparison uses the results of a number of different pharmacokinetic studies (some of them reviewed above) and an in-vitro study using rat, dog, and human liver slices.

Results:

Table K1 shows the amounts of ibutilide and its metabolites excreted in urine after administration of ^{14}C ibutilide (i/v in all three species; oral in the rat); A is ibutilide and/or its N-oxide. According to the sponsor's statements: Metabolites identified as B and C are formed by ω-1 oxidation of the haptyl chain (C6-hydroxy and C-6 keto oxidations respectively); subsequently sequential one carbon loss yields G, I, J, K, and H metabolites. This ω-1 oxidation/one carbon loss pathway (called pathway I) is the main metabolic pathway in the rat and dog. ω-oxidation/β-oxidation (called pathway III), is the major metabolic pathway in man. ω-oxidation yields metabolite E; subsequent β-oxidation (two carbon loss) yields I and K metabolites.

Table K2 shows amounts of radioactivity excreted in urine and feces in these species. After i/v dosing, urinary excretion is the main route of elimination in man; it constitutes ≈60% of the elimination in the dog, and ≈ 43% in the rat.

Pharmacokinetics of U-107246 in Rat, Dog, and Man: (Report #7256/95/026 in Amendment #103 dt June 14, 1995 to (for rat and dog), and Report #7215/95/011 in amendment #025 dt March 27, 1995 to NDA 20,491 (for man).

As stated earlier in the Pharmacodynamics section of this review, U-107246 (a ω hydroxy metabolite) has been shown to be a metabolite of ibutilide by using a newer method to separate it from U-86092 (a ω-1 hydroxy metabolite). For man: Plasma samples collected for pharmacokinetic studies done earlier, were used to determine the concentrations of U-107246 and U-86092. For rat and dog, plasma samples from the No adverse effect (NAE) dose groups from the 14 day toxicology studies were analyzed for these metabolites. *Note:* Plasma concentrations of ibutl and U-107246 from clinical trials reported in this submission are not very useful for purposes of comparison across species, since the dose of ibutl administered in individual cases is not mentioned; the doses administered varied from 0.012 mg/kg/30 minutes to 2 mg/30 minutes (wt range of patients in this protocol is not mentioned).

Results:

Table below compares C_{max} and AUC of ibutilide and its ω hydroxy and ω-1 hydroxy metabolites in man (n=4), rat (n=6), and dog (n=4 for ibutilide and n=5 for the two metabolites. In one dog ibutl C_{max} was > 2.4 times the highest C_{max} of the rest of the group; this dog's ibutilide values were excluded from the group means. plasma from the 6th animal in this dose group was lost.)

	Ibutilide	U-107246	U-86092
C_{max} (ng/ml)			
Human	6.9 ± 5.8	0.053 ± 0.014	0.075 ± 0.024
Dog	512.3 ± 29	1.7 ± 0.8	7.6 ± 2.5
Rat	2077 ± 567	(-)*	34.0 ± 16.0
AUC_{0-24} (ng.hr/ml)			
Human	6.1 ± 1.0	0.50 ± 0.18	0.72 ± 0.52
Dog	653 ± 79	5.0 ± 2.3	62.0 ± 21
Rat	1846 ± 425	(-)*	144 ± 92

Note: * U-107246 was detected in only 2/6 rats, and at only one time point in each; the concentrations were < 1 ng/ml in both; ibutilide concentrations at that time point were 104 ng/ml and 127 ng/ml; U-86092 concentrations were 8.75 ng/ml and 11.2 ng/ml.

Plasma Protein Binding of Ibutilide in Human, Rat, and Dog Plasma: (Report #7256/95/017 in amendment # 103 dt June 14, 1995 to)

Results:

Table K3 shows the % of ibutl bound to plasma proteins in the 3 species over a range of ibutl plasma concentrations. Over the ranges tested, protein binding was independent of plasma concentrations, but the % binding was s-s different across species.

Table 3K.1. Species Comparison of Urinary Metabolites after IV and Oral Administration of [^{14}C]Ibutilide Fumarate

Species	Route (Time)	Dose (mg/kg)	Percent Ibutilide or Metabolite in Urine Pool											
			A	B	C	D	Σ	F	G	H	I	J	K	L
Rat[1]	IV (0-24hr)	0.511	8.0 ± 5.7	20.3 ± 4.5	16.8 ± 3.1	1.7 ± 1.8	4.5 ± 0.6	1.4 ± 0.2	15.8 ± 1.9	11.2 ± 1.3	1.8 ± 1.5	5.8 ± 0.4	1.6 ± 1.0	*
Rat[2]	Oral (0-24hr)	0.448	0.1 ± 0.2	5.3 ± 0.8	1.3 ± 0.7	0.2 ± 0.3	8.0 ± 1.1	5.0 ± 5.9	28.3 ± 2.0	23.0 ± 2.7	5.8 ± 0.5	12.7 ± 1.6	5.6 ± 0.8	*
Rat[3]	Multiple Oral	100.0	2.6	20.0	30.2	3.5	1.4	0.7	12.4	8.4	9.4	7.8	2.1	*
Dog[4]	IV (0-24hr)	0.294	2.4 ± 1.9	35.2 ± 7.5	6.7 ± 2.3	5.0 ± 1.0	4.6 ± 1.8	1.8 ± 0.8	8.0 ± 1.0	1.2 ± 0.2	6.0 ± 1.0	12.9 ± 5.5	9.6 ± 2.0	1.7 ± 0.6
Dog[5]	IV (0-24hr)	2.923	2.5 ± 1.2	31.8 ± 6.2	15.7 ± 3.8	3.8 ± 1.4	4.6 ± 0.8	0.6 ± 0.3	4.0 ± 1.6	1.3 ± 0.9	13.7 ± 1.5	± 2.7	13.0 ± 1.7	0.8 ± 0.1
Dog[6]	IV (0-24hr)	2.923	2.8	34.5	14.9	3.6	4.9	0.5	2.6	*	15.9	3.7	12.9	0.7
Dog[6]	IV (0-24hr)	0.279	*	37.3	4.1	4.6	2.6	0.7	7.4	0.5	11.5	18.3	11.5	0.4
Dog[6]	Oral (0-24hr)	0.279	*	3.3	9.9	4.5	1.7	1.0	15.1	1.0	17.8	25.6	15.7	0.5
Human[7]	IV (0-24hr)	0.010	6.7 ± 1.5	7.9 ± 3.0	1.8 ± 0.6	0.9 ± 0.3	29.6 ± 6.0	*	0.2 ± 0.6	*	17.0 ± 2.0	20.5 ± 2.5	4.0 ± 2.2	*

1. TR 7256/89/039 (protocol 88-232) (1)
2. TR 7256/89/079 (protocol 88-195) (3)
3. TR 7256/90/054 (protocol 89-038) (9)
4. TR 7256/94/049 (protocol 92-530) (11)
5. TR 7256/94/046 (protocol 92-530) (12)
6. TR 7256/89/088 (protocol 88-252) (10)
7. Jungbluth TR in preparation (protocol P7550-0016)

* Below detection limit

TableK2 Species Comparison of Mean Recovery (% Dose ± SD) and Half-Life of [^{14}C]Ibutilide Related Radioactivity After Single IV and Oral Dose Administration of [^{14}C]Ibutilide Fumarate

Parameter	SPECIES (Route of Administration)					
	Rat (IV) N=4	Rat (Oral) N=4	Dog (IV) N=3	Dog (Oral) N=3	Dog (Oral[1]) N=3	Human (IV) N=6
Dose (mg/kg)	0.511 ± 0.006	0.445 ± 0.008	0.26 ± 0.03	0.26 ± 0.03	0.26 ± 0.03	0.010 ± 0.001
Urinary Recovery	42.9 ± 5.3	36.6 ± 3.0	57.5 ± 6.8	56.0 ± 3.2	52.7 ± 0.8	51.87 ± 2.19
Fecal Recovery	58.0 ± 6.6	73.7 ± 4.1	37.5 ± 5.7	36.6 ± 3.9	41.0 ± 4.6	19.34 ± 1.31
Total Recovery	100.8 ± 2.5	100.3 ± 2.1	95.1 ± 3.0	92.7 ± 1.5	93.7 ± 3.8	101.20 ± 2.11
Urinary $T'_{1/2}$(hr)	21.1 ± 2.0	19.6 ± 4.3	27.3 ± 0.2	21.7	24.2 ± 4.3	10.9 ± 0.6
Fecal $T'_{1/2}$(hr)	23.3 ± 0.8	20.5 ± 0.8	19.9	26.1	26.3	12.9 ± 2.8
Reference TR No.	7256-89-039	7256-89-079	7256-89-086	7256-89-086	7256-89-086	Jungbluth, TR in Preparation

1. Oral dose with food
* parameter estimates based on total radioactivity

Table K3 Concentration Dependence of U-70226 Binding to Plasma.

U-70226 Plasma Concentration (ng/mL)	Mean U-70226 Binding ± s.d.(%)		
	Rat (N)	Dog (N)	Human (N)
1	na	50.3 ± 3.9 (2)	37.7 ± 1.5 (4)
10	45.0 ± 1.1 (2)	50.8 ± 1.8 (4)	31.8 ± 4.0 (4)
40	42.8 ± 3.0 (2)	50.1 ± 2.2 (2)	na
50	na	52.1 ± 2.2 (2)	33.2 ± 3.4 (4)
200	na	52.7 ± 0.8 (2)	34.6 ± 1.3 (4)
400	43.7 ± 3.6 (2)	48.1 ± 1.8 (2)	na
1000	na	50.0 ± 1.3 (2)	32.3 ± 3.9 (4)
2000	40.0 ± 1.2 (2)	51.0 ± 2.5 (2)	na
10000	36.6 ± 0.9 (2)	49.2 ± 1.0 (2)	na
Mean ± s.d.	41.5 ± 3.6	50.4 ± 2.0	33.9 ± 3.5

na = not assayed
N = number of replicates

Table K3

Toxicology

Note: In the toxicology review under 'Results' usually only adverse drug related effects are mentioned. If any parameter is not mentioned, it means that there were no adverse drug related effects on that parameter. All studies reviewed below (except where a different study site is mentioned) were done in the sponsor's Lab, and all studies (including those done at contract labs) are certified as having been done in compliance with GLP regulations of the agency.

§1: Acute:

Rat i/v study; (SD CRL): (Report #: 7227/88/116)

n=5/sex/group; treatment groups 1-4 received 50, 75, 100, and 125 mg/kg ibutl respectively, control group received saline; standard LD_{50} methodology. (*Note: the volume of solution administered is not mentioned.*)

Results:

There were no deaths at 50 mg/kg; no of deaths in groups 2-4 were 2, 3, and 5 respectively in males, and 0, 1, and 5 respectively in females; LD_{50}=94.2 mg/kg (According to the sponsor, 95% confidence intervals were not determinable). Deaths occurred within a few minutes of dosing, and were preceded by depression and gasping for air. There were no signs of toxicity in group-1. Survivors of groups 2 & 3 exhibited depression, rapid breathing and shaking; the animals appeared normal by the end of the day. Gross necropsy did not show any abnormality in any animal. In 1-2 animals each in groups 1-3, there was necrosis/inflammation at the site of injection; this according to the sponsor was most probably due to some drug leaking into the subcutaneous tissue during injection.

Rat i/v Study: Comparison of the Effects of Ibutilide with the Effects of Ibutilide containing of the Degradation Product (SD CRL): (Report # 7227/91/002)

According to the sponsor, solutions of ibutilide when heat sterilized or when subjected to an extended shelf life may form up to of a degradation product. This study was done to compare acute toxicity of ibutl with acute toxicity of ibutilide solutions containing of the degradation product. For this purpose ibutilide solution was heated to 90°C for 8.5 hours; assay of the drugs administered showed that ibutl(HS) contained at each strength used.

10/sex/group; groups 2-4 received 50, 75, and 100 mg/kg ibutl respectively; groups 5-7 received 50, 75, and 100 mg/kg ibutl(HS); group-1 received vehicle; rest of the methodology was the same as in the previous study.

Results:

Mortality: Ibutl: 2/20 in Mid-dose, 19/20 in High-dose; all but one deaths occurred within 3 minutes of dosing; one mid dose death occurred at 5 minutes. Ibutl(HS): 1/20 in Low-Dose, 17/20 in Mid-Dose, and 20/20 in High-Dose; all deaths occurred within 2 minutes of dosing.

LD_{50} (mg/kg): Ibutl: 85.1 (

LD_{50} (mg/kg): Ibutl(HS): 64.1

Clinical signs: There were no clinical signs in the ibutl low dose group; animals in all other groups exhibited depression, gasping, and general body tremors; the number of animals exhibiting these signs and the severity of the signs were dose related; the signs in the survivors lasted approximately 5 minutes.

Comments: creased the toxicity of ibutl. The amount of this compound administered was 2.65, 4.2, and 5.7 mg/kg respectively in the low, mid and high dose ibutl(HS) groups. As stated above, none of the clinical signs were unique to the ibutl(HS) group.

Dog i/v studies:

Beagle: (Report # 7227-89-094)

3 males/group; single i/v doses; 6 mg/kg administered over 5 minutes; 6 mg/kg administered over 30 minutes; 8.5 mg/kg administered over 30 minutes. Drug administration was repeated at weekly intervals in such a way that each dog received all three dose regimens. Dogs were examined clinically once/day; neurological examination during the first trial; body wts periodically; hematology and serum chemistry before start of treatment; the day following each treatment, and three weeks after the administration of the last dose.

Results:

CNS signs: Similar CNS signs were seen with all three regimens; within any regimen there were variations in the signs exhibited by different animals, but all animals exhibited some signs; at the 8.5 mg/kg dose, the signs were more intense and of longer duration than with the other two regimens. The most common signs were apprehensive behavior, and decreased motor activity/recumbency. Other signs that were seen less consistently were restlessness, apparent disorientation, head bobbing/body rocking, aggressive behavior, hunched body posture, panting, unsteadiness/ataxia, tremors, defecation/urination. approximately two third of the animals had excessive salivation in all treatment regimens. Clinical signs occurred within a few minutes-two hours post dosing; decreased within 2-7 hours, and the animals appeared normal after approximately 12 hours post dose, except one dog (# 3) after the high dose in which the signs persisted until the day after dosing. During the time that the CNS signs were present, the animals did not eat.

Serum Chemistry & Osmolarity:

One animal (# 3) had increased creatine Phosphokinase (CPK), Na, and Cl; decreased glucose, and increased serum osmolarity after the high dose; another animal (# 4) had increased CPK after the high dose and the 6 mg/kg dose administered over a 30 minute period. The range & Mean ± SE for all animals (excluding the values in animal # 3 at the high dose and in animal # 4 for CPK when these values were high) and the individual values for animals 3 & 4 are shown in table T1.

Comments:

Changing the rate of drug administration did not affect the severity or duration of CNS signs. The changes in serum electrolytes, glucose, and serum osmolarity in dog #3 after the high dose are ascribed by the sponsor to the animal having not eaten or taken water during the prolonged duration of CNS signs in this animal; this explanation seems reasonable. Increase in CPK after the high dose in this animal and in dog #4 is ascribed by the sponsor

Table T1

Parameter	Pre-Treatment	6 mg/kg (5 min)	6 mg/kg (30 min)	8.5 mg/kg (30 min)	(D 37)
Na (mmol/L)					
Range	(n=9)	(n=9)	(n=9)	(n=8)	(n=9)
Mean ± SE	145.8±0.47 (n=9)	148.1±0.6 (n=9)	147.9±0.6 (n=9)	147.8±0.7 (n=8)	149.8±0.5 (n=9)
# 3	146	149	147	160 (D 16)	150
#4	148	150	146	147	150
Cl (mmol/L)					
Range	(n=9)	(n=9)	(n=9)	(n=8)	(n=9)
Mean ± SE	112.2±0.7 (n=9)	112.9±0.4 (n=9)	112±0.6 (n=9)	112±0.7 (n=8)	110.6±0.4 (n=9)
# 3	113	113	111	116 (D 16)	110
# 4	113	112	113	112	110
Glucose (mg/dL)					
Range	(n=9)	(n=9)	(n=9)	(n=8)	(n=9)
Mean ± SE	108±2.1 (n=9)	104.9±3.2 (n=9)	101.9±3.03 (n=9)	104.3±3.4 (n=8)	94.9±1.9 (n=9)
# 3	93	98	95	69 (D 16)	90
# 4	111	102	114	114	38
CPK (U/L)					
Range	(n=9)	(n=9)	(n=8)	(n=7)	(n=9)
Mean ± SE	20[illegible]±16.3 (n=9)	175.2±13.4 (n=9)	179.8±15.6 (n=8)	166.4±22.3 (n=7)	232.5±14.5 (n=9)
# 3	244	165	242	396 (D 16)	242
# 4	169	178	398 (D 2)	498 (D 9)	217
Osmolarity (mosm/kg)					
Range	(n=9)	(n=9)	(n=9)	(n=8)	(n=9)
Mean ± SE	300.9±0.5 (n=9)	303±1.5 (n=9)	303±1.3 (n=9)	304.5±1.3 (n=8)	298.6±1.2 (n=9)
# 3	301	306	306	316	299
# 4	302	301	300	301	297

Note: 'n' is the number of animals used for determining the range and mean values; '(D n)' is the day on which the parameter value for animal/s #3 and/or #4 was obtained.

to prolonged recumbency; however this reviewer has not been able to find such an effect of less than one day of recumbency (Harrison's Principles of Medicine lists the following conditions involving skeletal muscles that may cause an increase in this enzyme: i/m . injection, muscular diseases, muscle damage secondary to trauma, convulsions, and *prolonged immobilization;* less than a day of recumbency does not fall into the last category.) However, whatever the mechanism, the effect was transient. Since next serum chemistry was done only three weeks later, the duration of this effect is not determinable. The CNS effects would seem to be due to a secondary pharmacological effect of the drug. The highest dose at which no efferts other than the primary cardiovascular effects of the drug are seen is not determinable from this study.

§2: Subchronic:

Rat (SD) CRL:Upj [BR] (14 day study; Report # 7227/89/062)

n=15/sex/group; one control and three treatment groups; groups 2-4 received 12.5, 25, and 50 mg/kg/day ibuti i/v for 14 days; group-1 received vehicle; volume injected was 10 ml/kg in all groups. At the end of dosing period, the first 10 animals /sex/group that had no evidence of perivenous leakage of solution, and all animals that had such leakage were sacrificed; the remainder were sacrificed at the end of one month recovery. The number of animals sacrificed at end of dosing (End Dose) and end of recovery (End Rec) are given below:

	Males				Females			
Group	1	2	3	4	1	2	3	4
End Dose	10	10	10	11	10	11	11	11
End Rec	5	5	5	3	5	4	2	2

Animals were observed twice/day for any clinical signs during the dosing period; recovery animals were observed once/day during recovery period. Body wts: pre dosing; daily during the dosing period; twice/week during the recovery period. Food consumption: pre dosing; weekly during dosing and recovery. Urinalysis, chemistry, hematology, gross necropsy, and organ wts were determined at end of dosing period for the animals sacrificed at 2 weeks, and at end of recovery for the recovery animals. Histopathology of all organs and of injection sites was done in the following: All control and high dose animals at end of dosing; all animals that died. Histopathology of aorta, heart, kidneys, liver, urinary bladder, and reproductive organs was done in all animals at necropsy.

Results: (Dosing Period)

Deaths: *High dose:* Three deaths (2 F and 1 M); one female was killed on D 10, when further injections became impossible because of severe tail lesions at injection site; the other two animals died while being restrained for dosing. *Middle dose:* Two deaths (F). One female found dead on D 13; the skin of its tail was accidently pulled off while dosing on D 9, and there was gangrene of its tail at death; the other female died during restraint while dosing.

Clinical signs: *12.5 mg/kg:* There were no adverse effects in this group. *25 mg/kg:* One Female had excessive salivation for approximately 5 minutes post dose on D 10. *50 mg/kg:* Excessive salivation occurred in 28/30 animals on days 8-14, and lasted for approximately 5 minutes post dose; two females had depression, generalized shaking, and hyperpnea/ dyspnea for 1-2 days (on days 3-5 of treatment); one female had dyspnea on D 5 (the duration of these symptoms is not mentioned).

Tail lesions: Discoloration and swelling were present in two low dose, two middle dose, and two high dose females (in addition to the high dose female that had to be killed), and one high dose male.

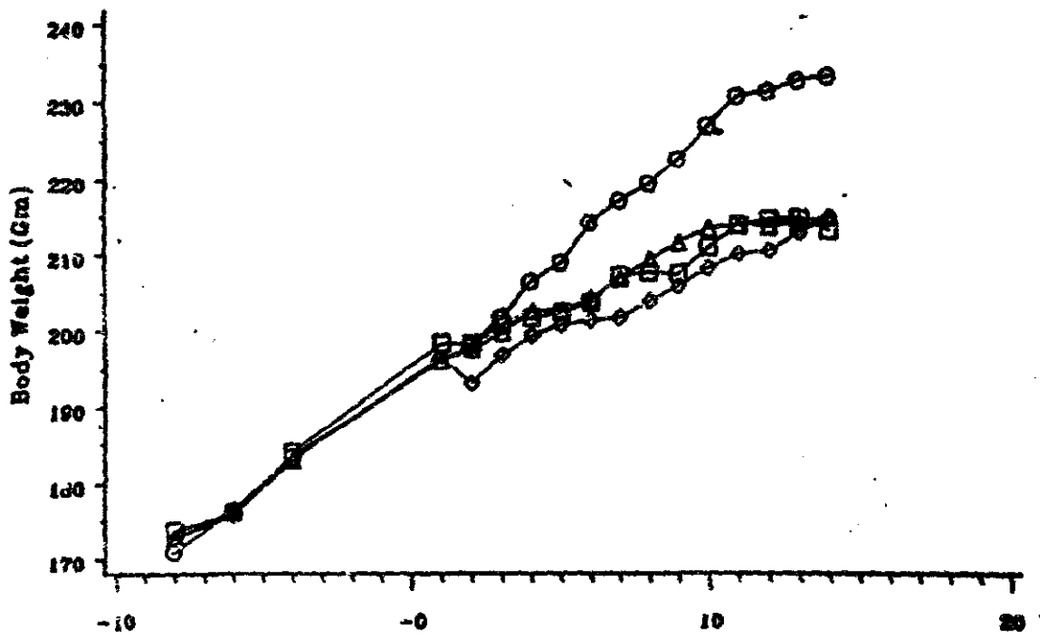
Body wt: *Females:* Mean wt of high dose group was higher than that of control from D-4 of treatment (Fig T1), and the difference was s-s from D-8 onwards; on D-14, the increase was ≈9.6%. *Males:* Mean body wts of mid and high dose groups were lower than that of control

T|

Body Weight

Females

STUDY:88-277 SPECIES/STRAT (SPRAGUE-DAWLEY)



through most of the treatment period (Fig T2); at the end of treatment, mean wts of mid and high dose groups were ≈ 5% lower than that of control (s-s; p=0.03, two tailed t-test, s-rev) .

Food Consumption: *Females:* Food consumption of the high dose group was higher than that of the control group during the dosing period (3% higher pre dose; ≈10% higher at 8 days, and 16% higher at 14 days); the difference was s-s at the end of treatment (p=0.006, two tailed t-test, s-rev). *Males:* Food consumption of mid and high dose groups was slightly lower than that of control during the treatment period; on D-14, the deference from control was ≈ 9% and was s-s (for both groups, p <0.007; two tailed t-test, s-rev).)

Water Consumption: Water consumption of high dose females was ≈ 50% higher than that of control group (s-s; p=0.0007; two tailed t-est, s-rev) during the second week of treatment. According to the sponsor, this increase coincided with onset of increased salivation in this group.

Hematology, Serum chemistry & Urinalyses: There were no drug related adverse effects on any hematological or urinary parameters. *Serum chemistry:* In high dose female group ALT, and serum cholesterol were higher than in control group and the differences were s-s (*ALT* (U/L, mean ± SD), Control: 25.1± 3.14; High: 30 ± 4.8; p=0.012 (s-rev). *Serum cholesterol* (mg/dL, mean ± SD), Control: 51±9.26; High: 67.73±12.74; p=0.003 (s-rev). Note: The sponsor makes a special note of the following: One high dose female had the highest value of BUN (24 mg/dL; next highest was 20 mg/dL in a control animal), and one high dose male had the highest alkaline phosphatase value (418 u/L; next highest value was 344 u/L in a group-2 animal). However the differences between mean values of BUN of high-dose and control females, and mean values of alkaline phosphatase of high-dose and control males were s-ns (BUN (F): mean high-dose > mean control by 7%; p=0.394. Alkaline Phosphatase (M): mean high-dose > mean control by 5%; p= 0.652. (s-rev))

Organ wts: Liver wt of group-4 females was increased approximately 13% compared to controls (s-s); the relative liver wts in the two groups were s-ns.

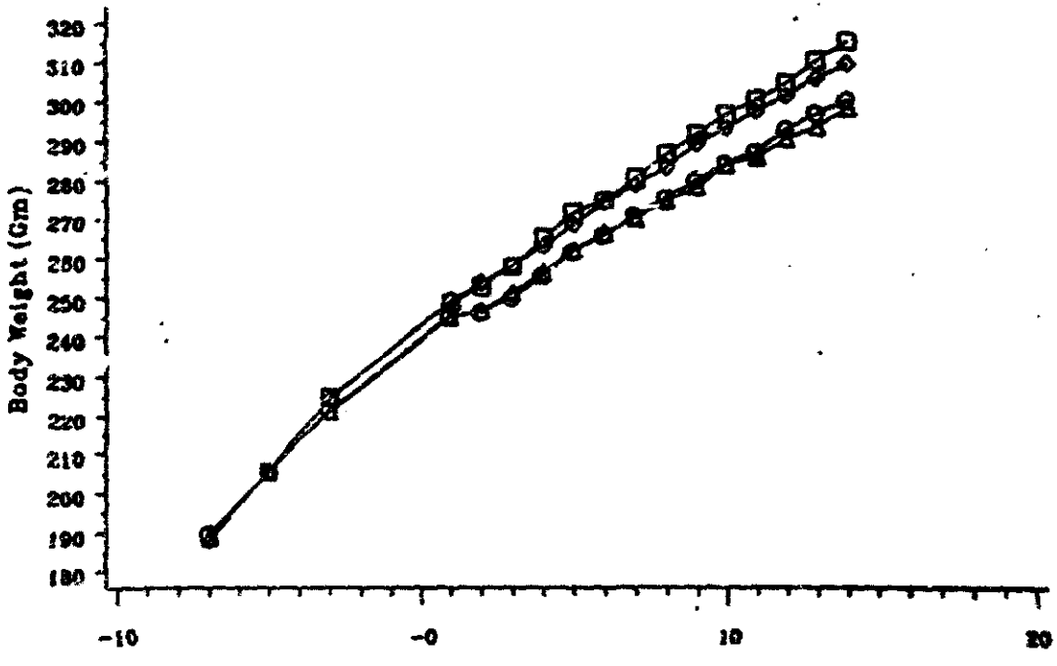
Histopathology (Other than at injection site). Females: *High dose:* 5 females had mucification of the vaginal epithelium (in 3, the change was moderate and in 2, minimal); 3 females had moderate proliferation of the mammary glands (one of these three also had moderate mucification of vagina). *Mid dose:* 3 females had mucification of vagina (one moderate, one slight, and one minimal); 2 females had proliferation of the mammary glands (one of these also had mucification of vagina). Males: One middle dose rat had multifocal degeneration/ atrophy of seminiferous tubules in one testes. One middle dose recovery rat had similar lesions in both testes; the epididymal ducts contained no sperms, but contained degenerated germinal cells. Injection site (males & females): Frequency and severity of lesions is stated to be comparable in treated and control animals.

FIGURE 22

Body Weight

Males

STUDY:88-277 SPECIES:RAT (SPRAGUE-DAWLEY)



p. 26 (1)

Comments: *Liver wt:* It is difficult to understand why increase in body wt of mature rats would be accompanied by increase in liver wt, but there was a clear linear relationship between body wt and liver wt of individual females of control and group-4 (Fig T3). Since ALT was also increased in high dose females, the high dose may have been hepatotoxic. *Vaginal and mammary gland effects* in high and mid dose females indicate secondary effects via some gonadal hormonal changes. Analyses of chemistry, body wt, liver wt, and histopathology in the recovery females cannot provide any useful information about reversibility of the effects observed in treated animals, since there were only 2 animals each in groups 3 and 4. *Testicular lesions:* The sponsor comments that unilateral findings in one middle dose rat was considered incidental, particularly as it was unilateral, and was not dose related; the sponsor also states that this is a common incidental finding in this strain of rats. Lesions similar to the bilateral lesions in the middle dose recovery rat were also found in high dose rats in subchronic oral (gavage) toxicity studies, and therefore may be drug related. (Rats that received 600 mg/kg/day orally for a week, had testicular degeneration, and rats that received 150 mg/kg/day orally for a week had degenerated cells present in epididymal tubes). In the two week oral study, 7/10 high dose rats (250 mg/kg/day given in two divided doses) had degenerative/atrophic changes in testes (bilateral in 5 and unilateral in 2), and presence of degenerated germinal cells in the epididymii; 3/5 recovery rats in this group had bilateral testicular atrophy, and aspermia and presence degenerated germinal cells in the epididymal ducts.)

Rat, (SD; CRL): 7 Day i/v Toxicity Study of I alone and in Combination with Ibutilide: (Report # 7227/94/009).

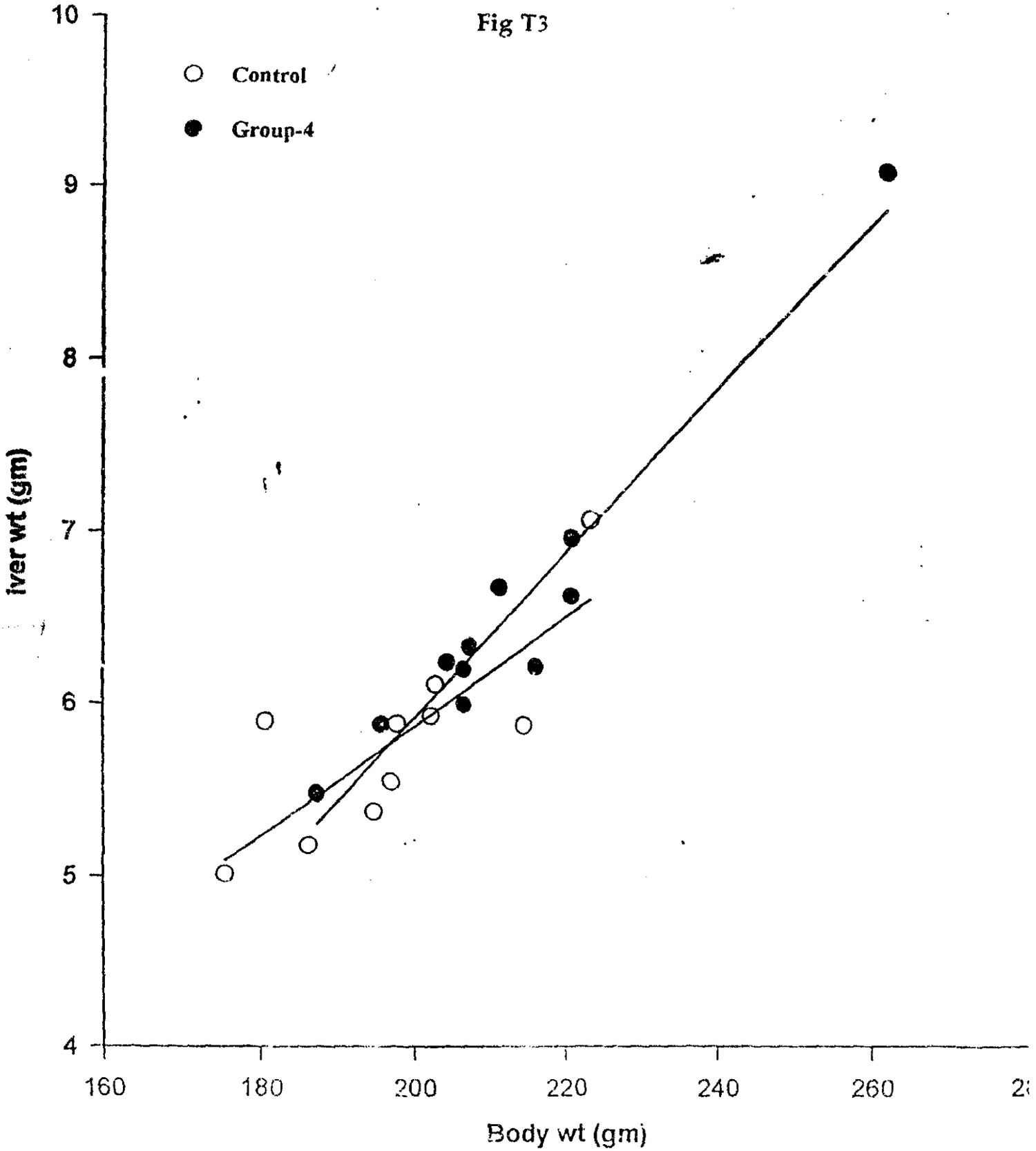
The sponsor refers to a 14 day toxicity study in which 12.5-100 mg/kg/day heat sterilized ibutl (ibutl(HS)) was used; it is stated that ibutl(HS) was more toxic than ibutl alone, and there was no NAE dose. The present study was undertaken to determine the toxicity of at lower doses. *Note:* The nature of toxicity found in the 14 day study is not mentioned; the 14 day study is not in this submission. It is not clear why doses higher than 50 mg ibutl(HS) were tried in the 14 day study since in the acute toxicity study reviewed above, 17/20 animals given 75 mg/kg ibutl(HS) as a single dose had died;

10/sex/group; group-1, vehicle control; group-2 received 3 mg/kg/day ibutl; groups 3-6 received 3 mg/kg/day ibutl and respectively; groups 7-10 received

Clinical examination was done once/day; body wts twice pre dose and daily during the treatment period; food consumption pre dose and over a six day period during treatment. Hematology, urinalysis, and serum chemistry were not done; the reason given is that in the 14 day study much higher doses of ibutl and ibutl(HS) were found to have no effect on these parameters. Organ wts were not determined (no reason given). Histopathology of thymus, heart, liver, kidneys, testes, epididymi, ovaries, uteri, vagina and mammary glands was done in control, ibutl,), and 'ibutl+ groups.

Results: No dose related abnormalities were detected in any of the parameters examined.

Fig T3



Regression Parameters: C: r=0.796; Slope=0.031 ± 0.019 (95% CI); p for slope=0.006
Group-4: r=0.969; Slope=0.048 ± 0.009 (95% CI); p for slope <0.00001

Dog, Beagle: (14 day i/v study; Report # 7227/89/059)
n=3/sex/group; groups 2-4 received 1.25, 2.5, and 5 mg/kg/day ibutl respectively; group-1 (C) received vehicle; doses were injected in approximately 5 minutes; plasma samples were collected on several occasions for toxicokinetics; rest of the methodology similar to that in the rat.

Results:
Clinical signs: *High Dose:* All dogs in this group had excessive salivation and exhibited apprehensive behavior; most dogs also exhibited some or all of the following CNS signs: restlessness, disorientation, and head bobbing/body rocking; one female in addition showed aggressive behavior, and had decreased motor activity and convulsions. These signs appeared immediately after dosing, were most pronounced at 1-2 hours, and the animals appeared normal at approximately 8 hours post dose. The incidence and severity of these signs was less pronounced after 3-4 days of treatment; in the second week only 3/6 dogs showed some of the signs seen in the first week. *Mid & Low Dose:* Slight apprehensive behavior was present in 2 females in each group for 1-2 days.

Body wt: *High Dose:* High dose males had lost some wt by the end of the study (since there were only 3 animals/sex/group, statistical comparison of Δ wt with control group is not very helpful).

Necropsy: *Heart wts* were increased by approximately 11% in medium and high dose males, and dose relatedly increased 18-36% in all treated females. *Thymus wts* were dose related increased by 60-77% in medium and high dose females, but the increase was s-s only in the high dose group (s-ns, p=0.092, s-rev. However, as stated before, with such small group sizes lack of s-s does not mean that the change is not biologically relevant.)

Histopathology: *High Dose:* One high dose dog had focal testicular degeneration, and an increased no. of degenerate cells in the epididymis. *Injection site:* Some animals showed phlebitis and perivascular signs of inflammation, and one animal had venous thrombosis. (non occlusive).

Toxicokinetics:
On treatment days 1 and 14, blood samples from 2/sex/group from the low and high dose groups were drawn pre dose, and at 5 min, and 1, 2, 4, and 6 hours post dose; pre dose blood samples were also collected on days 2, 4, 7, 9, and 11.

Results: Except in the case of one high dose dog (#20), repeated doses did not seem to produce any significant accumulation of drug. Table below shows some of the pharmacokinetic parameters; values in dog #20 in the high dose group are shown separately.

Dose	1.25 (mg/kg/day)		5 (mg/kg/day);n=3		5 (mg/kg/day; # 20)	
Day	1	14	1	14	1	14
C_{max} (ng/ml)	256.3±24.5	248.5±26.9	1398.7±61.7	1232±61.1	1478	1708
AUC_{0-t} (ng-hr/ml)	306.8±20.8	338.5±48	1561.±158.8	1759±172.6	2942	5844
$t_{1/2}\beta$(hr)	1.5±0.15	1.48±0.15	1.37±0.09	1.45±0.07	2.7	4.7
Pre dose Conc ng/ml		0.618±0.25		2.01±0.765		8.05

Comments: Normalized for dose, C_{max} and AUC increased (30% and 28% respectively) and clearance and volume of distribution decreased (23% and 26% respectively) at the higher dose; these changes were s-s. The sponsor points out that testicular degeneration was seen in dog #20, which had a much higher $t_{1/2}\beta$ than the other 3 dogs in the high dose group.

§3: Reproduction Toxicity Studies:

Rat (CrlCD[BR]): Segment I Fertility and General Reproductive Performance Study (Report #7224/92/051)

18m+36f/group; one control and 3 treatment groups; groups 2-4 received 5, 10, and 20 mg/kg/day ibutl by gavage; control group (group-1) received vehicle; volume of fluid administered by gavage was 10 ml/kg/day in all cases. Treatment of males started 70 days before start of mating and continued throughout mating; treatment of females started 14 days before mating and continued for 12 days of gestation for 50% of the females in each group (these animals were sacrificed on day 13 of gestation, and their uteri examined to determine various reproductive parameters); and up to day 20 of lactation for the other half; estrous cycles of 12 females from each group were monitored daily during the first 14 days of treatment. All pups born live or dead were examined externally for malformations; litters were culled on day 1 to 4m+4f/litter; all pups that were culled or that died between days 0 and 21, were examined for visceral malformations. Besides body wt and general condition, pups were tested by the following tests for development: Pinna detachment on day 2; responses to negative geotaxis on days 6, 8, and 10; auditory startle reflex on days 12, 13, and 14; eye opening on day 15; and maze test on days 25, 26, and 27. 1m+1f from each litter was selected for breeding. *Note:* Reproductive performance of F_1 is not reviewed, as this NDA is for only one or two doses of the drug. According to the sponsor's summary, there were no dose related adverse effects on the reproductive performance of F_1 .

Results (F_0 Dams):

Wt Gain: There were no differences between mean wts of different groups at the beginning of gestation; wt gains of all groups at 12 days of gestation were similar; between day 13 and day 20 of gestation, wt gain of the high dose group was approximately 16% lower than the wt gain of the control group (s-s; $p < 0.05$, two tailed t-test, s-rev; analysis was done by calculating wt gain of each animal, and then calculating the means and SDs of the two groups). During days 0-6 and 6-9 of gestation, wt gains of high dose group were 9% and 19% respectively lower than the wt gains of the control group; the differences were s-ns ($p=0.185$ for the 6-9 day interval; two tailed t-test; s-rev); wt gains for the periods 0-12 and 0-20 are shown in table R1.

Estrous Cycle Length: There were no differences between groups.

Fertility Index (100x(no. pregnant)/(no. mated)): 92, 83, 89, and 92% in groups 1-4 respectively.

Reproductive Parameters of Dams Sacrificed on Day 13 of Gestation: Table R2 shows various parameters. None of the values which numerically indicated adverse drug related findings in group 4 or groups 3 & 4, were s-s.

Reproductive parameters of Dams scheduled for delivery are shown in table R1. The high dose was associated with an embryocidal effect; number of live pups/litter was reduced 25%; post implantation loss/dam was nearly three times that in the control group; number of dams with litter sizes ≤ 14 was nearly 8 times the number in the control group. % of dams with some post implantation loss was also higher in the high dose group, but the difference was s-ns (s-rev)

NDA # 20,491

Table R1

Reproductive Data for F_0 Dams Scheduled for Delivery

Dose-Group	0 mg/kg/day	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Wt Gain (gm) 0-12 days	73.6±13.6 n=32	68.8±10.7 n=29	69.1±7.6 n=32	71.7±11.7 n=31
Wt Gain (gm) 0-20 days	170.1±20.6 n=18	158.4±17.8 n=16	163.3±13.9 n=17	142.2±32.8* n=17
Gestation (days)	21.7±0.4	22.1±0.3	21.9±0.5	21.8±0.5
Live pups(/Litter)	16.4±1.6	15.7±1.9	16.2±1.8	12.3±5.0**
Dead pups(/Litter)	0.2±0.4	0.1±0.5	0.2±0.5	0.2±0.5
PstImpL (/dam)	1.5±1.1	1.4±1.5	1.4±1.5	4.4±3.8**
Dams with PstImpL	15/19	11/17	11/17	18/18
Imp Scars(/Dam)	17.9±1.8	17.1±2.0	17.5±1.2	16.7±2.6(n-s)
# of Litters with ≤ 14 live pups	1	4	3	8**

Note: Gestation stands for duration of gestation; PstImpL stands for 'post implantation Loss' and includes dead pups; Imp stands for Implantation; '*', $p < 0.05$; '**', $p < 0.01$ (two tailed t-test, s-rev). The smallest litter size in the control group was 14, and this number is chosen to determine the number of litters with sizes ≤ this number.

NDA # 20,491

Table R2

13 Day Hysterotomy Data

Dose Group	0 mg/kg/day	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
No Pregnant	14	13	15 (14)[1]	14
Corpora Lutea	19.2±2.8	17.9±1.6	18.5±1.76	18.6±1.8
Complete Resorp	0	0	0	0
Pre Imp Loss	1.14±1.7	0.62±1.12	1.14±1.7	1.5±2.07 (ns;p=.622)
Pre&Post Imp Loss	2.14±1.92	1.39±1.19	2.43±2.14	3.07±2.23 (ns;p=.249)
Dead Embryos	1±0.9	0.8±0.9	1.29±1.44	1.6±1.3 (ns;p=.168
No. with Dead Embryos	9	7	9	11 (ns; p=.339)
Live Embryos	17.1±1.7	16.5±2.0	15.5±2.2	15.6±2.7 (ns;p=0.09)

Note: All parameters in the table above are mean±SD; '1', in group-3, one dam had only 9 corpora lutea, one implantation site, and one live embryo; the values in this group are means of 14 dams, excluding this one dam; Resorp' stands for Resorption; 'Imp' stands for Implantation; Statistics are from two-tailed t-tests done by this reviewer.

Results (F_1 pups):
Note: For all parameters, numbers of pups and litters are indicated as follows: "pups(Litters).
Body wts: Body wts of pups of groups 2 and 3 were not different from those of controls at any time; body wts of group-4 pups were 1.6, 2.9, 3.5, 2.9, 3.2, and 3.9 % lower than the control group on days 0, 1, 4, 7, 14, and 21, respectively, but the differences were s-ns at any time.
Mortality: Before culling, there were 5(5), 2(1), 15(7), and 9(5) deaths in groups 1-4, respectively. After culling, there were 1, 0, 1, and 6(5) deaths in groups 1-4 respectively (all these deaths occurred within 6 days). Deaths between days 0-21 were 6(6), 2(1), 16(7), and 15(8) in groups 1-4, respectively; difference between groups 1 and 4 is s-ns (p=.367; fisher's test; s-rev). *Comments:* Statistical test was done using litters as the units tested, since litter is the appropriate unit to use for these studies.
Malformations: All malformations are listed in the table below; visceral and skeletal examination results are from pups that died up to day 4; visceral[2] examination results are from pups that died after day 4, or were killed after day 20.

	C	2	3	4
Malformations:				
External:				
Pups (litters) Examined:	316(19)	269(17)	280(17)	236(18)
No. Affected	0	1 (1)	2 (2)	10 (8)**
Visceral & skeletal:				
Pups (litters) Examined:	5 (5)	2 (1)	6 (5)	8 (7)
Visceral:				
No. Affected	0	1 (1)	0	0
Skeletal:				
No. Affected	0	0	0	2 (2)
Visceral[2]:				
Pups (Litters) examined:	103(18)	102(17)	101(17)	91(17)
No. Affected	0	0	2 (2)	6 (5)*

Note: "*" and "**" indicate $p < 0.05$, and $p < 0.01$ respectively (Fisher's test using litter as the unit tested; s-rev). External malformations in all cases were: no tail, kinked tail, or thread like tip of tail. Visceral and skeletal examination was done only on pups that died between days 0-4; the visceral malformation was an interventricular septal defect, and the skeletal malformations in both high dose pups were bent tails (the sponsor states that if these pups had lived, tail abnormality would have become apparent to external examination also). The *visceral[2]* malformations were: hydronephrosis in group-3; in group-4: diaphragmatic hernia, 2; absent innominate artery, 1; rt sided aortic arch, 1; vestigial testes, 1; and hydrocephaly 1.

Developmental Parameters: *Pinna detachment:* There was no difference in the percentage of pups that had one/both pinnae detached on day 2. *Auditory Startle Response:* On day 12, the percentage of pups with positive response was 97.2, 94.1, 82.4, and 86.8 % in groups 1-4 respectively; the difference in the response rate of groups 3 & 4 v C was s-s (p=0.02; Fisher's test, s-rev); by day 14, all pups in all groups had a positive response. *Eye opening:* On day 15, 97.2, 100, 99.3, and 96.8 % pups in groups 1-4 respectively had their eyes opened. *Maze*

test: (Done on days 25, 26, and 27). There were no dose related adverse effects on mean time to escape and mean no. of errors on any of the days. Note: The results of the negative geotaxic test are not evaluable, as there are mistakes in the presentation of the results.
Body wts after weaning: (1M+1F/litter; wts on days 31, 37, 44, 51, 58, and 65) *Males* wts of high dose males were 8-13 % lower than those of controls, and the differences were s-s at all time points; body wts of mid dose males were 4-6 % lower than those of controls, but the difference was s-s only on day 58 (s-rev; two tailed t-tests). *Females:* Body wts of high dose females were 5-7 % lower than those of controls, but the differences were s-s only at the last two time points (s-rev; two tailed t-tests).

Comments: The sponsor thinks that the occurrence of external malformation in 2 mid dose litters (even though the incidence is s-ns) may be drug related, since the malformation was of the same type as found in the high dose group. In view of this the NAED in terms of fetal effects in 5 mg/kg/day; 20 mg/kg/day was embryocidal and teratogenic; 10 mg/kg/day may be teratogenic. Body wts of F_1 after weaning were s-s lower than control in the 20 mg/kg/day dose group.

#1: **Segment II Teratology Study in the Rat: Crl:CD[BR](SD):** (Report # 7224/92/003)
24 mated females/group; one control, and 3 treatment groups; groups 2-4 received 20, 40, and 80 mg/kg/day ibutilide by gavage from days 6-15 of pregnancy; control group received the vehicle by gavage during the same period; volume of fluid administered was 10 ml/kg in all cases. Doses were selected on the basis of a range finding study in which 50 mg/kg/day was embryocidal. Dams were weighed on days 0, 6, 10, 12, 15, and 20. Hysterotomies were performed on day 20 of gestation; all fetuses were examined for external abnormalities; half the fetuses in each litter were processed for visceral and the other half for skeletal abnormalities.

Results:
Dams:
Clinical signs: *Post dose salivation* occurred in a dose related manner in terms of the number of animals affected and the number of days on which it occurred. 8 dams in the low dose group exhibited the sign for 1-2 days; 20 in mid dose for 1-4 days (average: 2 days), and all animals in the high dose group for 2-10 days (average: six days). *Red vaginal discharge:* In 10 mid dose dams (one day in 9; 3 days in one), and in 6 high dose dams (one day in 5; 2 days in one).
Body wts: (Table R 3) Body wts of the low dose group were not different from those of the control group at any time point. Up to day 12, body wts of groups 3 and 4 were < 1.5% lower than those of the control group; day 15, groups 3 & 4 wts 2.6% and 3.9%, respectively, lower than control; day 20, groups 3 and 4 wts 14% and 18%, respectively lower than control.
Hysterotomy Data: Table R 4 shows the data. All dams in the high dose group and 50% of the dams in the mid dose group had complete resorption ($p<0.0001$); No of dams with some resorptions were 6, 10, 24, and 23 in groups 1-4 respectively; difference between control and low dose group was s-ns ($p=0.174$; s-rev). Mean number of live fetuses/dam (using only dams with some live fetuses for the mid dose group) was markedly reduced in the mid dose group. Even though litter size in the low dose group was not reduced, mean no. of resorptions/dam (which indicates post implantation loss) was s-s increased.

Table R3

Body & Uterus Wts

Group	Day-0	Day-10	Day-12	Day-15	Day-20	Uterus	B-Uterus
Control n=22	195.0	251.7	262.9	279.62 ±15.42	339.59 ±23.18	60.0	279.59
20 mg/kg n=22	198.0	251.1	263.1	279.7 ±16.58	334.9 ±26.44	58.2	276.7
40 mg/kg n=24	195.2	249.4	260.2	272.3 ±11.91	292.86** ±18.11	16.6 (12)	274.26
80 mg/kg n=23	194.6	248.6	258.9	268.6* ±16.35	278.19** ±18.72	No wt[1]	

Note: Wts are in gm; '[1]' in group-4, there were complete resorptions in all animals, and the uteri were not weighed. '*', p <0.05; '**', p <0.01.; 'B-Uterus stands for 'Body wt-Uterus wt'.

Table R4

Hysterotomy Data

Observations	Ibutilide Dose: mg/kg/day			
	0 (Control)	20	40	80
No Pregnant	22	22	24	23
No. with All Resorptions	0	0	12[*4]	23[*4]
No. of Litters	22	22	12	0
Mean No of Corpora Lutea/Dam[1]	14	13.5	13.4 (12)[f]	-
Mean No Live Fetuses/Dam	11.1 ±3.58	11.2	3.1±3.15[*4] n=12[f]	0
Mean No Dead Fetuses/Dam	0	0	0	-
No Dams with Resorptions	6	10 (n-s;p=.174)	24[*4]	23[*4]
Mean No Resorptions/Dam	0.32±0.57	0.91±1.23*	9.5±2.8[*4] n=12[f]	-

Note: Data, where it is not binary is given as 'Mean±SD'; binary data was analyzed by Fisher's exact test; non binary by two tailed t-test (s-rev); '*', p<0.05; '**', p<0.01; '[4]', p<0.0001. [1]: Corpora lutea were countable only in dams that had some live fetuses; numbers within '( )' after a parameter indicate the number of dams from which parameter values were taken; '[f]' indicates that only dams that had some fetuses were considered for that parameter.

Fetuses:

Fetal wts: Mean fetal body wts were: C, 3.34±0.197 gm; Low Dose, 3.26±.535 gm; Mid Dose, 2.19±0.312 gm. Difference between C and Mid dose is s-s (p<0.00001; two tailed t-test, s-rev).

Fetal Abnormalities: The incidences of various *malformations* are listed in the table below. Table R5 lists fetal and litter incidences of all *variations* observed in the study; table R5b gives a consolidated summary of fetal and litter incidences of variations.

	Incidence	Description
External Malformations:		
Control:	1/245 (1/22)	1: Mandibular Agnathia (F3, L16)
Low:	3/247 (3/22)	2: Adactyly (F6, L31; F9, L35)
		1: Cleft Palate (F2, L33)
Mid:	10/ 37 (6/12)**	5: Adactyly (F1, L53; F2, L57; F6 F9, L60; F1, L68;
	(p=0.004)	F4, L70)
		1: Edema (F1, L53)
		1: Cleft Palate (F1, L60)
		1: Ablepharia (F1, L72)
Visceral Malformations:		
Control:	1/118 (1/22)	1: Interventricular Septal Defect (F1, L11)
Low:	3/122 (1/22)	1. Retroesophageal Rt Subclavian (F5 F7 F10, L45)
Mid:	5/ 14 (3/ 6)*	1: Lung: Portion of a lobe absent (F1, L57)
	(p=0.022)	2: Malformed Pharynx & Palate (F7 F8, L60; F3, L70)
Skeletal Malformations:		
Control:	1/127 (1/22)	1: Scoliosis (F3, L16)
Low:	8/125 (5/22)	5: Scoliosis (F8, L26; F4, L28; F2, L31; F2, L37;
	(p=0.09)	F6,L47)
		1: Absent Metcarpals (F9 F14, L31)
Mid:	6/ 23 (4/12)*	3: Scoliosis (F1, L50; F5, L60; F1 F4, L70)
	(p=0.042)	1: Bifurcated Rib (F6, L57)
		1: Absent Metacarpals (F6, L60)
All Malformations:		
Control:	(2/22)	1: Visceral (L11)
		1: External & Skeletal(L16)
Low:	(8/22)*	2: External (L33, L35)
	p=0.034	4: Skeletal (L26, L28, L37, L47)
		1: Visceral (L45)
		1: External & Skeletal (L31)
Mid:	(7/12)**	3: External (L53, L68, L72)
	p=0.004	3: All three (L57, L60, L70)

Note: In the second column, pup and litter incidences are listed as 'pup (litter)'; in the 3rd column, 'n:' is the number of litters in which the abnormality listed was found; after the abnormality, the fetus/es and their litters in which the abnormality occurred are listed (Fn Fn, Ln). At the end, the litter incidences of all malformations are given. Statistics used is fisher's exact test with the litter as the unit (s-rev). In the mid dose group only 6 litters were available for visceral examination (the other 6 had only one fetus each, which was examined for skeletal malformations). Statistical test used is Fisher's exact test with the litter as the unit (s-rev).

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Table 7: Summary of the Incidence of Individual Variations

	U-70226E (mg/kg/day)			
	0.0	20.0	40.0	80.0
No Litters Examined	22	22	12[a]	0
No. Examined Grossly	245	247	37	0
No. Examined Viscerally	118	125	14	0
No. Examined Skeletally	127	125	23	0
Gross Variations Observed	No. Fetuses/No. Litters			
None observed	-	-	-	-
Visceral Variations Observed				
Left umbilical artery	4/4	1/1	0/0	-[b]
Hydroureter	0/0	3/2	0/0	-[b]
Grade 0 kidney	0/0	3/2	0/0	-[b]
No innominate	4/4	6/6	1/1	-[b]
Skeletal Variations Observed				
Hyoid: body unossified[c]	11/7	7/4	0/0[d]	-[b]
Pubes: unossified	1/1	0/0	2/2	-[b]
Ilia: incomplete ossification	1/1	0/0	0/0	-[b]
Ischia: incomplete ossification	2/2	0/0	2/2	-[b]
Ischia: unossified	1/1	0/0	0/0	-[b]
Rib(s): accessory	1/1	1/1	3/1	-[b]
Rib(s): cervical #7	0/0	2/2	0/0	-[b]
Zygoma(s): incomplete ossification	2/1	1/1	0/0	-[b]
Frontal(s): incomplete ossification	1/1	0/0	0/0	-[b]
Squamosal(s): incomplete ossification	5/2	4/2	0/0	-[b]
Interparietal(s): incomplete ossification	25/13	24/13	6/5	-[b]
Supraoccipital(s): incomplete ossification	20/10	10/7	4/4	-[b]
Parietal(s): incomplete ossification	5/5	4/2	1/1	-[b]
Nasal(s): incomplete ossification	1/1	0/0	0/0	-[b]
Sternebrae: #5 unossified[c]	48/16	55/18	22/11[d]	-[b]
Sternebrae: lack of apposition	0/0	1/1	2/2	-[b]
Sternebrae: bipartite[c]	0/0	1/1	8/8[f]	-[b]
Sternebrae: other than #5 incomplete ossification[c]	4/4	19/10[f]	14/9[d]	-[b]
Sternebrae: other than #5 unossified[c]	7/5	15/8	20/11[d]	-[b]
Vertebrae: 27 presacral[c]	0/0	0/0	6/5[d]	-[b]
Vertebrae: 25 presacral	0/0	1/1	0/0	-[b]
Centra: incomplete ossification[c]	0/0	0/0	7/7[d]	-[b]

[a]Fetuses from only 6 of the 12 litters were examined viscerally.
[b]All pregnant dams had resorptions only; thus, there were no fetuses to examine
[c]The Modified Jonckheere Ordered Alternatives Test for Dose Response was statistically significant, $p = 0.032$
[d]Statistically significantly different from the control group, $p < 0.01$
[e]The Modified Jonckheere Ordered Alternatives Test for Dose Response was statistically significant, $p < 0.0001$
[f]Statistically significantly different from the control group, $p < 0.05$
- = Not applicable
Individual fetuses may have more than one variation.

90-162: A Segment II Teratology Study (Oral) of U-70226E in Rats
Table 6: Summary of Variations

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
In Fetuses:				
Gross	**0/245(0.0)**	**0/247(0.0)**	**0/37(0.0)**	**-[b]**
Visceral	**7/118(5.9)**	**9/122(7.4)**	**1/14(7.1)**	**-[b]**
Skeletal[c]	**71/127(55.9)**	**69/125(55.2)**	**23/23(100.0)[d]**	**-[b]**
Total[c,e]	**78/245(31.8)**	**78/247(31.6)**	**24/37(64.9)[d]**	**-[b]**
In Litters:				
Gross	**0/22(0.0)**	**0/22(0.0)**	**0/12(0.0)**	**-[b]**
Visceral	**7/22(31.8)**	**7/22(31.8)**	**1/6(16.7)**	**-[b]**
Skeletal	**21/22(95.5)**	**20/22(90.9)**	**12/12(100.0)**	**-[b]**
Total[e]	**21/22(95.5)**	**21/22(95.5)**	**12/12(100.0)**	**-[b]**

[a]Data are: Number remarkable/Number examined (%).
[b]All pregnant dams had resorptions only; thus, there were no fetuses to examine.
[c]The Modified Jonckheere Ordered Alternatives Test for Dose Response was statistically signficant, $p<0.0001$
[d]Statistically significantly different from the control group, $p<0.01$
[e]Fetuses with multiple variations were counted only once.
- = Not applicable

Table R5b

Comments: For determining whether a certain dose has a teratogenic effect, the litter incidences of all malformations lumped together should be considered. Considered in this manner, 20 mg/kg/day as well as 40 mg/kg/day in this study were teratogenic. There is a dose response relationship; 36% litters in low dose and 58% in mid dose had abnormal fetuses. (*Note:* As all high dose dams had total litter loss, teratogenic effects could only be assessed in mid and low dose groups.)

#2: Segment II Teratology Study in the Rat: Crl:CD[BR](SD): (Report # 7224/94/027)
Note: This repeat study was done to determine the NAED. All methodology except the doses were the same as in the #1 study reviewed above. Groups 2-4 of mated female rats received: 5, 10, and 20 mg/kg/day ibuti respectively; group-1 (Control) received the vehicle.

Results:
Dams:
Clinical signs: There were no clinical signs of an any toxicological significance in any group.
Body wts: Body wts of low and mid dose groups were not different from the body wt of control group at any time point. Body wt of the high dose group was ≈3.4% lower than that of the control group (s-ns; p=0.193, s-rev); after subtracting the mean gravid uterine wts from the mean body wts, the adjusted body wts of the two groups were not dissimilar. According to the sponsor's statement wt gain of the high dose group between days 15 and 20 was 8.3% lower than that of the control group and the difference was s-s ($p<0.01$).
Hysterotomy data: Table R6 shows the data. High dose group had a 9% lower no of live fetuses/dam, and a higher post implantation loss (as a % of the number of implantations), but the differences were s-ns.

Fetuses:
Fetal wts: Mean fetal wt of high dose group was 9% lower than that of control group, and the difference was s-s ($p<0.01$).
Fetal abnormalities: Fetal *malformations* are listed in the table R7. External malformations, and all malformations taken together are s-s increased in the high dose group (Fishers exact test; s-rev). Table R8 lists fetal and litter incidences of all *variations* observed in the study; table R8b gives a consolidated summary of fetal and litter incidences of variations.

Comments: 10 mg/kg/day is the no adverse effect dose in this study. The sponsor states that 10 mg/kg/day may also have been teratogenic, since scoliosis was present in 2 litters (3 fetuses) in this group, and in only one litter (one fetus) in the control group. To be on the safe side one may consider the slight numerical increase in litter incidence to be a possible teratogenic effect. Taking this approach, 5 mg/kg/day is the NAED.

Table 1: Summary of Reproductive Data
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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
No. Dams Inseminated	24	24	24	24
No. Dams Pregnant	23	23	24	22
No. Dams Nongravid	1	1	0	2
Percent that Conceived	95.8	95.8	100.0	91.7
No. Dams that Died	0	0	0	0
No. Dams with Resorptions Only	0	0	0	0
No. of Litters	23	23	24	22
Total No. Corpora Lutea	325	332	348	287
Mean No. Copora Lutea/Pregnant Dam[NS]	14.1	14.4	14.5	13.0
Total No. Implantations	299	304	319	257
Mean No. Implantations/Pregnant Dam[NS]	13.0	13.2	13.3	11.7
Total No. Live Fetuses	286	286	304	239
Mean No. Live Fetuses/Pregnant Dam[NS,**]	12.4	12.4	12.7	10.9
Total No. Dead Fetuses	0	0	0	0
Mean No. Dead Fetuses/Pregnant Dam[NS,**]	0.0	0.0	0.0	0.0
No. of Dams with Resorptions	9	12	12	9
Total No. of Resorptions	13	18	15	18*
Mean No. Resorptions/Pregnant Dam[NS]	0.6	0.8	0.6	0.8
Mean Body Weight Live Fetuses (g)[*,**]	3.5	3.4	3.4	3.2
Sex Ratio Live Fetuses (M:F)	1.0:1.2	1.0:0.8	1.0:1.2	1.0:1.0
Group Mean Preimplantational Loss (%)[b,**]	7.3	8.3	8.3	12.8
Group Mean Postimplantational Loss (%)[c,**]	4.5	5.7	4.6	7.2

** $P \leq 0.01$

Table R7

Incidences of Abnormalities

	Incidence	Description
External Malformations:		
Control:	0/286 (0/23)	
Low:	1/286 (1/23)	1: Mandibular agnathia & Cleft Palatee (F3, L37)
Mid:	0/304 (0/24)	
High:	6/239 (5/22)*	2: Anasarca (F8, L85; F2, L86)
	(p=0.022)	2: Adactyly (F5, L78; F4, L84)
		1: Syndactyly (F2, L78)
		1: Thread Like Tail & Anal Atresia (F14, L90)
Visceral Malformations:		
Control:	1/142 (1/23)	1: Situs Inversus Complete (F8, L18)
Low:	1/141 (1/23)	1: Microphthalmia (F10, L27)
Mid:	0/152 (0/24)	
High:	6/116 (5/22)	4: Interventricular Septal Defect (F3, L74; F8, L77; F1,
	(p=0.083)	L78; F8, L84)
		2: Retroesophageal Subclevian Rt (F6, L84; F11, L85)
		1: Rt sided aortic arch (F1, L76)
		1: Vestigial Pulmonary Trunk (F8, L84)
Skeletal Malformations:		
Control:	2/144 (2/23)	1: Scoliosis (F6, L19)
		1; Ribs bent (Thoracic) (F6, L6
Low:	0/145 (0/23)	
Mid:	4/152 (3/24)	2: Scoliosis (F2, L64; F1 F3, L7)
	(p=0.125)	1: Ribs bent (Thoracic) (F8, L59)
High:	13/123 (7/22)	5: Scoliosis (F2 F9, L77; F4 F10, L84; F7 F8, L85;
	(p=0.058)	F8 F11, L89; F 4 F13, L93)
		1: Metacarpals Fused (F5 L85)
		1: Metacarpals Absent (F2, L78)
		1: Ribs bent (Thoracic) (F1, L73)
All Malformations:		
Control:	(3/23)	2: Skeletal (L6, L19)
		1: Visceral (L18)
Low:	(2/23)	1: External (L37)
		1: Visceral (L26)
Mid:	(3/24)	3: Skeletal (L59, L64, L71)
High:	(9/22)*	2: External (L86, L90)
	(p=0.037)	2: Skeletal (L89, L93)
		2: Visceral & Skeletal (L74, L77)
		3: All three (L78, L 84, L85)

Note: In the second column, pup and litter incidences are listed as 'pup (litter)'; in the 3rd column, 'n:' is the number of litters in which the abnormality listed was found; after the abnormality, the fetus/es and their litters in which the abnormality occurred are listed (Fn Fn, Ln). At the end the litter incidences of all malformations are given. Statistics used is fisher's exact test with the litter as the unit (s-rev).

Table R8

P&T: 90-513

U-70226E:A Segment II Teratology Study (Oral) in Rats (Repeat Study)

Table R8 Summary of the Incidences of Individual Variations

	U-70226E (mg/kg/day)			
	0.0	5.0	10.0	20.0
No Litters Examined	23	23	24	22[a]
No. Examined Grossly	286	286	304	239
No. Examined Viscerally	142	141	152	116
No. Examined Skeletally	144	145	152	123
Gross Variations Observed	No. Fetuses/No. Litters			
None Observed	-	-	-	-
Visceral Variations Observed				
Grade 0 Kidney	1/1	2/2	3/3	1/1
Hydroureter	0/0	2/2	3/3	1/1
Left Umbilical Artery	1/1	2/2	0/0	0/0
No Innominate	2/2	2/2	0/0	4/4
Skeletal Variations Observed				
Hyoid: Unossified	14/8	22/11	18/12	14/8
Interparietal: Unossified	0/0	0/0	0/0	1/1
Parietal(s): Incomplete Oss.	11/5	7/2	2/2	4/3
Interparietal: Incomplete Oss.	4/2	3/2	5/3	7/6
Supraoccipital: Incomplete Oss.	11/8	12/8	10/7	12/10
Squamosal(s): Incomplete Oss.	7/6	10/4	1/1	2/2
Zygoma(s): Incomplete Oss.	9/4	7/4	3/3	2/2
Frontal(s): Incomplete Oss.	4/2	0/0	0/0	0/0
Vertebrae: 25 Presacral	1/1	0/0	0/0	1/1
Vertebrae: Incomplete Oss.	0/0	1/1	0/0	3/3
Rib(s): Accessory[b]	1/1	0/0	0/0	8/6[c]
Rib(s): Rudimentary	4/3	1/1	5/3	1/1
Rib(s): 7th Cervical[b]	4/4	0/0	1/1	0/0[c]
Rib(s): Incomplete Oss.	0/0	2/1	1/1	0/0
Sternebrae: Other than #5/6 Incomplete Oss.	3/2	5/4	4/4	11/7
Sternebrae: Other than #5/6 Unossified	3/3	4/3	1/1	4/3
Sternebrae: #5/6 Unossified	56/21	53/17	66/21	60/21
Sternebrae: Lack of Apposition	0/0	0/0	1/1	1/1
Sternebrae: Bipartite[b]	0/0	0/0	0/0	4/3
Pube(s): Unossified[b]	0/0	0/0	2/2	4/4[c]
Ischia: Incomplete Oss.	0/0	0/0	2/1	1/1
Tibia(s): Incomplete Oss.	0/0	0/0	0/0	1/1
Fibula(s): Incomplete Oss	0/0	0/0	0/0	1/1
Femur(s): Incomplete Oss.	0/0	0/0	0/0	1/1
Metacarpal(s): Incomplete Oss.	0/0	0/0	0/0	1/1
Metatarsal(s): Incomplete Oss.	4/2	0/0	0/0	0/0

[a] Fetuses from only 21 of the 22 litters were examined viscerally.
[b] The Modified Jonckheere Ordered Alternatives for Dose Response was statistically significant, $p<0.05$.
[c] Statistically significantly different from the control group, $p<0.05$.
Individual fetuses may have more than one variation.
- = Not applicable Oss. = ossification

TR No.: 7224-94-027

Table R8b

P&T: 90-513
U-70226E: A Segment II Teratology Study (Oral) in Rats (Repeat Study)
Table 6: Summary of Variations

Observation	[illegible]	[illegible]	[illegible]	[illegible]
Fetuses:				
Gross	0/286(0.0)	0/286(0.0)	0/304(0.0)	0/239(0.0)
Visceral	4/142(2.8)	6/141(4.3)	3/152(2.0)	5/116(4.3)
Skeletal	74/144(51.4)	69/145(47.6)	85/152(55.9)	75/123(61.0)
Total[b]	78/286(27.3)	75/286(26.2)	88/304(28.9)	80/239(33.5)
Litters:				
Gross	0/23(0.0)	0/23(0.0)	0/24(0.0)	0/22(0.0)
Visceral	4/23(17.4)	6/23(26.1)	3/24(12.5)	5/21(23.8)[c]
Skeletal	21/23(91.3)	20/23(87.0)	23/24(95.8)	22/22(100.0)
Total[b]	22/23(95.7)	20/23(87.0)	23/24(95.8)	22/22(100.0)

[a]Data are: Number remarkable/Number examined (%).
[b]Fetuses with multiple variations were counted only once.
[c]Dam 91 had a litter of only one fetus which was examined grossly and skeletally only.

Segment II Teratology Study in the Rabbit: Dutch belted (Report # 7224/92/001)

4 groups of 16 does/group. After insemination, groups 2-4 were given 0.5, 1, and 2 mg/kg/day ibutl respectively by gavage, from days 6-18 of gestation; group-1 (control) received the vehicle; volume of fluid administered was 10 ml/kg in all cases. Doses were selected on the basis of the results of a dose range finding study, in which 1, 10, 40, and 100 mg/kg/day doses were tested, and doses ≥ 10 mg/kg/day resulted in deaths of all animals in these groups (*Note:* It is not clear why a dose of 4-5 mg/kg/day was not chosen as the highest dose for the present study.) Hysterotomy was performed on day 28 of gestation, and various reproductive parameters determined; body wts were determined on day 0, daily during the treatment period, and on day 28. All fetuses were weighed, measured crown to rump, and examined externally; all fetuses were examined for visceral as well as skeletal abnormalities.

Results:

Does:

Mortality: One doe from the mid dose group died on da 27 of gestation; the pathologist diagnosed the cause of death as toxemia of pregnancy.

Clinical signs: There were no dose related adverse clinical signs.

Body wt gain: There were no dose related adverse effects on wt gain for any time interval.

Hysterotomy Data: Table R9 shows the hysterotomy data. None of the reproductive parameters were adversely affected by treatment.

Fetuses:

Fetal wts and lengths: There was no drug related adverse effect on these parameters (Table R9).

Fetal abnormalities: Fetal *malformations* are listed in the table R10. Individual fetal *variations* are listed on table R11, and a consolidated summary of the incidences of variations is given in table R11b. Ibutilide in the rabbit was not teratogenic up to the highest dose tested. The litter incidences of skeletal variations and all variations were higher in the treatment groups; the difference between the high dose group and the control group, however, was s-ns (p=0.14, Fisher's exact test: s-rev).

Comments: Since the highest dose tested had no adverse effects on the does at all, it cannot be stated that the highest possible dose has been tested for teratogenicity in this species. Moreover, since there is no information about the bioavailability of the drug in this species, no comparison of exposure levels to the maximum exposure level in the clinical setting is possible. The results of this study, therefore, are not relevant to assessing the risk to a pregnant woman.

Table R9
P&T 90-503 (U-70,226E)
Summary and Analysis of Reproductive Data

	U-70,226E (mg/kg/day)			
	0	0.5	1.0	2.0
No. of Does that were Inseminated	14[a]	16	14[a]	16
No. of Does that Conceived	13	15	13[b]	14
Fertility Index %[ns]	92.9	93.8	92.9[b]	87.5
No. of Does that Died	0	0	1	0
No. of Does that Aborted	0	0	0[c]	0
No. of Does with Resorptions only	0	0	0[c]	0
No. of Does with Embryo/Fetal Loss	4	8	3[c]	7
No. of Litters (Live Fetuses)	13	15	12[c]	14
Total No. of Corpora Lutea	104	121	100[c]	124
Mean No. of Corpora Lutea/Preg. Doe[ns]	8.0	8.1	8.3[c]	8.9
Total No. of Live Fetuses	69	91	67[c]	93
Mean No. of Live Fetuses/Preg. Doe[ns]	5.3	6.1	5.6[c]	6.6
Proportion Live Fetuses[ns]	0.93	0.88	0.94[c]	0.90
Total No. of Dead Fetuses	0	0	0[c]	0
Total No. of Resorptions	5	12	4[c]	10
Mean No. of Resorptions/Preg. Doe[ns]	0.4	0.8	0.3[c]	0.7
Proportion Resorbed Fetuses[ns]	0.07	0.12	0.06[c]	0.10
Total No. of Implantations	74	103	71[c]	103
Mean No. of Implantations/Preg. Doe[ns]	5.7	6.9	5.9[c]	7.4
Mean Body Wt. of Live Fetuses[ns]	30.1	32.2	31.8[c]	32.2
Mean Fetal Crown-to-Rump Length (cm)[ns]	8.3	8.7	8.3[c]	8.6

[a] - Excludes does that were removed from the study because of accident, or pre-study death
[b] - Includes one doe that died pregnant
[c] - Excludes one doe that died pregnant
[ns] - Not statistically significant @ 5% level

Table R10

Incidences of Fetal Abnormalities

	Incidence	Description
External malformations:		
Control:	0/69 (0/13)	
Low:	0/91 (0/15)	
Mid:	1/67 (1/12)	1: Carpal Flexure Left (F3, L33)
High:	1/93 (1/14)	1: Multiple Abnormalities (F6, L60)
Visceral malformations:		
Control:	0/69 (0/13)	
Low:	0/91 (0/15)	
Mid:	1/67 (1/12)	1: Hydrocephalus (F2, L33)
High:	2/93 (2/14)	1: Multiple Abnormalities (F6, L60)
	(p=0.259)	1: Vestigial Lt. Carotid (F5, L64)
Skeletal malformations:		
Control	2/69 (1/13)	1: Sternebrae 4-5 fused (F6, L14)
		1: Basisphenoid malformed (F9, L14)
Low:	1/91 (1/15)	1: Scoliosis (F2, L17)
Mid:	0/67 (0/12)	
High:	1/93 (1/14)	1: Multiple malformations (F6, L
All Malformations:		
Control:	2/69 (1/13)	1: Skeletal (L14)
Low:	1/91 (1/15)	1: Skeletal (L17)
Mid:	2/67 (1/12)	1: External (L33)
		1: Visceral (L33)
High:	2/91 (2/14)	1: External (L60)
	(p=0.529)	1: Skeletal (L60)
		2: Visceral (L60; L64)

Note: In the second column, pup and litter incidences are listed as 'pup (litter)'; in the 3rd column, 'n:' is the number of litters in which the abnormality listed was found; after the abnormality, the fetus/es and their litters in which the abnormality occurred are listed (Fn Fn, Ln). At the end the litter incidences of all malformations are given. Statistics used is fisher's exact test with the litter as the unit (s-rev).

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P&T 90-503
U-70226E

Table R11 Fetal Variations Observed*

	Dosage Levels (mg/kg/day)			
Observations:	**0.0**	**0.5**	**1.0**	**2.0**
GROSS				
No. of Fetuses Examined (No. of Litters)	69(13)	91(15)	67(12)	93(14)
Albino	1(1)	3(3)	1(1)	0(0)
VISCERAL				
No. of Fetuses Examined (No. of Litters)	69(13)	91(15)	67(12)	93(14)
Accessory Left Subclavian	0(0)	1(1)	0(0)	0(0)
Left Carotid Arises from Innominate	1(1)	5(1)	2(2)	0(0)
Thoracic Cavity: Intermediate Portion of Diaphragmatic Lung Lobe, Absent	1(1)	3(3)	1(1)	1(1)
SKELETAL				
No. of Fetuses Examined (No. of Litters)	69(13)	91(15)	67(12)	93(14)
Hindpaw(s): Tali Unossified	2(2)	0(0)	1(1)	1(1)
Hyoid Body: Incomplete Ossification	1(1)	2(2)	1(1)	6(2)
Hyoid Body: Unossified	1(1)	0(0)	1(1)	2(2)

*Data given as the number of fetuses (litters) with the finding; individual fetuses may have more than one variation.

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U-70226E

Table R11 (cont.): Fetal Variations Observed (Continued)*

	Dosage Levels (mg/kg/day)			
Observations:	**0.0**	**0.5**	**1.0**	**2.0**
SKELETAL				
Hyoid Arch(es): Incomplete Ossification	3(3)	1(1)	0(0)	3(3)
Hyoid Arch(es): Unossified	0(0)	0(0)	1(1)	1(1)
Rib(s): 12th Rudimentary	1(1)	0(0)	0(0)	1(1)
Rib(s): Accessory	2(1)	11(7)	18(7)	19(6)
Skull: Frontal(s): Incomplete Ossification	1(1)	1(1)	0(0)	0(0)
Skull: Suture Bone	1(1)	1(1)	0(0)	1(1)
Skull: Parietal(s): Incomplete Ossification	0(0)	0(0)	1(1)	0(0)
Sternebra(e): #5 Unossified	10(6)	22(9)	5(2)	18(8)
Sternebra(e): Other than #5 Incomplete Ossification	0(0)	1(1)	2(2)	1(1)
Sternebra(e): Other than #5 Unossified	0(0)	2(1)	0(0)	0(0)
Sternebra(e): Accessory	0(0)	1(1)	0(0)	0(0)
Vertebra(e): 27 Presacral	0(0)	4(3)	5(5)	6(4)
Vertebra(e): 25 Presacral	1(1)	0(0)	0(0)	0(0)
Bone Island of Dorsal Skull Bone	0(0)	0(0)	0(0)	1(1)

*Data given as the number of fetuses (litters) with the finding; individual fetuses may have more than one variation.

Table R11b **Summary of Fetal Variations**

	Dosage Levels (mg/kg/day)			
Observations:	**0.0**	**0.5**	**1.0**	**2.0**
No. of Fetuses with Gross Variations/No. Examined (%)	1/69 (1.4)	3/91 (3.3)	1/67 (1.5)	0/93 (0.0)
No. of Fetuses with Visceral Variations/No. Examined (%)	2/69 (2.9)	8/91 (8.8)	3/67 (4.5)	1/93 (1.1)
No. of Fetuses with Skeletal Variations/No. Examined (%)	16/69 (23.2)	33/91 (36.3)	24/67 (35.8)	40/93 (43.0)
Total No. of Fetuses with Variations/No. Examined (%)	18/69 (26.1)	39/91 (42.9)	26/67 (38.8)	41/93 (44.1)
No. of Litters with Gross Variations/No. Examined (%)	1/13 (7.7)	3/15 (20.0)	1/12 (8.3)	0/14 (0.0)
No. of Litters with Visceral Variations/No. Examined (%)	2/13 (15.4)	4/15 (26.7)	3/12 (25.0)	1/14 (7.1)
No. of Litters with Skeletal Variations/No. Examined (%)	9/13 (69.2)	12/15 (80.0)	9/12 (75.0)	13/14 (92.9)
Total No. of Litters with Variations/No. Examined (%)	9/13 (69.2)	14/15 (93.3)	10/12 (83.3)	13/14 (92.9)

Segment III Peri-Postnatal Study in the Rat: Crl:CD[BR] (Report # 7224/92/046)

This study is not reviewed in detail, since this NDA is for a maximum of two doses for termination of atrial fibrillation. 5, 10, and 20 mg/kg/day ibutilide were administered to groups of pregnant dams (n=24/group) from day 15 of gestation through post partum day 20; dams were weighed periodically during pregnancy and the lactation period; no. of live, dead, and abnormal pups in each litter were recorded; live pups were weighed on days 0, 4, and 21; all pups that died were necropsied at death, and the survivors were necropsied on day 20.

Results: (From the sponsor's summary):

Dams: There were no adverse effects on dams at any dose level; litter size was not affected by treatment.

Pups:

Wt & viability: Mean pup wt, and pup viability were not affected by treatment.

Visceral anomalies: Examination of pups on day 20 post partum showed that 0, 2(1), 4(3), and 5(4) pups(litters) in groups 1(control)-4 respectively had hydronephrosis; C v 4 (for litter incidence) just misses s-s (p=0.055, fisher's exact test, s-rev); Peto's exact trend test is s-s (p=0.02; s-rev). In the high dose groups, 2(2) had hydrocephaly, and 1(1) had anophthalmia. These abnormalities were not seen in any litters in the other three groups. Considering all abnormalities together, 7(6) (pups(litters)) in the high dose group had visceral abnormalities; C v 4 (litter incidence) is s-s (p=0.021, fisher's exact test; s-rev)

aments: The fetal no adverse effect dose is considered to be 5 mg/kg/day by the sor; the litter incidence of hydronephrosis in this group (4.4%) is within the range for istorical control from the lab (in 3 studies: highest incidence: (8.7%); Mean: (4.5%)), but the litter incidence in the mid dose group (12.5%)) is outside this range.

§4: Mutagenicity Studies:

Ames test: (Report # 7227/89/032).

TA97, TA98, TA100, TA102, and TA1535 strains of Salmonella typhimurium were used. Up to 5000 µg/plate of ibutilide was tested in the presence and absence of S-9, which was obtained commercially and stored in liquid N_2 in small aliquots.

Results: Table M1 shows the detailed results, the drug was not mutagenic in any strain with or without metabolic activation.

AS52 /XPRT Mammalian Cell Forward Gene Mutation Assay: (Report #7228/90/028; study done by Pharmakon Res Int at their lab in Waverly, PA)

Note: According to the sponsor, this cell line is a genetically engineered line derived from Chinese Hamster Ovary (CHO), and is more sensitive to chromosome breakage than the CHO cell line. Ibutilide was tested at concentrations up to 1000 µg/ml with S-9, and at concentrations up to 250 µg/ml without S-9; these concentrations were chosen based on the results of preliminary cytotoxicity tests.

Table M1

TABLE 2. Raw plate counts showing lack of mutagenicity of U-70,226E toward strains TA-97,TA-98, TA-100, TA-102 and TA-1535. U-70,226E was dissolved in DMSO at 50 mg/ml(highest dose) and appropriate serial dilutions were made and incorporated into top agar(see text). Each value represents a single independent plate. See legend to TABLE 1 for positive control information, i.e. identity and concentrations.

U-70,226E	TA-97		TA-98		TA-100		TA-102		TA-1535	
RAW DATA	+S-9	-S-9	+S-9	-S-9	+S-9	-S-9	+S-9	-S-9	+S-9	-S-9
Positive control										
Vehicle control										
Dose 5,000 ug/plate										
Dose 2,500 ug/plate										
Dose 1,250 ug/plate										
Dose 625 ug/plate										

* Strain specific positive control compounds were used at appropriate concentrations based on dose response data (TR7268/86/066 or TR7268/87/009) as follows: 2-AA (with activation at 5ug/pl --TA-102 and at 1ug/pl in the other 4 strains), 2-NF(10 ug/pl--TA98 and TA-100 without activation), NaN_3 (2 ug/pl without activation in TA-1535), CHP (100 ug/pl without activation in TA-102), Dexon (10 ug/pl without activation in TA-97).

Results: Tables M2 (b) and M2(c) show the mutant frequencies in plates containing different concentrations of ibutl in the absence of S-9 in the presence of S-9 respectively. Table M2 (a) shows the mutant frequencies with negative and positive controls. Ibutilide up to the concentrations tested was not mutagenic to this cell system.

Unscheduled DNA Synthesis (UDS) Assay in Rat Hepatocytes: (Report # 7227/89/079)

Rat hepatocytes were placed in monolayer cultures, and incubated in the presence of ^3H thymidine, and different concentrations of ibutilide, a positive control, and a negative control for 18-20 hours; then slides were prepared and two slides/dose and 30 cells/slide were scored for grain counts in nuclei, & cytoplasms; net no. of grains/nucleus (NG) were calculated. The criterion for positivity in this test is stated to be: An NG count of ≥ 5/nucleus and % cells in repair ≥10% (a cell being considered in repair if it has ≥ 5 NG). *Note:* the rationale for choosing ≥ 5 NG as the criterion for considering UDS to have occurred in a cell is not given; nor is the reason for both the mean NG to be ≥ 5, and the % of cells in repair to be ≥ 10%, as the criterion for a positive test result is given. But it is stated that the criteria were set pre test)

Results: The results are shown in tab M3. The assay was negative up to 100 µg/ml drug concentration; at concentrations of 1000 µg/ml and above, the drug was toxic to the cells and the slides were not scorable. At concentration of 300 µg/ml and 500 µg/ml(used only in 1/2 tests), more than 10% cells were in repair according to the criterion of 5 NG/nucleus. But at these concentrations, the cytoplasmic grain count was reduced below negative control; and it is stated that at 500 µg/ml, the cytoplasm showed severe morphological changes indicative of toxicity. The sponsor's explanation that reduction in the cytoplasmic grain count artificially led to positive values of NG/nucleus (NG=(nuclear grain count)-(cytoplasmic grain count in an equal area)) seems reasonable.

Comments: The conclusion that up to the dose of 300 µg/ml, (500 µg/ml was tested only in one of the tests) the drug did not increase UDS seems valid.

Micronucleus test in mouse bone marrow: (Report # 7227/89/074; Study site,

Based on a preliminary range finding study in which deaths occurred at doses ≥ 250 mg/kg of the drug given i/p, the highest dose used in the test was 175 mg/kg.

(15m+15f)/group in groups 1-4, 5m+5f in group-5; groups 2-4 were given 50, 100, and 175 mg/kg ibutilide i/p respectively; group-1 (control) received vehicle (distilled water), and group-5 received 0.5 mg/kg triethylenemelamine (TEM) i/p; 5m+5f in groups 1-4 were sacrificed at 30, 48, and 72 hours post dose; the bone marrow slides prepared for examination; group-5 animals were sacrificed at 30 hours. The slides were scored blinded. 1000 polychromatic erythrocytes (PCEs)/animal were scored, and the number of micronucleated PCEs(MNPCEs)/1000 PCEs determined.

Table M2a

PH 314-UP-005-88
Amended Final Report
U-70,226E

AS52/XPRT Mammalian Cell Forward Gene Mutation Assay
Mutagenicity Data - Control Cultures ±S9

Compound	µg/ml	S9 (±)	Relative Survival[a] (%)	Total No. of Mutants (5 plates)	Cloning Efficiency (%)	Mutant Frequency (mutants/10^6 clonable cells)	Average Mutant Frequency
Untreated	0	-	95.41	14	66.67	21.00	
Untreated	0	-	104.59	18	63.50	28.35	24.67
Untreated	0	+	68.09	29	61.33	47.28	
Untreated	0	+	72.38	17	69.33	24.52	35.90
DMSO[b]	10.0	-	84.00	11	74.17	14.83	
DMSO	10.0	-	88.07	7	43.83	15.97	15.40
DMSO	10.0	+	67.05	7	74.33	9.42	
DMSO	10.0	+	85.83	24	48.00	50.00	29.71
EMS	200	-	67.69	76	35.00	217.14	
EMS	200	-	65.65	107	40.17	266.39	241.77**
DMN	100	+	42.81	142	30.50	465.57	
DMN	100	+	40.37	64	33.50	191.04	328.31**

[a]Absolute cloning efficiency = 81.75%.
[b]µl/ml.
**Significant increase ($p<0.01$; Snee and Irr, 1981).

Pooled negative control cultures: $\bar{x}$ = 26.42 ± 14.93 (1SD)
$2\bar{x}$ = 52.84
$\bar{x}+3\sigma$ = 56.42
95% confidence interval = 56.28

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U-70,226E

AS52/XPRT Mammalian Cell Forward Gene Mutation Assay
Mutagenicity Data - Treated Cultures -S9

Compound	µg/ml	Relative Survival[a] (%)	Total No. of Mutants (5 plates)	Cloning Efficiency (%)	Mutant Frequency (mutants/10^6 clonable cells)	Average Mutant Frequency
U-70,226E	10.0	83.59	14	63.67	21.99	
U-70,226E	10.0	81.75	14	67.00	20.90	21.44
U-70,226E	25.0	82.57	29	59.17	49.01	
U-70,226E	25.0	86.44	5	60.00	8.33	28.67
U-70,226E	50.0	80.94	10	54.50	18.35	
U-70,226E	50.0	81.69	20	62.33	32.09	25.22
U-70,226E	100	83.18	5	69.33	7.21	
U-70,226E	100	85.63	13	58.50	22.22	14.72
U-70,226E	150	58.10	34	62.33	54.55	
U-70,226E	150	74.21	12	69.83	17.18	35.86
U-70,226E	200	82.16	14	67.00	20.90	
U-70,226E	200	60.16	19	66.17	28.72	24.81
U-70,226E	250	57.08	18	64.67	27.84	
U-70,226E	250	62.79	11	63.75	17.25	22.54

[a]Absolute cloning efficiency = 81.75%.

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PH 314-UP-005-88
Amended Final Report
U-70,226E

AS52/XPRT Mammalian Cell Forward Gene Mutation Assay
Mutagenicity Data - Treated Cultures +S9

Compound	µg/ml	Relative Survival[a] (%)	Total No. of Mutants (5 plates)	Cloning Efficiency (%)	Mutant Frequency (mutants/10^6 clonable cells)	Average Mutant Frequency
U-70,226E	25.0	80.94	24	49.17	48.81	
U-70,226E	25.0	84.00	9	59.50	15.13	31.97
U-70,226E	50.0	78.90	9	61.83	14.56	
U-70,226E	50.0	76.25	11	58.00	18.97	16.76
U-70,226E	100	89.50	12	50.83	23.61	
U-70,226E	100	76.86	32	56.83	56.30	39.96
U-70,226E	250	69.93	9	85.83	10.49	
U-70,226E	250	68.09	4	74.33	5.38	7.93
U-70,226E	500	57.49	13	78.67	16.53	
U-70,226E	500	63.00	9	63.33	14.21	15.37
U-70,226E	750	67.48	7	72.17	9.70	
U-70,226E	750	65.44	5	80.00	6.25	7.97
U-70,226E	1000	55.05	15	73.50	20.41	
U-70,226E	1000	56.07	9	64.50	13.95	17.18

[a]Absolute cloning efficiency = 81.75%.

TABLE 1 . .TS OF THE IN VITRO UDS ASSAY WITH U-70,226E

TREATMENT	DOSE (ug/ml)	FIRST EXPERIMENT N	MEAN NUC	MEAN CYT	MEAN N.G.	S.E.	MEDIAN N.G.	% IR	SECOND EXPERIMENT N	MEAN NUC	MEAN CYT	MEAN N.G.	S.E.	MEDIAN N.G.	% IR
Medium	0	2	17.19	28.30	-11.11	0.02	-12.84	0.0	2	20.44	34,06	-13.62	0.50	-12.84	0.0
U-70,226E	1	2	12.66	24.66	-11.98	1.03	-10.70	0.0	-	N.T.					
	3	2	17.67	30.87	-13.20	1.36	-11.77	0.0	2	22.57	38.63	-15.96	0.05	-18.19	1.7
	10	2	14.37	25.50	-11.13	2.53	-10.70	1.7	2	18.33	32.78	-14.44	1.00	-12.84	1.7
	30	2	22.02	31.42	-9.40	1.66	-9.63	6.7	2	18.71	31.03	-12.32	4.16	-10.70	1.7
	100	2	18.44	28.30	-9.86	0.84	-8.56	3.3	2	21.36	31.87	-10.50	2.84	-8.56	6.7
	300	2	17.03	18.23	-1,19*	2.87	-2.14	23.3§	2	15.27	17.96	-2.69	3.62	-5.35	21.7
	500	-	N.T.						2	15.23	11.95	3.28*§	3.67	2.14	35.0§
	1000	-	TOXIC						-	N.T.					
	3000	-	TOXIC						-	N.T.					
2-AAF	0.1 ug/ml	2	97.08	38.25	58.83	4.37	62.06	100.0	2	77.18	33.67	43.51	9.88	41.73	100.0

= Number of slides scored per dose.
UC = Nuclear grain count.
YT = Maximum cytoplasmic grain count.
.G. = Net grains/nucleus.
IR = Percentage of cells in repair.
.E. = Standard error of the mean N.G. (slide-to-slide variation).
.T. = Not tested at this concentration.
= Mean of N.G. data (or ranked N.G. data) significantly > medium control mean ($p<0.05$).
= Statistically significant dose response ($p<0.05$).
-AAF = 2-Acetylaminofluorene, positive control compound.
)XIC = Cytotoxic dose, slides not scorable.
search Notebook 21701, experiments CI and CK, study 88-430, scored by SK Wiser.

Results:
Animals in groups 2-4 exhibited various clinical signs of toxicity (decreased body tone, abnormal gait, piloerection etc; the high dose group also exhibited writhing). Mean ± SD of MNPCEs/1000 PCEs are shown below; n=10 in each case.

Group	30 hours	48 hours	72 hours
Vehicle Control	0.60±0.70	0.00±0.00	0.40±0.70
50 mg/kg	0.50±0.97	0.50±0.71	0.90±1.20
100 mg/kg	0.20±0.42	0.60±0.70	1.00±1.33[ns]
175 mg/kg	0.40±0.84	0.60±0.52[1]	0.80±1.03
TEM	40.70±9.11**		

Note: "**", p<0.01; "1", according to the sponsor, since the SD in the vehicle group at 48 hours was 0, t-test cannot be done, and it is stated that mean no. of MNPCEs in the dosed groups is within the historical range; at 72 hours, in the 100 mg/kg group in which the mean no. of MNPCEs is the highest, the difference from control is s-ns (p=0.113, one tailed t-test, s-rev).

Comments: Ibutl up to 175 mg/kg i/p (which was the highest testable dose) did not cause a s-s increase in the proportion of MNPCEs.

Micronucleus test in mouse bone marrow with Ibutilide containing
(Study no. 7228-94-044, in amendment # 099 to

Doses for this study were based on the results of a dose range finding study in which animals that received ≥250 mg/kg of ibutl-u /p died, and 3/6 animals that received 125 mg/kg had convulsions and irregular breathing that lasted for approximately 40 minutes post dose.

15/sex/group in groups 1-4, and 5/sex in group-5; groups 2-4 received 36, 90, and 180 mg/kg ibutl-u i/p respectively; group-1(C) received vehicle; and group-5(P) received 1 mg/kg triethylenemelamine (TEM) i/p. 5/sex/group from groups 1-4 were sacrificed at 24, 48, and 72 hours, all group-5 (P) animals were sacrificed at 24 hours. Bone marrow slides from each animal were prepared and scored blind for the number of MNPCEs/1000 PCEs; 1000 PCEs/animal were counted.

Results:
Some animals in the high dose group had convulsions, but recovered 30 minutes post dose. Mean±SD of MNPCEs/1000 PCEs are shown below; n=10 in each case. The sponsor has analyzed males and females separately, but that reduces the power of the test to detect a difference as significant (In the study with ibutilide reviewed above, the sponsor analyzed the results after combining the data from males and females in each group).

Group	24 hours	48 hours	72 hours
Vehicle Control	0.5±0.527	0.4±0.516	0.2±0.422
36 /mg/kg	0.2±0.422	0.6±0.843[2]	0.6±0.516[*4]
90 mg/kg	0.7±0.675[1]	0.5±0.527[3]	0.4±0.516[5]
180 mg/kg	0.5±0.527	0.3±0.483	0.5±0.527[6]
TEM	66.2±7.349[***]		

Note: [***], p<0.001; [1 2 3 4 5 6] all p values given below are from one tailed t-tests (s-rev); [1] ns (p=0.235); [2] ns (p=0.265); [3] ns (p=0.337); [4] s-s (p=0.037235); [5] ns (p=0.1.8); [6] ns (p=0.088).

Comments: Except for the low dose group at 72 hours, which had a s-s increase in MNPCEs/1000 PCEs compared to control (one tailed test is used, as it is only the s-s of the increase that one is interested in), the results in all other cases were s-ns compared to control, and the high dose group value was ≤ control value at 24 and 48 hours. Since at 72 hours, the increase in the high and mid dose groups was s-ns, the increase in the low dose group is biologically not relevant. Therefore it can be inferred that micronucleus test with ibutilide containing ie degradation product which is formed during heat sterilization of ibutilide solution) up to the highest testable dose is negative.

§5: Hemolysis and Plasma Compatibility test with Human Blood:

- **Hemolysis:** (Report # 7236/89/002)
  25 mg/ml, 2.5 mg/ml, 1.25 mg/ml and 0.125 mg/ml ibutl formulations were tested for hemolysis at drug solution/blood ratios of: 24:1, 4:1, and 1:1 each. The sponsor's estimate is that in the worst case scenario (bolus administration in a small vein which could give a maximum drug infusion rate of ≈ 24 ml/min and a minimum blood flow rate of 6 ml/min) drug/blood ratios of 4:1 could be attained.
  Results: At the drug solution/blood ratios tested: 25 mg/ml ibutl produced 52%, 5.85%, and 1.03% hemolysis; 2.5 mg/ml produced 1.55, 0.23, and 0.14% hemolysis; 1.25 mg/ml produced 0.9, 0.19, and 0.28% hemolysis; hemolyses results for 0.125 mg/ml were similar to those for 1.25 mg/ml. Comments: The formulation to be marketed will contain 1 mg/ml ibutilide; in the worst case scenario estimated by the sponsor, 0.3% of < 6 ml blood in a patient may be hemolyzed.

- **Plasma compatibility:** (Report # 7256/89/042)
  Solubility, precipitation of plasma proteins, and platelet aggregation were studied in mixtures of various concentrations of ibutl formulation and plasma/platelet rich plasma (for studying platelet aggregation) in drug-solution/plasma ratios of ≈1:10 .

  Results:
  Solubility: The drug was soluble in platelet rich plasma (PRP) up to a final concentration of 9 mg/ml.
  Protein precipitation: There was no protein precipitation up to a final drug concentration of 5 mg/ml in the formulation-plasma mixture, but there was some turbidity (probably due to plasma lipid separation as suggested by the sponsor, since drug solubility in plasma is 9 mg/ml, and the turbidity therefore could not be due to drug precipitation). *At 1 mg/ml,* there was no turbidity.

Platelet aggregation: At final concentrations ≤ 0.5 mg/ml, there was no indication of platelet aggregation in PRP; at a final concentration of 2.5 mg/ml, transmittance increase began at 2 min and was nearly complete at 20 min (in the case of ADP, the positive control, transmittance increase was complete within two minutes). Microscopic examination of plasma showed no platelet aggregation but platelets appeared swollen, and the sponsor's conclusion that transmittance increase was due to platelet lysis seems reasonable.

§5: Venous irritation study in the rabbit:

In six rabbits one ear was injected perivenously with .05 ml of 2.5 mg/ml of the drug and the other with .05 ml of either vehicle, 0.9% NaCl, or 65 mg/ml of sodium pentobarbital solution (positive control). Six other rabbits had one ear injected in a similar manner with 25 mg/ml of the drug and the other ear with the same controls as mentioned earlier.

The ears were clinically examined and their thicknesses measured daily for eight days; at the end of that time histopathology of the injection site was done.

Results: Neither 2.5 mg/ml of the drug nor the vehicle produced any gross or histopathological signs of tissue irritation. (25 mg/ml ibutilide was moderately irritating, but it is stated to be less irritating than the positive control.

Pritam Gill-Kumar

Pritam Gill-Kumar, M.D.
9/28/95

Attachment: Annotated Proposed Package Insert

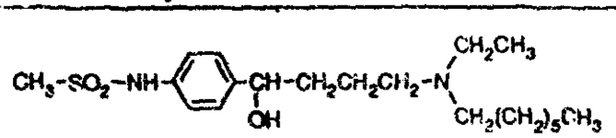
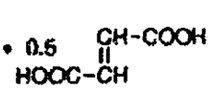
cc: Original (NDA, IND)
HFD 110
HFD 110/CSO
HFD 345/G.W. James
HFD 502
CSO 10/16/95

NDA # 20,491

Attachment

ANNOTATED PROPOSED PACKAGE INSERT

The proposed package insert has been annotated to the submission volume and page of the application summary and technical sections (eg, volume 1.18, page 5/1/10). References to individual study reports appear within brackets in bold print in the text (eg, [6.3] in the Clinical Pharmacology section refers to reference no. 3 in Item 5).

DRAFT PACKAGE INSERT	Location in Summary and Technical Sections
CORVERT™ Injection **(brand of ibutilide fumarate injection)** **For intravenous infusion only**	
DESCRIPTION	
CORVERT Injection is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.067 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection.	1.18, 5/1/109; 1.1, 2/1/57 1.2, 3/1/7
CORVERT Injection is an isotonic, clear, colorless aqueous solution.	1.2, 3/1/9
Ibutilide fumarate has one chiral center, and exists as a racemate of the (+) and (-) enantiomers.	1.2, 3/1/2
The chemical name for ibutilide fumarate is N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is $C_{22}H_{36}N_2O_3S$ and its molecular weight is 442.62.	1.2, 3/1/2
Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower.	1.2, 3/1/3
The structural formula is represented below:	
 • 0.5  **Ibutilide Fumarate**	1.2, 3/1/2

CLINICAL PHARMACOLOGY **Mechanism of Action**: CORVERT Injection prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness in vivo **[5.3-5.5, 5.13-5.15, 5.17-5.20, 5.23-5.28]**. Voltage clamp studies indicate that CORVERT Injection, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which most other class III antiarrhythmics act **[5.6-5.10, 5.12]**.	1.18, 5/1/109; 1.1, 2/1/57
The antiarrhythmic effects of CORVERT Injection are thought to be primarily due to these class III electrophysiologic properties, ie, prolongation of atrial and ventricular action potential duration and refractoriness. **[5.17-5.20, 5.23, 5.26-5.28]**. In humans, the predominant electrophysiologic property of CORVERT Injection is demonstrated by prolongation of effective refractory periods in atrial and ventricular muscle.	1.18, 5/1/109; 1.1, 2/1/59
Hemodynamics: When CORVERT Injection was given intravenously to animals at doses greater than ten times the human dose, mild, negative inotropic effects were observed (less than 8% decrease in left ventricular contractility) **[5.43]**. A study of hemodynamic function in patients stratified for ejection fractions (greater than or equal to 35% and less than 35%) demonstrated no significant effects on cardiac output, mean pulmonary arterial pressure, or capillary wedge pressure at doses up to 0.03 mg/kg.	1.18, 5/1/184; 1.1, 2/1/60 1.52, 8/1/469; 1.1, 2/1/112
Pharmacology: CORVERT Injection produces mild slowing of the sinus rate and atrioventricular conduction. CORVERT Injection produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship of plasma concentration to antiarrhythmic effect, CORVERT Injection produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity **[6.3, 8.11, 8.12]**. (See WARNINGS for relationship between QTc prolongation and torsades de pointes-type arrhythmias.) In a study in healthy volunteers, **[6.3, 6.4, 8.12]** intravenous infusions of CORVERT Injection resulted in prolongation of the QT intervals that were directly correlated with ibutilide plasma concentrations during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was demonstrated. The maximum effect was a function of both the dose of CORVERT Injection and the infusion rate **[6.3]**.	1.52, 8/1/474 1.52, 8/1/461; 1.1, 2/1/141 1.42, 6/1/40; 1.1, 2/1/91 1.42, 6/1/40 1.42, 6/1/40

Pharmacokinetics: After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a multi-exponential fashion. The pharmacokinetics of ibutilide are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg) and a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers **[6.2, 6.5, 6.6, 6.7]**. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation **[6.1, 6.2, 8.15, 8.16]**. The elimination half-life averages about 6 hours (typically ranges from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT Injection over the dose range of 0.01 mg/kg to 0.10 mg/kg **[6.1, 6.3]**. The enantiomers of ibutilide fumarate have pharmacokinetic properties similar to each other and to ibutilide fumarate **[6.5, 6.6, 6.7]**. The pharmacokinetics of CORVERT Injection in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, patient age, sex, or the concomitant use of digoxin, calcium channel blockers, or beta blockers **[6.1, 6.2]**.	1.42, 6/1/19; 1.1, 2/1/90 1.42, 6/1/25 1.42, 6/1/31 1.42, 6/1/19 1.42, 6/1/38 1.42, 6/1/36 1.42, 6/1/37 1.42, 6/1/39
Elimination: In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [^{14}C]ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (19%) was recovered in the feces **[6.6]**. **Metabolism:** Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω-oxidation followed by sequential β-oxidation of the heptyl side chain of ibutilide. These metabolites have no activity or weak class III activity relative to ibutilide **[6.6]**. **Distribution:** Ibutilide exhibits moderate plasma protein binding (41% bound) over the concentrations achieved in clinical studies, and, therefore is not expected to displace other drugs bound to plasma proteins **[5.130]**. Ibutilide is rapidly and extensively distributed extravascularly as evidenced by the large volume of distribution **[6.1–6.7, 8.15, 8.16]**.	1.42, 6/1/34; 1.1, 2/1/90 1.42, 6/1/31; 1.1, 2/1/90 1.42, 6/1/35 1.1, 2/1/90 1.42, 6/1/19 1.42, 6/1/25

Clinical Studies: A multicenter, placebo-controlled study of 242 non-postsurgical patients was conducted to assess the response to a single 1-mg dose of CORVERT Injection versus placebo and to allow a second infusion (either 0.5 or 1 mg) to be administered to those who did not convert following the initial dose. These results are discussed below [8.14].	1.52, 8/1/227; 1.1, 2/1/116
Atrial Flutter: Following administration of placebo, 1 of 41 (2.4%) patients with atrial flutter cardioverted to sinus rhythm. In contrast, 19 of 80 (24%) patients with atrial flutter converted within 20 minutes of starting a single, 10-minute, 1-mg infusion of CORVERT Injection. Administration of a second dose of 0.5 mg to those patients who did not respond to the first dose resulted in an overall cumulative conversion rate of 54% (21 of 39 patients), while administration of a second dose of 1 mg resulted in an overall cumulative conversion rate of 71% (29 of 41 patients). Consequently, the sequential administration of 1 mg followed by 0.5 mg, started 20 minutes apart, results in an overall conversion rate in patients with atrial flutter that is not statistically different than the sequential administration of two 1-mg doses of CORVERT Injection (54% and 71%, respectively) [8.14].	1.52, 8/1/227; 1.1, 2/1/116
Atrial Fibrillation: Following administration of placebo, 1 of 40 (2.5%) patients with atrial fibrillation cardioverted to sinus rhythm. In contrast, 16 of 81 (20%) patients with atrial fibrillation converted within 20 minutes of starting a single, 10-minute, 1-mg infusion of CORVERT Injection. Administration of a second 10-minute infusion of 0.5 mg to those patients who did not respond to the first dose resulted in an overall cumulative conversion rate of 35% (14 of 40 patients), while administration of a second 1-mg dose resulted in an overall cumulative conversion rate of 27% (11 of 41 patients). Accordingly, the sequential administration of 1 mg followed by 0.5 mg, started 20 minutes apart, results in an overall conversion rate in patients with atrial fibrillation that is not statistically different from the sequential administration of two 1-mg doses (35% and 27%, respectively) [8.14].	1.52, 8/1/227; 1.1, 2/1/116
INDICATIONS AND USAGE CORVERT Injection is indicated for the rapid conversion of atrial fibrillation or atrial flutter to sinus rhythm.	1.52, 8/1/240; 1.1, 2/1/126; 1.1, 2/1/152
CONTRAINDICATIONS CORVERT Injection is contraindicated in patients who have previously demonstrated hypersensitivity to ibutilide fumarate or any of the other product components. CORVERT Injection is contraindicated in patients who have previously demonstrated torsades de pointes.	1.52, 8/1/220

WARNINGS Proarrhythmia:	
Like other antiarrhythmic agents, CORVERT Injection can induce or worsen ventricular arrhythmias in some patients. This may have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia that develops in the setting of a prolonged QT interval, may occur because of the effect CORVERT Injection has on cardiac repolarization. In general, with drugs that prolong the QT interval, the risk of torsades de pointes is thought to increase progressively as the QT interval is prolonged and may be worsened with bradycardia and a varying heart rate. Also, the frequency of proarrhythmia is higher in women than men [8.30]. In the more recent clinical trials conducted in patients with atrial fibrillation and atrial flutter, those with QTc intervals > 440 msec were not allowed to participate [8.14].	1.52, 8/1/484-91; 1.1, 2/1/151 1.52, 8/1/220; 1.1, 2/1/142 1.52, 8/1/200 1.52, 8/1/202
During clinical trials, 2.4% of patients with atrial flutter or atrial fibrillation treated with CORVERT Injection developed sustained polymorphic ventricular tachycardia requiring cardioversion; 4.0% experienced nonsustained polymorphic ventricular tachycardia. In these clinical trials, all initial episodes of polymorphic ventricular tachycardia occurred during or within 30 minutes of an infusion. Management of the polymorphic ventricular tachycardia included magnesium sulfate infusions and cardiac pacing. Nonsustained monomorphic ventricular tachycardias occurred in 4.0% of the patients treated with CORVERT Injection 2.7% were possibly related to drug. (See Adverse Reactions.)	1.52, 8/1/449; 1.1, 2/1/135 1.52, 8/1/490
Proarrhythmic events must be anticipated and proper equipment, such as a defibrillator, and medication for treatment of sustained ventricular tachycardias must be available during administration of CORVERT Injection. Before treatment with CORVERT Injection, plasma hypokalemia and hypomagnesemia should be corrected to reduce the potential for proarrhythmia.	1.52, 8/1/220; 1.1, 2/1/152
PRECAUTIONS **General Precautions:**	
Antiarrhythmics: Class Ia antiarrhythmic drugs (Vaughan Williams Classification), such as disopyramide, quinidine, and procainamide, and other class III drugs, such as amiodarone and sotalol, should not be given concomitantly with CORVERT Injection because of their potential to prolong refractoriness.	1.59, 8/8/116 1.68, 8/17/133; 1.1, 2/1/151
Other Drugs that prolong the QT interval: The potential for proarrhythmia may increase with the administration of CORVERT Injection to patients who are being treated with drugs that prolong the QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and antihistamine drugs (H1 receptor antagonists).	1.52, 8/1/487; 1.1, 2/1/143
Laboratory Test Interactions: None known.	

Drug Interactions: Digoxin: Supraventricular arrhythmias may mask the cardiotoxicity associated with excessive digoxin levels. Therefore, cardioversion with CORVERT Injection may be hazardous in patients whose plasma digoxin levels are above the usual therapeutic range. Acute dosing with CORVERT Injection does not affect serum digoxin levels [8.13, 8.15, 8.16]. The pharmacokinetics of CORVERT Injection are not different in patients treated concomitantly with digoxin when compared with those who were not concomitantly treated [6.1, 6.2]. Calcium channel blocking agents: The pharmacokinetics of CORVERT Injection are not different in patients treated concomitantly with calcium channel blocking agents when compared with those who were not concomitantly treated [6.1, 6.2]. Beta Adrenergic Blocking Agents: The pharmacokinetics of CORVERT Injection were not different in patients treated concomitantly with beta adrenergic blocking agents when compared with those who were not concomitantly treated [6.1, 6.2].	1.52, 8/1/254; 1.1, 2/1/131 1.42, 6/1/39; 1.1, 2/1/91 1.42, 6/1/39 1.42, 6/1/39
Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been conducted to determine the carcinogenic potential of CORVERT Injection; however, it was not mutagenic in a battery of mutagenicity assays including the Ames assay, mammalian cell forward gene mutation assay, unscheduled DNA synthesis assay, and mouse micronucleus assay [5.77–5.81]. Similarly, no drug-related effects on fertility or mating were noted in a reproductive study in rats [5.69].	1.18, 5/1/380; 1.1, 2/1/69 1.18, 5/1/76; 1.1, 2/1/67 1.18, 5/1/75 1.18, 5/1/321; 1.1, 2/1/68
Pregnancy, Labor, and Delivery: Pregnancy Category CORVERT Injection was teratogenic and embryocidal in reproduction studies in rats. These findings indicate that the potential risk to the fetus must be considered when anticipating treatment of pregnant women or women of child-bearing potential.	1.18, 5/1/75; 1.1, 2/1/67 1.18, 5/1/324
Nursing Mothers: The excretion of ibutilide into breast milk has not been studied; accordingly, breastfeeding should be discouraged during CORVERT Injection therapy. **Pediatric Use:** Clinical trials with CORVERT Injection in patients with atrial fibrillation and atrial flutter did not include anyone under the age of 18.	

Use in Elderly Patients: No age-related pharmacokinetic differences were observed in a Phase II dose-response trial conducted in patients 25 to 82 years old (mean = 64) in which pharmacokinetic parameters were compared for patients less than 65 with those of patients 65 years and older [6.1]. **Use in Patients with Hepatic or Renal Dysfunction:** The safety, effectiveness, and pharmacokinetics of CORVERT Injection have not been established in patients with hepatic or renal dysfunction. However, it is unlikely that dosing adjustments would be necessary in patients with compromised renal or hepatic function based on the following considerations: 1) CORVERT Injection is indicated for rapid intravenous therapy (duration ≤ 30 minutes) and is dosed to a known, well-defined pharmacologic action (termination of arrhythmia) or to a maximum of two 10-minute infusions; 2) less than 10% of the dose of CORVERT Injection is excreted unchanged in the urine; 3) the hepatic metabolic clearance of ibutilide is perfusion-rate limited [6.5, 6.6]; and 4) drug distribution appears to be one of the primary mechanisms responsible for termination of the pharmacologic effect. In 285 patients with atrial fibrillation or atrial flutter who were treated with CORVERT Injection, the clearance of ibutilide was independent of renal function as measured by creatinine clearance (range 21 to 140 mL/min), and also independent of hepatic function, as measured by serum ALT and AST [6.2].	1.42, 6/1/36; 1.1, 2/1/91 1.42, 6/1/?1 1.42, 6/1/19 1.42, 6/1/38; 1.1, 2/1/91 1.42, 6/1/37
ADVERSE REACTIONS CORVERT Injection was generally well tolerated in clinical trials. Of the 375 patients who received CORVERT Injection, 86 (23%) reported medical events related to the cardiovascular system, including sustained polymorphic ventricular tachycardia (2.4%) and nonsustained polymorphic ventricular tachycardia (4.0%). Other clinically important adverse events with uncertain relationship to CORVERT Injection include the following (0.3% represents 1 patient): sustained monomorphic ventricular tachycardia (0.3%), nonsustained monomorphic ventricular tachycardia (4.0%), A-V block—1st degree (1.6%), A-V block—2nd degree (0.5%), A-V block—3rd degree (0.3%), A-V block—variable (0.3%), ventricular/bigeminal extrasystoles (3.5%), hypotension/postural hypotension (2.9%), bradycardia/sinus bradycardia (1.1%), nodal arrhythmia (0.8%), congestive heart failure (0.5%), supraventricular tachycardia (0.5%), idioventricular rhythm (0.3%), syncope (0.3%), and renal failure (0.3%). Although no cause-effect relationship has been established, the incidence of these events, except for syncope, was greater in the CORVERT Injection group than in the placebo group. Other adverse reactions that may be associated with the administration of CORVERT Injection were nausea and headache, both of which occurred with a frequency greater than 1% more in ibutilide-treated patients than those treated with placebo.	1.52, 8/1/448; 1.1, 2/1/136 1.52, 8/1/485 1.52, 8/1/527 1.52, 8/1/449; 1.1, 2/1/134

Gender Differences in Frequency of Proarrhythmia: As with other class III antiarrhythmic agents, the incidence of **proarrhythmia** in patients treated with CORVERT Injection is greater in women than men **[8.30]**. This was borne out in clinical trials conducted in patients with **atrial fibrillation** and atrial flutter, in which more women than men developed polymorphic ventricular tachycardia **[8.14]**. Also, the pharmacokinetics of CORVERT Injection are similar in men and women with atrial fibrillation and atrial flutter **[6.1, 6.2]**. In studies in healthy volunteers, there were no gender differences in the pharmacokinetics of ibutilide **[6.7]**, or with respect to prolongation of the QTc interval **[6.7]**.	1.52, 8/1/487; 1.1, 2/1/143 1.42, 6/1/37; 1.1, 2/1/91 1.42, 6/1/37 1.42, 6/1/40
Details of the gender distribution of the different ventricular tachycardias in the 38 patients treated with CORVERT Injection are provided in the following table.	1.52, 8/1/487 1.52, 8/1/508

Percentage of Patients With New or Worsened Ventricular Tachycardia

Sex	N	Polymorphic VT		Monomorphic VT		Total No. of Patients	
		Sustained	Nonsustained	Sustained	Nonsustained	n	%
Male	312¶	2.2	2.9	0.3	2.9	25	8.0
Female	63*	3.2	9.5	0	9.5	13	20.6

¶ One male patient had a sustained polymorphic VT and a sustained monomorphic VT.
* One female patient had a sustained and a nonsustained polymorphic VT.

The medical events reported for more than 1% of the patients are shown in the following table.

Treatment-Emergent Medical Events with Frequency of More Than 1% Protocols 0003, 0005, 0014, 0015

Event	Placebo N=127		All Ibutilide N=375	
	Patients		Patients	
	n	%	n	%
CARDIOVASCULAR				
Nonsustained Monomorphic VT	1	0.8	15	4.0
Nonsustained Polymorphic VT	–	–	15	4.0
Ventricular Extrasystoles	1	0.8	13	3.5
Hypotension	2	1.6	11	2.9
AV Block	1	0.8	9	2.4
Sustained polymorphic VT	–	–	9	2.4
Chest Pain	2	1.6	6	1.6
Hypertension	–	–	5	1.3
Tachycardia	1	0.8	4	1.1
GASTROINTESTINAL				
Nausea	1	0.8	10	2.7
Vomiting	2	1.6	6	1.6
Diarrhea	3	2.4	6	1.6
LABORATORY VALUES				
Increased Serum Creatinine	1	0.8	4	1.1
RESPIRATORY				
Dyspnea	3	2.4	7	1.9
CENTRAL NERVOUS SYSTEM				
Headache	4	3.1	18	4.8
Dizziness	2	1.6	7	1.9
UROGENITAL				
Urinary Retention	2	1.6	–	–
MISCELLANEOUS				
Back Pain	6	4.7	7	1.9
Fever	4	3.1	5	1.3
Localized Pain	1	0.8	4	1.1

[1.52, 8/1/449; 1.1, 2/1/134]

OVERDOSAGE **Acute Experience in Animals:** Acute overdose in animals results in CNS toxicity; notably, CNS depression, rapid gasping breathing, and convulsions. The intravenous median lethal single dose is more than 50 mg/kg but less than 100 mg/kg in two species; this dose is at least 1500 times more than the maximum recommended therapeutic dose.	1.18, 5/1/78; 1.1, 2/1/65 1.18, 5/1/227; 1.1, 2/1/71
Human Experience: In the clinical trials with CORVERT Injection, four patients were unintentionally overdosed. The largest dose was 3.4 mg administered over 15 minutes. One patient developed increased ventricular ectopy and monomorphic ventricular tachycardia, another patient developed A-V block—3rd degree and nonsustained polymorphic VT, and two patients had no medical event reports. Based on known pharmacology, the clinical effects of an overdosage with ibutilide could exaggerate the expected prolongation of repolarization seen at usual clinical doses. Medical events (eg, proarrhythmia, A-V block) that occur after the overdosage should be treated with measures appropriate for that condition.	1.52, 8/1/543; 1.1, 2/1/145
DOSAGE AND ADMINISTRATION The recommended dose of CORVERT Injection for patients 60 kg (132 lb) or more is 1 mg administered by intravenous infusion over a 10-minute period. For patients less than 60 kg, administer 0.01 mg/kg over a 10-minute period. If the arrhythmia does not terminate within 10 minutes after the end of the initial infusion, a second 10-minute infusion of equal strength may be administered. More rapid infusion is not recommended. CORVERT Injection may be administered undiluted or diluted in 50 mL of diluent (see Dilution). If new or worsened ventricular arrhythmia develops during administration of CORVERT Injection, the infusion should be stopped immediately. Additional doses are not recommended because of the risk of adverse events associated with QT interval prolongation.	1.52, 8/1/258; 1.1, 2/1/129
Dilution: CORVERT Injection may be added to 0.9% Sodium Chloride Injection or 5% Dextrose Injection before infusion. The contents of one 10-mL vial (0.1 mg/mL) may be added to a 50-mL infusion bag to form an admixture of approximately 0.017 mg/mL ibutilide fumarate.	1.3, 3/2/1
Compatibility and Stability: The following diluents are compatible with CORVERT Injection (0.1 mg/mL): 5% Dextrose Injection 0.9% Sodium Chloride Injection The following intravenous solution containers are compatible with admixtures of CORVERT Injection (0.1 mg/mL): polyvinyl chloride plastic bags polyolefin bags	1.3, 3/2/422
Storage: Store the product at controlled room temperature (15° to 30°C or 59° to 86°F). Keep the product in its original carton until used. When kept at controlled room temperature, CORVERT Injection can be stored for 24 months. Admixtures of the product, with approved diluents, are chemically and physically stable for 24 hours at room temperature (15° to 30°C or 59° to 86°F) and for 48 hours at refrigerated temperatures (2° to 8°C or 36° to 46°F). Strict adherence to the use of aseptic technique during the preparation of the admixture is recommended in order to maintain sterility.	1.3, 3/2/415 1.3, 3/2/422
HOW SUPPLIED CORVERT Injection is supplied as an acetate-buffered isotonic solution at a concentration of 0.1 mg/mL that has been adjusted to approximately pH 4.6 in 10-mL clear glass flip-top vials.	1.3, 3/2/1 1.3, 3/2/47
Caution: Federal law prohibits dispensing without prescription. **The Upjohn Company** • Kalamazoo, Michigan 49001, USA Revised: **October 1994**	

MICROBIOLOGIST'S REVIEW

D. Willard

NOV 21 1995

REVIEW FOR HFD-110
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF

MICROBIOLOGIST'S REVIEW #2 OF NDA 20-491
21 November 1995

A. 1. NDA 20-491
APPLICANT: The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

2. PRODUCT NAMES: Corvert® (ibutilide fumarate) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile solution for intravenous administration at a concentration of 0.1 mg active drug product/mL.

4. METHODS OF STERILIZATION:
The drug product is sterile filtered followed by aseptic filling.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of atrial fibrillation and atrial flutter.

B. 1. DATE OF INITIAL SUBMISSION: 27 October 1994

2. DATE OF AMENDMENT: 14 November 1995

3. RELATED DOCUMENTS: Three Investigational New Drug Applications are referenced:
IND -
IND -
IND -

4. ASSIGNED FOR REVIEW: 20 November 1995

C. REMARKS: The amendment is a response to deficiencies found in the 13 April 1995 review of the New Drug Application.

D. CONCLUSIONS: The application is recommended for approval on the basis of the information supplied.

21 Nov 1995
Paul Stinavage, Ph.D.

11/21/95

DWelia

APR 19 1995

Consultative Review to HFD-110
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #2
13 April 1995

A. 1. NDA 20-491
APPLICANT: The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

2. PRODUCT NAMES: Corvert® (ibutilide fumarate) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile solution for intravenous administration at a concentration of 0.1 mg active drug product/mL.

4. METHODS OF STERILIZATION:
The drug product is sterile filtered followed by aseptic filling.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of atrial fibrillation and atrial flutter.

B. 1. DATE OF INITIAL SUBMISSION: 27 October 1994

2. DATE OF AMENDMENT: 16 March 1995

3. RELATED DOCUMENTS: Three Investigational New Drug Applications are referenced:
IND -
IND -
IND -

4. ASSIGNED FOR REVIEW: 24 March 1995

C. REMARKS: The amendment is a response to deficiencies found in the 31 January 1995 review of the New Drug Application.

D. CONCLUSIONS: Since filtration is the only sterilizing step for this preparation and the adequacy of the filtration process has not been demonstrated, the application is not recommended for approval. Importantly, the Agency is aware of specific cases of inadequate bacterial retention validation of filtration processes resulting in non-sterile product. Specific comments are

provided in "E. Review Notes" and
"Microbiologist's Draft of Letter to Applicant".

19 April 1995

Paul Stinavage, Ph.D.

PHC 4/19/95

cc: Original NDA 20-491
HFD-160/Stinavage/Consult File
HFD-110/Div File/D. Roeder
Drafted by: P. Stinavage
R/D initialed by P. Cooney

CSO

FEB - 2 1995

Consultative Review to HFD-110
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
31 January 1995

A. 1. NDA 20-491
APPLICANT: The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

2. PRODUCT NAMES: Corvert® (ibutilide fumarate) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile solution for intravenous administration at a concentration of 0.1 mg active drug product/mL.

4. METHODS OF STERILIZATION:
The drug product is sterile filtered followed by aseptic filling.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of atrial fibrillation and atrial flutter.

B. 1. DATE OF INITIAL SUBMISSION: 27 October 1994

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: Three Investigational New Drug Applications are referenced:
IND -
IND -
IND -

4. ASSIGNED FOR REVIEW: 3 January 1995

C. REMARKS: The application is for a new aseptically filled product. The applicant has provided comments, information, and data to support the use of aseptic processing in the manufacture of this product. At this time there is no requirement to terminally sterilize drug products nor to provide the rationale for use of aseptic processing rather than terminal sterilization.

D. CONCLUSIONS: The application is not recommended for approval. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to Applicant".

31 Jan 1995

Paul Stinavage, Ph.D.

2/2/95

cc: Original NDA 20-491
HFD-160/Stinavage/Consult File
HFD-110/Div File/D. Roeder
Drafted by: P. Stinavage
R/D initialed by P. Cooney

STATISTICAL

REVIEW

1/11

2

STATISTICAL REVIEW AND EVALUATION
(Addendum)

NDA #: 20-491 SEP 29 1995
Applicant: Upjohn Company
Drug Name: Corvert (ibutilide fumarate) injection
Indication: Atrial Fibrillation/Flutter
Document Reviewed: Amendment No. 039, Vols. 1-9
SAS efficacy database

1. INTRODUCTION

This review pertains to the non-IND European Study, Study #19 (M/7550/0019), submitted as an amendment in support of the New Drug Application for ibutilide in treating patients with atrial flutter or atrial fibrillation. Based on the SAS database provided by the sponsor, the results of this reviewer's analyses are consistent with the results presented in the NDA report. Thus, only major discrepancy will be noted.

2. OVERVIEW OF STUDY #19 (M/7550/0019) AND REVIEWER'S COMMENTS

This 40-center, double-blind, randomized, parallel group trial was conducted to compare intravenous ibutilide (1 and 2 mg doses) with intravenous dl-sotalol(1.5 mg/kg) in hemodynamically stable patients with recent onset atrial flutter (AFL) or atrial fibrillation (AF). Patients were stratified based on diagnosis: AF or AFL. Those with a mixture AF/AFL were randomized to the AF stratum. Previous studies, Study #14 (P/7550/0014) and Study #15 (P/7550/0015), utilized a dose based on weight. According to the sponsor's report, the doses of 0.01 and 0.025 mg/kg correlate to doses of 1 and 2 mg, respectively. This study utilized fixed 1 and 2 mg doses of ibutilide. The dose of 1.5 mg/kg of dl-sotalol was selected because it was felt to represent the maximally effective dose based on input from investigators and the medical literature. This corresponds approximately to a dose of 100 mg for the average person. Patients were randomized to receive ibutilide 1 mg, ibutilide 2 mg, or 1.5 mg/kg sotalol in a single 10-min intravenous infusion.

According to the protocol, to maintain the blinding of the investigator giving the drugs to the patients, the investigator

would be presented with a syringe containing 25 ml of solution. 20 mls only will be infused equivalent to 1 or 2 mg of ibutilide or 1.5 mg/kg of dl-sotalol. The syringe containing 25 ml would be prepared by an individual (probably a pharmacist) unseen by the investigator who would perform the infusions and be responsible for all measurements.

Efficacy variables Treatment was considered as successful if the atrial arrhythmia terminated, for any length of time, during the infusion or within one hour of the start of infusion of the study drug. The success rate is of primary interest. Other variables of interest are time to conversion, duration of conversion (time in sinus rhythm from analysis of the Holter tapes and from telephone contact made approximately 72 hours after start of infusion), ECG intervals (QRS, QT, QTc), and atrial cycle length.

Concomitant medications Current treatment with Class I or III antiarrhythmic medications, with beta adrenergic blocking agents (including sotalol), or with the calcium antagonists varapamil and diltiazem was not permitted.

Sample size calculation The sample size of 300 patients (divided equally among the three treatment groups) was believed to be sufficient to detect a minimum difference in conversion rates of the atrial arrhythmia of about 20% for the pairwise comparison of any two single treatment groups, or about 17% for the comparison of the sotalol and ibutilide combined groups, with 80% power and at two-sided 5% level of significance, assuming expected conversion rates of 35% to 60% for the ibutilide groups.

EFFICACY RESULTS

A total of 319 patients (59 AFL, 260 AF) were randomized. The sample size was quite different among centers, ranging from one (in five centers) to 34 (in one center). Eleven patients were considered nonevaluable for efficacy: nine because the duration of arrhythmia prior to treatment was greater than 45 days and two because they received an incorrect dose of study medications. Nonevaluable patients are approximately evenly distributed among the three treatment groups.

Baseline balance

There was no statistical evidence of treatment group imbalance with respect to demographic and baseline characteristics (Table A.1). Eighty-five percent of all evaluable patients received an infusion that lasted 10 minutes. The mean duration of infusion was 10 minutes (range 2-15 min). There were no statistically significant differences among treatment groups in duration of infusion. The mean total doses for success and failure patients were similar, see the table below.

Table 19-1. Total dose received (mg) - evaluable patients

Dose	Success Patients			Failure Patients		
	n	Mean	Range	n	Mean	Range
Ibutilide 1 mg	26	0.94	0.2-1.0	73	0.99	0.5-1.0
Ibutilide 2 mg	52	1.90	0.8-2.5	54	1.98	1.0-2.3
Sotalol	13	125	73-150	89	121	25-180

Success rate

The distribution of successes (patients whose arrhythmia terminated within one hour of the start of infusion) differed significantly across the treatment groups, as shown in the following tables (Table 19-2, Table 19-2a).

Table 19-2. Evaluable patients (N=308) with successes

Stratum	Sotalol			Ibutilide						p-value
				1 mg			2 mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	103	13	13	99	26	26	106	52	49	<0.0001
AFL	21	4	19	16	9	56	20	14	70	0.0034
AF	82	9	11	83	17	20	86	38	44	<0.0001

P-value is computed using Pearson's chi-square test

Table 19-2a. All randomized patients (N=319) with successes

Stratum	Sotalol			Ibutilide						p-value
				1 mg			2 mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	108	13	12	102	28	27	109	52	48	<0.0001
AFL	22	4	18	17	9	53	20	14	70	0.0027
AF	86	9	10	85	19	22	89	38	43	<0.0001

P-value is computed using Pearson's chi-square test.

Differences between treatment groups and 95% confidence intervals are provided in the table below (Table 19-3). Pairwise comparison indicated that the conversion rates were statistically significantly different between any two treatment groups, except the difference between the two ibutilide doses for AFL patients and the difference between the ibutilide 1 mg and sotalol for AF patients.

Table 19-3. Differences (Δ) in success rates (%) for evaluable patients (N=308)

	AFL/AF			AFL			AF		
	Δ	95% CI	p	Δ	95% CI	p	Δ	95% CI	p
ibutilide 1 mg minus sotalol	14	(3,24)	.014	37	(8,67)	.019	10	(-2,21)	.096
ibutilide 2 mg minus sotalol	36	(25,48)	<.0001	51	(25,77)	.001	33	(21,46)	<.0001
ibutilide 2 mg minus ibutilide 1 mg	23	(10,36)	.001	14	(-18,45)	.39	24	(10,37)	.001

Time to termination of arrhythmia

The mean time to termination of arrhythmia was shortest for the success patients in the ibutilide 2 mg group, as shown in the following table (Table 19-4).

Table 19-4. Mean time (min) to termination of atrial arrhythmia for evaluable success patients

	Sotalol	Ibutilide		p-value#
		1 mg	2 mg	
AFL/AF (N=91)	25●	19●	13*&	0.002
AFL (N=27)	19	23	15	0.083
AF (N=64)	27*●	17&	12&	0.005

overall group comparison (detect if there is a pairwise difference)
* compared to ibutilide 1 mg ($p < 0.05$)
● compared to ibutilide 2 mg ($p < 0.05$)
& compared to sotalol ($p < 0.05$)

Time out of AF or AFL

Holter monitoring recordings were made for about 24 hours after the patients' discharge from the hospital. The sponsor reported that due to technical errors Holter tapes were only available from 281 of 319 patients. Once converted, most patients remained out of AFL or AF until the end of this assessment with no apparent difference between the three treatment groups; see Table 19-5.

Table 19-5. Mean and median time (hours) out of AF or AFL for evaluable success patients

		Sotalol	Ibutilide		p-value
			1 mg	2 mg	
AFL/AF (N=66)	Mean	34	28	32	0.082
	Median	32	31	31	
AFL (N=21)	Mean	31	25	30	0.18
	Median	31	30	31	
AF (N=45)	Mean	35	30	32	0.30
	Median	41	31	31	

Time to reversion to AFL or AF

Ten success patients provided data for estimating the time elapsed for the success patients who reverted back to AFL or AF from the Holter tape analyses. There was no sufficient evidence to show difference between treatment groups; see Table 19-6.

Table 19-6. Mean and median time (hours) to reversion to AFL and AF for evaluable success patients

		Sotalol	Ibutilide		p-value
			1 mg	2 mg	
AFL/AF (N=10)	Mean Median	1.2 1.2	2.9 2.9	5.0 4.6	0.36
AFL (N=2)	Mean Median	0.03 0.03	2.9 2.9	--- ---	---
AF (N=8)	Mean Median	2.4 2.4	2.8 2.8	5.0 4.6	0.69

Subgroup analysis

Table A.2 (this reviewer's analysis) presents summary statistics on various subgroups. Ibutilide 2 mg seemed to be more effective than sotalol in all subgroups. Numerically, the superiority of ibutilide 1 mg over sotalol did not seem as apparent in males, patients with AFL/AF or patients using digitalis (digoxin or digitoxin) at baseline as in other subgroups.

Effect of duration of arrhythmia on success rate There appeared to be a statistically significant ($p<0.05$) association between duration of arrhythmia prior to treatment and conversion after adjusting for dose in all evaluable patients. There also appeared to be a marginally significant ($p=0.10$) interaction of dose with the duration of arrhythmia prior to treatment, suggesting the possibility of differential degrees of association between duration of arrhythmia and conversion for the three treatment groups. The intent-to-treat patient analysis did not support this interaction ($p=0.28$). Success rate was negatively

associated with duration of arrhythmia prior to treatment. So, generally speaking, the patients with shorter duration of arrhythmia seemed to have a higher probability of being converted. This agrees with the observation made in Study 14 and Study 15. In this study, the mean duration of arrhythmia over all dose groups for success patients was 11 days as compared to 17 days for failure patients; the median duration was 2 days versus 11 days, respectively.

Effect of noninvestigational medication on success rate There was no statistical evidence of association between conversion and the use of digitalis during the 24 hours prior to infusion (p=0.10), of association between conversion and the use of calcium channel blockers (p=0.30).

Effect of ibutilide on PR, QRS, QT, and QTc Intervals

The PR, QRS, QT, and Qtc interval data were collected at baseline (screen), Minute 30, Minute 60, and Hour 7. Data at Minutes 30 and 60 come from all evaluable patients; however, data at Hour 7 come from success patients and some failure patients who had ECGs recorded at Hour 7.

The sponsor reported that a large number of patients with AF whose PR interval cannot be accurately measured. The PR interval data cannot be meaningfully assessed.

The QRS interval increased slightly from baseline at Minute 30, Minute 60, and Hour 7 in all three treatment groups, generally in the range of 1-4 msec. There was no statistically significant differences among treatment groups at any time point.

All treatment groups showed a significant increase from baseline in QT and QTc intervals at Minute 30, Minute 60, and Hour 7 (Table 19-7 and Table 19-8). The ibutilide 1 mg and ibutilide 2 mg groups appeared to have a significantly greater increase in QTc than sotalol ($p<0.05$). The ibutilide 2 mg group appeared to have a significantly greater increase than the ibutilide 1 mg group ($p < 0.05$).

Table 19-7. Mean value and mean change from baseline in QTc interval (msec) from evaluable patients

Time	Ibutilide				Sotalol	
	1 mg		2 mg			
	Mean	Change	Mean	Change	Mean	Change
Baseline	399	----	401	----	399	----
Minute 30	458	59*@&	483	81*@$	439	41*
Minute 60	446	49*&	480	80*@$	439	40*
Hour 7	430	18*	434	30*	422	25*

* change from baseline ($p = 0.0001$)
@ different from sotalol ($p < 0.05$)
$ different from ibutilide 1 mg ($p < 0.05$)

Table 19-8. Mean value and mean change from baseline in QT interval (msec) from evaluable patients

Time	Ibutilide				Sotalol	
	1 mg		2 mg			
	Mean	Change	Mean	Change	Mean	Change
Baseline	325	----	321	----	319	----
Minute 30	389	64*&	432	109*@$	397	77*
Minute 60	380	54*@&	427	105*@$	399	80*
Hour 7	378	64*	405	84*	394	90*

* change from baseline ($p = 0.0001$)
@ different from sotalol ($p < 0.05$)
$ different from ibutilide 1 mg ($p < 0.05$)

3. CONCLUSION (MAY BE CONVEYED TO THE SPONSOR)

The ibutilide 1 mg and 2 mg groups had a significantly greater rate of conversion of atrial arrhythmia than the sotalol group (Table 19-2, Table 19-2a). Ibutilide 2 mg seemed to be more effective than sotalol in all subgroups (Table A.2, this reviewer's table). Numerically, the superiority of ibutilide 1

mg over sotalol did not seem as apparent in males, patients with AFL/AF or patients using digitalis within 24 hours prior to infusion as in other subgroups.

All treatment groups showed a significant increase from baseline in QT and QTc intervals at Minute 30, Minute 60, and Hour 7 (Table 19-7 and Table 19-8). The ibutilide 1 mg and ibutilide 2 mg groups appeared to have a significantly greater increase in QTc than sotalol. The ibutilide 2 mg group appeared to have a significantly greater increase than the ibutilide 1 mg group.

James Hung

H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 10 pages of text, followed by 2 additional tables.

Concur: Dr. Chi chi 9/25/95

Dr. Dubey 9/25/95

cc: Orig. NDA
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Chen
HFD-110/Dr. Gordon
HFD-110/Dr. Raczkowski
HFD-110/Mrs. Willard/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Hung

Jhung/594-5436/SERB/CORVERT2.*/09-18-95

Table A.1. Demographic and Baseline Characteristics of Evaluable Patients (Study 19)

		Sotalol		Ibutilide 1 mg		Ibutilide 2 mg	
		N = 103		N = 99		N = 106	
Age (years)	Mean	58.9		61.7		59.5	
	Range						
Weight (kg)	Mean	82		81		82	
	Range						
Duration of Arrhythmia (days)	Median	5.4		14.9		5.1	
	Range						
		n	%	n	%	n	%
Race (n, %)	White	100	97	95	96	102	96
	Black	1	1	2	2	1	1
	Other	2	2	2	2	3	3
Sex (n, %)	Female	26	25	30	30	37	35
	Male	77	75	69	70	69	65
History of heart disease (n, %)	Present	52	50	51	52	45	42
	Absent	51	50	48	48	61	58
Use of digitalis (n, %)	Yes	32	31	38	38	40	38
	No	71	69	61	62	66	62

Table A.2. Success rates (SR in %) by subgroups [total sample size = 308, Study 19]

	Sotalol		Ibutilide 1 mg				Ibutilide 2 mg			
	n	SR (%)	n	SR (%)	D	C.I.	n	SR (%)	D	C.I.
Male	77	14	69	25	10	(-2, 28)	69	49	35	(21, 49)
Female	26	8	30	30	22	(3, 42)	37	49	41	(22, 60)
>=70yrs	30	10	27	30	20	(-1, 40)	22	55	45	(21, 68)
< 70yrs	73	14	72	25	11	(-1, 24)	84	48	34	(21, 47)
White	100	11	95	25	14	(4, 25)	102	49	38	(27, 49)
Black	1	100	2	100	0		1	100	0	
Others	2	50	2	0	-50		3	33	-17	
AFL/AF										
Yes	53	17	55	25	8	(7, 24)	63	51	34	(18, 50)
No	50	8	44	27	19	(4, 34)	43	47	39	(22, 55)
Digitalis										
Yes	32	9	38	16	6	(-9, 22)	40	48	38	(20, 57)
No	71	14	61	33	19	(4, 33)	66	50	36	(21, 50)

D = ibutilide dose group minus sotalol C.I. = 95% confidence interval for D

AUG 24 1995

STATISTICAL REVIEW AND EVALUATION
(Addendum)

NDA #: 20-491
Applicant: Upjoin Company
Drug Name: Corvert (ibutilide fumarate) injection
Indication: Atrial Fibrillation/Flutter
Document Reviewed: Amendment No. 041

After reviewing this amendment provided by the sponsor, I agree to the sponsor's corrections. Corrections are made below.

1) On page 11 of my original review (dated April 18, 1995), the last two sentences from the bottom of the page should read:

"Failure rate appeared to be positively associated with the duration of arrhythmia (p= 0.0096). This observation agreed with the negative association between success rate and duration of arrhythmia seen in Study 14."

2) On page 12, there are two typographical errors. In the 'CONCLUSION' section, 'fot' of the 5th line should be 'for' and '0.15' of the 6th line should be '0.015'.

H.M James Hung, Ph.D.
Mathematical Statistician

This review consists of 1 page of text.

Concur: For Dr. Chi 08/24/95
Dr. Dubey 8/24/95

cc: Orig. NDA
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Chen
HFD-110/Dr. Gordon
HFD-110/Dr. Raczkowski
HFD-110/Mrs. Willard/Mrs. Natalia Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Hung

Jhung/594-5436/SERB/CORVERT.*/08-24-95

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-491
Applicant: Upjoin Company
Drug Name: Corvert (ibutilide fumarate) injection
Indication: Atrial Fibrillation/Flutter
Document Reviewed: Vols. 1.78, 1.85-1.100.
SAS efficacy database

This review is completed after discussions with the medical reviewers, Dr. Maryann Gordon and Dr. Victor Raczkowski.

1. INTRODUCTION

This review pertains to the two major studies (Study 14 and Study 15) contained in the New Drug Application for ibutilide in treating patients with atrial flutter or atrial fibrillation. Based on the SAS database provided by the sponsor, the results of this reviewer's analyses are consistent with the results presented in the NDA report. Thus, only major discrepancy will be noted.

2. OVERVIEW OF PIVOTAL STUDIES AND REVIEWER'S COMMENTS

2.1. Study #14 (P/7550/0014)

This nine-center, double-blind placebo-controlled trial was conducted to determine the dose-response relationship of ibutilide and conversion of atrial flutter (AFL) or atrial fibrillation (AF). A secondary objective is to assess the effects of ibutilide on heart rate and blood pressure. Patients were stratified based on diagnosis: atrial flutter or atrial fibrillation.

In order to assess the safety of ascending doses, the study was conducted in two tiers. Tier I consisted of 25 patients in each stratum randomized in 1:2:2 ratio to receive a 10-minute infusion of either placebo, 0.005 mg/kg ibutilide, or 0.01 mg/kg ibutilide. Tier II is identical to Tier I except patients were randomized to either placebo, 0.015 mg/kg ibutilide, or 0.025 mg/kg ibutilide. Tier I began first and Tier II followed after Tier I was completed and safety was ascertained. The study began in April, 1991. Following the completion of Tier II, the protocol was amended (03/21/92) to permit randomization of 100 additional patients across all dose groups to further differentiate between dose groups. Patients treated under the extension amendment were stratified by AFL or AF, and were randomized to a 10-min infusion of placebo, 0.005, 0.010, 0.015, or 0.025 mg/kg ibutilide (10 patients per group in each stratum). The qualified patients must have rhythm of sustained atrial flutter (duration of 3 hours or greater) or atrial fibrillation (duration greater than 3 hours and less than 90 days).

During the 10-min infusion period, blood pressure and heart rate were recorded every 5 minutes. Twelve-lead ECGs were obtained if the arrhythmia terminated or if a significant rhythm change was observed. Three ECG leads were continuously monitored and recorded. During the postinfusion period (from the end of infusion till hour 24), a 12-lead ECG was done if the arrhythmia terminated or if a significant rhythm change occurred during the 1-hour period following the infusion. Three ECG leads were monitored and recorded until 30 minutes after the end of the infusion. From Minute 40 till Hour 24 patients were monitored with a standard single-lead ECG.

Efficacy variables Treatment was considered as successful if the atrial arrhythmia terminated, for any length of time, during the infusion or within one hour following infusion. The success rate is of primary interest. Other variables of interest are blood pressure, heart rate and QTc length.

Concomitant medications Class I or III antiarrhythmic medications were not permitted. Use of beta adrenergic blocking agents and calcium antagonists was permitted.

Efficacy results

A total of 200 patients (100 AFL, 100 AF) were randomized. Because of two-tiered design and the different recruitment rate at each center, randomization was done across centers within each tier, and for AFL and AF, separately. The sample size was quite different among centers. Three patients were considered nonevaluable for efficacy (patient #1201 received a dose much higher than any of the doses in the protocol, patient #2118 received an unknown amount of study medication, patient #2307 was not in atrial flutter or fibrillation at baseline).

Baseline balance

There was no statistical evidence of treatment group imbalance with respect to demographic and baseline characteristics (Table A.1), except that there appeared to be a larger percentage of patients with prior history of AFL/AF in the 0.010 mg/kg group (placebo: 70%, 0.05 mg/kg: 54%, 0.010 mg/kg: 85%, 0.015 mg/kg: 66%, 0.025 mg/kg: 62%, p = 0.05 for group differences).

Success rate

The distribution of successes (patients whose arrhythmia terminated within one hour of the end of infusion) differed significantly across dose groups, as shown in the following table (Table 14-1).

Table 14-1. Evaluable patients with successes (Study 14)

Stratum	Placebo			Ibutilide												p-value
				.005 mg/kg			.010 mg/kg			.015 mg/kg			.025 mg/kg			
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	
AFL/AF	40	1	3	41	5	12	39	13	33	38	17	45	39	18	46	<0.0001
AFL	20	0	0	21	3	14	20	6	30	19	11	58	19	10	53	0.0004
AF	20	1	5	20	2	10	19	7	37	19	6	32	20	8	40	0.050

P-value is computed using Pearson's chi-square test.

Pairwise comparison indicated that the conversion rates were statistically significantly greater in the 0.010, 0.015 and 0.025 mg/kg groups than that in the placebo group ($p < 0.0001$). The conversion rate of the 0.005 mg/kg group did not differ significantly from that of the placebo group ($p = 0.09$). Thus, 0.010 mg/kg appeared to be a reasonable first dose for the patient population. There was a dose-related increase in conversion rates for the combined AFL/AF groups. The success rates appeared to reach a plateau between 0.015 and 0.025 mg/kg. Similar trend was seen in both AFL and AF strata. *The results of all 200 patients receiving medication were consistent with those of evaluable patients, as presented in Table 14-1a.*

Table 14-1a. All randomized patients with successes (Study 14)

Stratum	Placebo			Ibutilide												p-value
				.005 mg/kg			.010 mg/kg			.015 mg/kg			.025 mg/kg			
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	
AFL/AF	41	1	2	41	5	12	40	13	33	38	17	45	40	19	48	<0.0001
AFL	20	0	0	21	3	14	20	6	30	19	11	58	20	11	55	<0.0001
AF	21	1	5	20	2	10	20	7	35	19		32	20	8	40	0.025

P-value is computed using Pearson's chi-square test.

A revised definition of success, <u>patients who converted from AFL or AF to sinus rhythm by Hour 1.5 without emergency intervention and remained in sinus rhythm for at least 24 hours</u>, was used by the medical reviewers, Dr. Gordon and Dr. Raczkowski, to reevaluate the efficacy of ibutilide. Table 14-1b presents the results of analysis for this new variable. The results are similar to those from the analysis of the original success rate, except in the AF stratum that statistical significance is only marginal.

Table 14-1b. Newly defined success rate prior Hour 24 (all randomized patients) [Study 14]

Stratum	Placebo			Ibutilide												p-value
				.005 mg/kg			.010 mg/kg			.015 mg/kg			.025 mg/kg			
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	
AFL/AF	41	1	2	41	5	12	40	11	28	38	16	42	40	17	43	<0.0001
AFL	20	0	0	21	3	14	20	6	30	19	11	58	20	10	50	0.001
AF	21	1	5	20	2	10	20	5	25	19	5	26	20	7	35	0.095

P-value is computed using Pearson's chi-square test.

Time to termination of arrhythmia

The mean time to termination of arrhythmia was 19 minutes (range of 3 to 70 minutes) for the AFL/AF patients, 20 minutes (range 5 to 70 min) for the AFL group, and 18 minutes (range 3 to 60 min) for the AF group.

Clinical outcome at Hour 24

The arrhythmia was terminated prior to the end of study (Hour 24) in 67% (46 of 69) of the AFL patients and 51% (38 of 74) of the AF patients who failed to covert as a result of study treatment. According to the sponsor's report, methods of arrhythmia termination are described in the following table.

Table 14-2. Number of patients converted by methods of termination

	Ibutilide infusion	Placebo infusion	Electro-cardioversion	Pacing	Medication	Spontaneous
AFL	30	0	21	19	2	4
AF	23	1	31	0	4	3

Subgroup analysis

Effects of duration of arrhythmia, cardiac structure or function (left atrial diameter, ejection fraction, valvular heart disease), QTc length, noninvestigational medication (digoxin, beta blockers, calcium channel blockers) on termination of AFL/AF were studied using descriptive statistics and logistic regression analysis. Table A.2 presents summary statistics on various subgroups.

Effect of duration of arrhythmia on success rate There was no statistical evidence indicating a significant dose by the duration of arrhythmia (truncated at 90 days prior to infusion) interaction (p=0.24). Success rate appeared to be negatively associated with the duration of arrhythmia (p=0.017). In the AFL/AF patients, the mean (or median) duration of arrhythmia truncated at 90 days over all dose groups was 18 (or 8) days for successes and 27 (or 21) days for failures.

Effect of cardiac structure/function on success rate There was no statistical evidence indicating any difference in the rates of success between the patients with normal left atrial diameters and the patients with enlarged left atrial diameters (p=0.46).

Effect of ejection fraction on success rate There was no statistical evidence indicating that the success rates of the dose groups were related to decreased ejection fraction (p=0.43).

Effect of valvular heart disease on success rate There was no statistical evidence indicating that the success rates of the dose groups were related to valvular heart disease (p=0.42).

Effect of QTc length on success rates There was no statistical evidence indicating a difference in the prolongation of QTc interval between successes and failures (p > 0.15).

Effect of noninvestigational medication on success rate There was no statistical evidence of dose by use of digoxin interaction (p=0.23), dose by use of beta adrenergic blocking agents (p=0.58), or dose by calcium channel blockers (p=0.69). Patients not receiving digoxin seemed to have a higher success rate than patients receiving digoxin in the AFL/AF group (p=0.03) and in the AFL group (p = 0.04). Patients taking beta adrenergic blockers seemed to have a higher success rate than patients not taking beta blockers in the AFL/AF group (p=0.073) and in the AF group (p=0.004). There was no statistical evidence of a difference in the success rates between the patients taking calcium channel blockers and the patients not taking calcium channel blockers (p = 0.67).

2.2. Study #15 (P/7550/0015)

This 21-center, double-blind, placebo-controlled trial was conducted to demonstrate the effectiveness of 1 mg (0.01 mg/kg in patients weighing less than 60 kg) of ibutilide fumarate in the termination of AFL and AF, and to investigate whether a second dose of 1 mg (or 0.01 mg/kg in patients weighing less than 60 kg) would increase the termination rate. Patients were stratified based on diagnosis (AFL or AF).

Patients in each stratum (AFL and AF) were randomized to receive

two 10-minute infusions: placebo/placebo, 1 mg/0.5 mg ibutilide, or 1 mg/1 mg ibutilide. If the arrhythmia did not terminate during or within 10 minutes after the end of the first infusion, the second infusion was administered. The infusion was discontinued at the time of arrhythmia termination.

Drug or placebo was infused according to schedule (first 10-minute infusion, a 10-minute wait, second 10-minute infusion) unless AFL or AF was terminated or a medical event occurred necessitating termination of treatment. During the infusion period, blood pressure and heart rate were recorded every 5 minutes, 12-lead ECGs were obtained at Minute 30 and if the arrhythmia terminated or if a significant rhythm change was observed, blood was drawn for an ibutilide plasma concentration (Minute 20), and the patients' ECGs were continuously monitored. During the postinfusion period (from the end of Minute 30 till Hour 24), a 12-lead ECG was done if the arrhythmia terminated or if a significant rhythm change occurred during the 1-hour period following the infusions (until Hour 1.5). A 12-lead ECG was also required at Hour 1.5 for patients whose arrhythmia did not terminate prior to that time, or if a significant adverse rhythm changes occurred through Hour 24. Patients' ECGs were continuously monitored through Hour 24.

Efficacy variables Treatment was considered as successful if the atrial arrhythmia terminated, for any length of time, by Hour 1.5 (Time 0 = start of infusion). The success rate was of primary interest. Other variables of interest are blood pressure, heart rate and ECG parameters.

Concomitant medications Class I or III antiarrhythmic medications were not permitted. Use of beta adrenergic blocking agents and calcium antagonists were permitted for heart rate control.

Efficacy results

A total of 266 (133 AFL and 133 AF) patients were randomized. Twenty-four patients were considered nonevaluable for efficacy. Of them, 13 patients were dosed with a dose of drug inconsistent with the protocol, 3 patients received other antiarrhythmic drugs within three half-lives of the infusion, 8 patients had duration of the current episode of AFL/AF greater than 45 days, one patient's rhythm at Minute -10 was not AFL/AF, and one patient was electrically converted prior to Hour 1.5 (excluding those who were emergently electrocardioverted due to VT). The total of evaluable patients is 242.

Baseline balance

There was no statistical evidence of treatment group imbalance with respect to demographic and baseline variables

(Table A.3), except that there appeared to be a much smaller percentage of patients in the AF group having other significant medical histories (placebo: 95%, 1 mg/0.5 mg: 98%, 1 mg/1 mg: 78%; p = 0.0061 for group differences) and there appeared to be a difference in the proportion of the AF patients reporting abnormalities of the extremities across dose groups (placebo: 30%, 1 mg/0.5 mg: 65%, 1 mg/1 mg: 41%; p=0.0059 for group differences).

Success rate

The distribution of successes (patients whose arrhythmias were terminated at any time within one and half hour period from the beginning of the first infusion) differed significantly across the dose groups ($p < 0.0001$, Table 15-1). Pairwise comparisons indicated highly significant differences in the success rate between the placebo group (2%) and the 1 mg/0.5 mg group (44%) and the 1 mg/1 mg group (49%), both $p < 0.0001$. Similar results were seen in the AFL patients and in the AF patients. *The results of the all patients (N=266) analysis were consistent with those of the evaluable patient analysis, as shown in Table 15-1a.*

Table 15-1. Success rates for the evaluable patients (N=242) [Study 15]

Stratum	Placebo			Ibutilide						p-value
				1 mg/0.5 mg			1 mg/ 1mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	81	2	3	79	35	44	82	40	49	<0.0001
AFL	41	1	2	39	21	54	41	29	71	<0.0001
AF	40	1	3	40	14	35	41	11	27	0.0011

P-value is computed using Pearson's chi-square test.

Table 15-1a. Success rates for all randomized patients (N=266) [Study 15]

Stratum	Placebo			Ibutilide						p-value
				1 mg/0.5 mg			1 mg/ 1mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	86	2	2	86	39	45	94	42	45	<0.0001
AFL	43	1	2	44	23	52	46	30	65	<0.0001
AF	43	1	2	42	16	38	48	12	25	<0.0001

P-value is computed using Pearson's chi-square test.

As presented in Table 15-1b, the results of analysis of the newly defined success rate at Hour 24 are also consistent with those from analysis of the originally defined success rate.

Table 15-1b. Newly defined success rates for all randomized patients (N=266) [Study 15]

Stratum	Placebo			Ibutilide						p-value
				1 mg/0.5 mg			1 mg/ 1mg			
	N	n	%	N	n	%	N	n	%	
AFL/AF	86	2	2	86	29	34	94	35	37	<0.0001
AFL	43	1	2	44	20	45	46	27	59	<0.0001
AF	43	1	2	42	9	21	48	8	17	0.027

P-value is computed using Pearson's chi-square test

Table 15-2. Success rates for the evaluable patients (N=242) [Study 15]

Stratum	1st infusion						2nd infusion								
	Placebo			1 mg			Placebo			0.5 mg			1 mg		
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
AFL/AF	81	0	0	161	35	22	81	2	3	60	16	27	66	24	36
AFL	41	0	0	80	19	24	41	1	2	30	12	40	31	19	61
AF	40	0	0	81	16	20	40	1	3	30	4	13	35	5	14

Table 15-2 presents the distribution of the proportion of patients who converted during the first infusion and the distribution of the proportion of patients who did not convert during or within 10 minutes following the first infusion but converted from beginning of the second infusion through Hour 1.5. The results were similar to those of the two infusions.

Time to Termination for successes

The mean time to termination for successes for AFL/AF patients was 27 minutes (range 5 to 88). In the AFL group, the mean was 30 minutes (range 7 to 88) and in the AF group the mean was 23 minutes (range 5 to 75).

For AFL/AF patients, the mean time to termination was 64 minutes for the placebo group, 25 minutes for the 1 mg/0.5 mg group and 27 minutes for the 1 mg/1 mg group. For AFL patients, the mean was 53 minutes for the placebo group, 29 minutes for the 1 mg/0.5 mg group and 30 minutes for the 1 mg/1 mg group. For

AF patients, the mean was 75 minutes for the placebo group, 20 minutes for the 1 mg/0.5 mg group and 21 minutes for the 1 mg/1 mg group.

Arrhythmia status through Hour 24

The following table presents the final efficacy assessment data pertaining to the timing of termination of AFL/AF.

Table 15-3. Final efficacy assessment for evaluable patients (N=242) [Study 15]

		AFL/AF Term. W/O intervn prior to Hour 1.5	Emergent term. prior to Hour 1.5	AFL/AF term. between Hour 1.5 and 24	AFL/AF not term. during 24 hours
AFL/AF	placebo	2 (3%)	0 (0%)	51 (63%)	28 (35%)
	1/0.5 mg	35 (44%)	2 (3%)	32 (41%)	10 (13%)
	1/1 mg	40 (49%)	0 (0%)	25 (30%)	17 (21%)
AFL	placebo	1 (2%)	0 (0%)	30 (73%)	10 (24%)
	1/0.5 mg	21 (54%)	2 (5%)	12 (31%)	4 (10%)
	1/1 mg	29 (71%)	0 (0%)	8 (20%)	4 (10%)
AF	placebo	1 (3%)	0 (0%)	21 (53%)	18 (45%)
	1/0.5 mg	14 (35%)	0 (0%)	20 (50%)	6 (15%)
	1/1 mg	11 (27%)	0 (0%)	17 (41%)	13 (32%)

The arrhythmia was terminated prior to Hour 24 in 67% (110 of 165) of the patients who failed to convert as a result of study treatment. The following table presents the number of patients converted by each method of arrhythmia termination.

Table 15-4. Methods of termination of AFL/AF [Study 15]

	Ibutilide infusion	Placebo infusion	Electro-cardioversion	Pacing	Medication	Spontaneous
AFL	50	1	40	7	0	5
AF	25	1	48	0	6	4

The following table presents the proportion of successes who remained in conversion rhythm through Hour 24.

Table 15-5. Successes who remained in conversion rhythm through Hour 24 [Study 15]

Stratum	Placebo			Ibutilide					
				1 mg/0.5 mg			1 mg/ 1mg		
	n	#	%	n	#	%	N	n	%
AFL/AF	2	2	100	35	28	80	40	34	85
AFL	1	1	100	21	20	95	29	26	90
AF	1	1	100	14	8	57	11	8	73

n = number of successes (patients who had the AFL/AF terminated prior to Hour 1.5)
# = number of successes who remained in conversion rhythm through Hour 24

At Hour 24 patients were categorized according to their rhythms during the study:

1) remained in NSR (normal sinus rhythm)
2) remained in rhythm to which they converted
3) reverted to AF and remained in AF
4) reverted to AFL and remained in AFL
5) alternated between AF, AFL, and NSR
6) other

The distribution of these categories is presented in the following table (Table 15-6).

Table 15-6. Distribution of resulting rhythm from time of AFL/AF termination for patients which converted from study medication [Study 15]

		Cat.1	Cat.2	Cat.3	Cat.4	Cat.5	Cat.6
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AFL/AF	Placebo	1 (50%)	1 (50%)				
	1/0.5 mg	25 (71%)	3 (9%)	1 (3%)		5 (14%)	1 (3%)
	1/1 mg	33 (83%)	1 (3%)	2 (5%)	2 (5%)		2 (5%)
AFL	Placebo		1 (100%)				
	1/0.5 mg	17 (81%)	3 (14%)	1 (5%)			
	1/1 mg	25 (86%)	1 (3%)		2 (7%)		1 (3%)
AF	Placebo	1 (100%)					
	1/0.5 mg	8 (57%)				5 (36%)	1 (7%)
	1/1 mg	8 (73%)		2 (18%)			1 (9%)

Cat.1: remained in NSR (normal sinus rhythm)
Cat.2: remained in rhythm to which they converted
Cat.3: reverted to AF and remained in AF
Cat.4: reverted to AFL and remained in AFL
Cat.5: alternated between AF, AFL, and NSR
Cat.6: other

Table 15-7. Distribution of resulting rhythm from time of AFL/AF termination for patients which converted by means other than study medication [Study 15]

		Cat.1	Cat.2	Cat.3	Cat.4	Cat.5	Cat.6
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AFL/AF	Placebo	43 (84%)	1 (2%)	3 (6%)		3 (6%)	1 (2%)
	1/0.5 mg	27 (79%)	2 (6%)	1 (3%)		3 (9%)	1 (3%)
	1/1 mg	22 (88%)	1 (4%)	1 (4%)			1 (4%)
AFL	Placebo	27 (90%)	1 (3%)			1 (3%)	1 (3%)
	1/0.5 mg	10 (71%)	2 (14%)			2 (14%)	
	1/1 mg	8 (100%)					
AF	Placebo	16 (76%)		3 (14%)		2 (10%)	
	1/0.5 mg	17 (85%)		1 (5%)		1 (5%)	1 (5%)
	1/1 mg	14 (82%)	1 (6%)	1 (6%)			1 (6%)

Cat.1: remained in NSR (normal sinus rhythm)
Cat.2: remained in rhythm to which they converted
Cat.3: reverted to AF and remained in AF
Cat.4: reverted to AFL and remained in AFL
Cat.5: alternated between AF, AFL, and NSR
Cat.6: other

Subgroup Analysis

Effects of duration of arrhythmia, cardiac structure or function (left atrial diameter, ejection fraction, valvular heart disease), QTc length, noninvestigational medication (digoxin, beta blockers, calcium channel blockers) on termination of AFL/AF were studied using descriptive statistics and logistic regression analysis. Table A.4 presents summary statistics on various subgroups.

Effect of duration of arrhythmia on success rate There was no statistical evidence indicating a significant dose by the duration of arrhythmia interaction (p=0.79). Success rate appeared to be positively associated with the duration of arrhythmia (p=0.0096). This observation contracted the negative association between success

rate and duration of arrhythmia seen in Study 14. In the AFL/AF patients, the mean (or median) duration of arrhythmia over all dose groups was 12 (or 6) days for successes and 15 (or 8) days for failures.

Effect of cardiac structure/function on success rate There was no statistical evidence indicating any difference in the rates of success between the patients with normal left atrial diameters and the patients with enlarged left atrial diameters (p=0.46).

Effect of ejection fraction on success rate There was no statistical evidence indicating that the success rates of the dose groups were related to decreased ejection fraction (p=0.85).

Effect of valvular heart disease on success rate There was no sufficient statistical evidence indicating that the success rates of the dose groups were related to valvular heart disease (p=0.08).

Effect of QTc length on success rates There was no statistical evidence indicating a difference in the prolongation of QTc interval between successes and failures ($p > 0.59$).

Effect of noninvestigational medication on success rate There was no statistical evidence that the success rates of the dose groups were related to the use of digoxin (p=0.45), the use of beta adrenergic blocking agents (p=0.41), or the use of calcium channel blockers (p=0.70). There was no statistical evidence of a difference in the success rate between the patients taking digoxin and the patients not taking it ($p = 0.96$). There was no statistical evidence of a difference in the success rate between the patients taking beta adrenergic blocking agents and the patients not taking it ($p = 0.56$). There was no statistical evidence of a difference in the success rates between the patients taking calcium channel blockers and the patients not taking calcium channel blockers ($p = 0.91$).

3. CONCLUSION (MAY BE CONVEYED TO THE SPONSOR)

From the results of Study 14, there was a dose-related increase in conversion rates for the combined AFL/AF group, the AFL group, and possibly the AF group (Tables 14-1, 14-1a, 14-1b). The 0.010 mg/kg appeared to be the a reasonable first dose for the average patient with AFL/AF. The success rates appeared to reach a plateu between 0.15 and 0.025 mg/kg. The data of Study 15 confirmed the efficacy of 0.010 mg/kg (Tables 15-1. 15-1a, 15-1b).

Only 16% of the patients were female (10% in Study 14 and 20% in Study 15) and 20% were black (28% in Study 14 and 15% in Study 15). There was no evidence that the 0.010 mg/kg dose is not effective in female or black patients. There was no

sufficient evidence that the 0.010 mg/kg dose is not effective in a specific subgroup (Tables A.2 and A.4, following the last page of the text of this review).

H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 13 pages of text, followed by 4 additional tables.

Concur: Dr. Chi 4/11/95

Dr. Dubey 4-18-95

cc: Orig. NDA
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Chen
HFD-110/Dr. Gordon
HFD-110/Dr. Raczkowski
HFD-110/Mrs. Willard/Mrs. Natalia Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey {File: DRU 1.3.2 NDA}
HFD-713/Dr. Chi
HFD-713/Dr. Hung

Jhung/594-5436/SERB/CORVERT.*/04-17-95

Table A.1. Demographic and Baseline Characteristics of Evaluable Patients (Study 14)

		PBO		0.005 mg/kg		0.010 mg/kg		0.015 mg/kg		0.025 mg/kg	
		N = 40		N = 41		N = 39		N = 38		N = 39	
Age (years)	Mean	63.2		64.1		66.0		65.6		61.9	
	Range										
Weight (lbs)	Mean	179.8		190.7		185.8		179.7		183.7	
	Range										
Duration of Arrhythmia (Days)	Median	8.1		22.5		14.0		12.6		10.5	
	Range										
		N	%	N	%	N	%	N	%	N	%
Race (n, %)	White	31	77.5	28	68.3	24	61.5	27	71.1	30	76.9
	Black	9	22.5	13	31.7	14	35.9	10	26.3	8	20.5
	Other	0	0.0	0	0.0	1	2.6	1	2.6	1	2.6
Sex (n, %)	Female	3	7.5	4	9.8	2	5.1	5	13.2	6	15.4
	Male	37	92.5	37	90.2	37	94.9	33	86.8	33	84.6
Left Atrial Diameter* (n, %)	Normal	9	23.7	10	25.6	7	18.9	11	29.7	11	31.4
	Enlarged	29	76.3	29	74.4	30	81.1	26	70.3	24	68.6
Ejection Fraction* (n, %)	Normal	16	42.1	18	48.6	25	65.8	13	39.4	17	54.8
	Decreased	22	57.9	19	51.4	13	34.2	20	60.6	14	45.2
Valvular Heart Disease* (n, %)	Present	23	57.5	19	47.5	21	55.3	25	65.8	23	65.7
	Absent	17	42.5	21	52.5	17	44.7	13	34.2	12	34.3
Concomitant digoxin (n, %)	Yes	20	50.0	20	48.8	23	59.0	24	63.2	23	59.0
	No	20	50.0	21	51.2	16	41.0	14	36.8	16	41.0
Concomitant β-blocker (n, %)	Yes	6	15.0	8	19.5	6	15.4	6	15.8	10	25.6
	No	34	85.0	33	80.5	33	84.6	32	84.2	29	74.4
Concomitant calcium channel blocker (n, %)	Yes	15	37.5	16	39.0	17	43.6	18	47.4	14	35.9
	No	25	62.5	25	61.0	22	56.4	20	52.6	25	64.1

* Not all patients had echocardiogram data prior to treatment.

Table A.2. Success rates (SR in %) by subgroups [total sample size = 200, Study 14]

	Placebo	0.005 mg/kg			0.010 mg/kg			0.015 mg/kg			0.025 mg/kg		
	n SR (%)	n	SR (%)	Δ C.I.	n	SR (%)	Δ C.I.	n	SR (%)	Δ C.I.	n	SR (%)	Δ C.I.
Male	38 3	37	14	11 (-1, 23)	38	34	32 (16, 47)	33	45	43 (25, 61)	34	53	50 (33, 68)
Female	3 0	4	0	0	2	50	50 (-19,119)	5	60	60 (17,103)	6	33	33 (-4, 71)
>=70yrs	9 0	12	0	0	16	25	25 (4, 46)	13	46	46 (19, 73)	9	33	33 (3, 64)
< 70yrs	32 3	29	17	14 (-1, 29)	24	42	39 (18, 59)	25	48	45 (24, 65)	31	55	52 (33, 70)
White	32 0	28	11	11 (-1, 22)	25	32	32 (14, 50)	27	37	37 (19, 55)	30	50	50 (32, 68)
Black	9 11	13	15	4 (-24, 33)	14	36	25 (-8, 57)	10	80	69 (37,101)	9	56	44 (6, 83)
AFL/AF													
Yes	29 3	22	14	10 (-6, 26)	33	33	30 (12, 47)	25	44	41 (20, 61)	24	50	47 (25, 68)
No	12 0	19	11	11 (-3, 24)	7	43	43 (6, 80)	13	54	54 (27, 81)	16	50	50 (26, 75)
Digoxin													
Yes	20 5	20	5	0 (-14, 14)	23	30	25 (4, 47)	24	29	24 (4, 45)	24	50	45 (23, 67)
No	21 0	21	19	19 (2, 36)	17	41	41 (18, 65)	14	79	79 (57,100)	16	50	50 (26, 75)
EF													
decre.	23 4	19	16	11 (-7, 30)	13	46	42 (13, 70)	20	50	46 (22, 69)	14	57	53 (26, 80)
normal	16 0	18	11	11 (-3, 26)	26	31	31 (13, 49)	13	38	38 (12, 65)	18	44	44 (21, 67)
LAD													
enlarge	29 3	29	10	7 (-6, 20)	31	39	35 (17, 54)	26	50	47 (26, 67)	25	52	49 (28, 69)
normal	10 0	10	10	10 (-9, 29)	7	29	29 (-5, 62)	11	36	36 (8, 65)	11	45	45 (16, 75)
VAD													
Yes	24 0	19	11	11 (-3, 24)	22	45	45 (25, 66)	25	40	40 (21, 59)	24	63	53 (43, 82)
No	17 6	21	14	8 (-10, 27)	17	24	18 (-5, 41)	13	62	56 (27, 84)	12	25	19 (-8, 46)

Δ = active dose group minus placebo C.I. = 95% confidence interval for Δ

Table A.3. Demographic and Baseline Characteristics of Evaluable Patients (Study 15)

		Placebo		1.0/0.5 mg		1.0/1.0 mg	
		N = 81		N = 79		N = 82	
Age (years)	Mean	65.6		67.3		67.8	
	Range						
Weight (lbs)	Mean	184.0		181.0		181.6	
	Range						
Duration of Arrhythmia (days)	Median	4.5		8.5		11.0	
	Range			(			
		N	%	N	%	N	%
Race (n, %)	White	72	88.9	66	83.5	65	79.3
	Black	9	11.1	13	16.5	13	15.9
	Other	0	0.0	0	0.0	4	4.9
Sex (n, %)	Female	13	16.1	15	19.0	20	24.4
	Male	68	84.0	64	81.0	62	75.6
Left Atrial Diameter* (n, %)	Normal	16	20.8	12	16.7	11	14.3
	Enlarged	61	79.2	60	83.3	66	85.7
Ejection Fraction* (n, %)	Normal	28	43.1	32	50.0	25	41.0
	Decreased	37	56.9	32	50.0	36	59.0
Valvular Heart Disease* (n, %)	Present	49	62.8	55	75.3	58	75.3
	Absent	29	37.2	18	24.7	19	24.7
Concomitant digoxin (n, %)	Yes	40	49.4	48	60.8	44	53.7
	No	41	50.6	31	39.2	38	46.3
Concomitant β-blocker (n, %)	Yes	27	33.3	11	13.9	15	18.3
	No	54	66.7	68	86.1	67	81.7
Concomitant calcium channel blocker (n, %)	Yes	32	39.5	33	41.8	42	51.2
	No	49	60.5	46	58.2	40	48.8

* Not all patients had echocardiogram data prior to treatment.

Table A.4. Success rates (SR in %) by subgroups [total sample size = 266, Study 15]

	Placebo		1.0/0.5 mg				1.0/1.0 mg			
	n	SR (%)	n	SR (%)	D	C.I.	n	SR (%)	D	C.I.
Male	72	3	70	46	43	(31, 55)	71	42	39	(27, 52)
Female	14	0	16	31	31	(9, 54)	23	48	48	(27, 68)
>=70yrs	36	3	40	40	37	(21, 53)	41	41	39	(23, 55)
< 70yrs	50	2	46	46	44	(29, 59)	53	45	43	(29, 57)
White	77	3	69	39	37	(24, 49)	76	39	37	(25, 48)
Black	9	0	17	59	59	(35, 82)	14	64	64	(39, 89)
AFL/AF										
Yes	46	4	46	41	37	(22, 52)	44	36	32	(17, 47)
No	40	0	40	45	45	(30, 60)	50	50	50	(36, 64)
Digoxin										
Yes	43	2	52	46	44	(30, 58)	52	38	36	(22, 50)
No	43	2	34	38	36	(19, 53)	42	50	48	(32, 63)
EF										
decre.	39	0	35	43	43	(26, 59)	42	52	52	(37, 67)
normal	28	0	35	46	46	(29, 62)	30	40	40	(22, 58)
LAD										
enlarge	65	3	65	42	38	(26, 51)	75	43	40	(28, 52)
normal	17	0	13	46	46	(19, 73)	14	50	50	(24, 76)
VAD										
Yes	52	2	59	39	37	(24, 50)	64	42	40	(28, 53)
No	31	3	20	55	52	(29, 74)	25	48	45	(24, 65)

D = active dose group minus placebo C.I. = 95% confidence interval for D

BIO/DISSOLUTION

REVIEW

AUG 22 [illegible]

DW

Biopharmaceutics/Pharmacokinetics Review

NDA:20-491

Ibutilide fumarate injection.
Corvert®
The Upjohn Company.
0.1 mg/ml solution.

Submission Data: October 27, 1994.
October 31, 1994.
January 27, 1995.
March 1, 1995.
March 2, 1995.
March 27, 1995.
March 31, 1995.
April 12, 1995.

Category: 1S.

Reviewer: Patrick J Marroum.

Type of submission: new molecular entity.

Synopsis:

Corvert® is a novel class III antiarrhythmic agent. It contains ibutilide fumarate which is a racemate of two enantiomers.
The sponsor has studied the intravenous pharmacokinetics of ibutilide (both bolus and constant IV infusion over 8 hours) since the drug will only be given intravenously. Human pharmacokinetic studies have shown that ibutilide has a high systemic clearance (about 29 ml/min/kg) that exceeds liver blood flow and a large steady state volume of distribution (about 11 l/kg). The elimination half-life averages 6 hours. The pharmacokinetics of ibutilide are linear with respect to the dose over the range of 0.01 to 0.1 mg/kg. The enantiomers of ibutilide have pharmacokinetic properties similar to each other and to ibutilide. However the (+) enantiomer has 3 to 4 times higher ability to prolong the QT interval compared to the (-) enantiomer in healthy volunteers.
In healthy male volunteers, about 82 % of the dose is excreted in the urine out of which 7 % is unchanged ibutilide. The remainder 18 % was recovered in feces.
8 metabolites were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω oxidation followed by sequential β oxidation of the heptyl side chain of ibutilide. Only the ω hydroxy metabolite of ibutilide [illegible] to possess class III electrophysiologic properties similar to that of ibutilide in an in vitro isolated rabbit myocardium model.
The sponsor investigated the effect of gender and age on the pharmacokinetics and pharmacodynamics of ibutilide and found that these two factors had no effect .
The sponsor studied the effect of atrial flutter, atrial fibrillation, the concomitant administration of digoxin, calcium channel blockers and β blockers, the effect of renal and liver impairment on the pharmacokinetics of ibutilide using a population style analysis on plasma concentrations

obtained from Protocols 14 and 15 (the two major safety and efficacy trials).
The sponsor established a pharmacokinetic pharmacodynamic model to correlate QTc prolongation with ibutilide plasma concentrations.
Ibutilide is moderately bound to plasma pro ins (41 %). However, the sponsor did not provide any information about its red blood cell partition coefficient.
The sponsor has adequately validated the chiral HPLC assay used in some of these studies.

RECOMMENDATION:

The sponsor's NDA 20-491 appears to be acceptable for meeting the biopharmaceutics requirements provided that the comments on Page 9-10 are adequately addressed by the sponsor.

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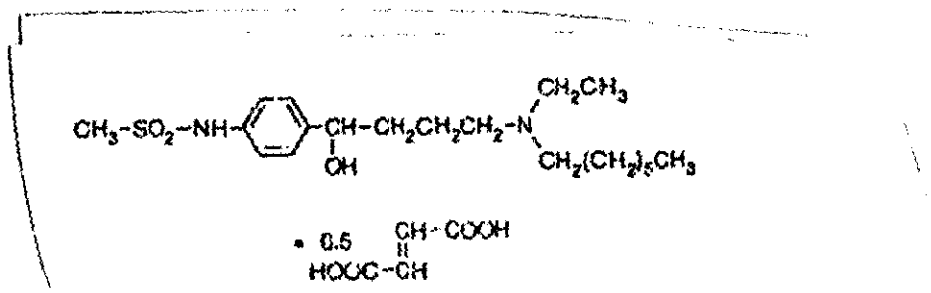
Background:

Ibutilide fumarate is N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]-phenyl]methanesulfonamide,(E)-2-butenedionate (1:0.5) salt. The molecular formula of ibutilide fumarate is C22H38N2O5S and it has a molecular weight of 442.62 g/mole. The structural formula is shown below:



Ibutilide Fumarate

The compound is a white to off white crystalline powder with an aqueous solubility of greater than 100 mg/ml at any pH less than 7. Between the pH 7 and 9.4 the aqueous solubility decreases and reaches a minimum of 6 mg/ml at pH 9.4. Above pH 9.5, the

aqueous solubility increases rapidly and is greater than 100 mg/ml above pH 10.5.
Ibutilide fumarate behaves as an ampholyte with pka of approximately 8.4 and 9.6.
Ibutilide fumarate has one chiral center and exists as a racemate of the (+) and (-) enantiomers.
Corvert[R] (ibutilide fumarate) is a novel class III antiarrhythmic agent that increases the refractory period and action potential duration of myocardial cells.
Ibutilide fumarate is proposed for the rapid termination of hemodynamically stable atrial flutter or atrial fibrillation. The drug will be administered as IV infusion of 1 mg over 10 minutes. If the arrhythmia does not terminate during the infusion or within 10 minutes after the end of the infusion, another 1 mg dose administered over 10 minutes may be given. For patients weighing less than 60 kg, a dose of 0.01 mg/kg should be administered over 10 minutes instead of 1 mg.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

I.PHARMACOKINETICS:

Human pharmacokinetic studies have shown that ibutilide has a high systemic clearance (mean value of 29 ml/min/kg) that approximates liver blood flow and a large volume of distribution at steady state (mean =11 l/kg). The apparent elimination half-life averaged approximately 6 hours. Post infusion ibutilide concentrations decreased rapidly in a multiexponential fashion with at least 2 distribution phases followed by an elimination phase. The following table summarizes the main pharmacokinetic parameters obtained from the triexponential model of 0.01 mg/kg (mean total dose of 0.78 mg) of ibutilide infused over 10 minutes (Study 7215-93-019).

	A (ng/ml)	B (ng/ml)	C (ng/ml)	Alpha (hrs^{-1})	Beta (hrs^{-1})	Gamma (hrs^{-1})
Mean	24.8	2.49	1.48	31.1	2.79	0.125
Sd	6.8	0.7	0.36	6.3	0.47	0.018

Ibutilide pharmacokinetics exhibited somewhat high interindividual variability. The interindividual coefficients of variation for Cl, Vss and Vc were estimated to be 69 %, 43 % and 85 % respectively. The residual variability expressed as % CV was estimated to be 95 %.
The (+) and (-) enantiomers of ibutilide (U-82208 and U 82209) have pharmacokinetic properties similar to each other and to ibutilide. The mean +/- SD CL (27.6 +/- 7 ml/min/kg) and mean Vss (13.2 +/- 6.9 l/kg) of the (+) enantiomer were similar to respective values estimated for the (-) enantiomer (CL= 30.7 +/- 9 ml/min/kg and Vss=12.9 +/- 4.3 l/kg) after dosing with each single enantiomer. Moreover, no concentrations of the other enantiomer were found after dosing with either U-82208E and U-

82209E indicating no in vivo interconversion between enantiomers. After administration of the racemate, 52.8 % is present as the (+) enantiomer while 48 % as the (-) enantiomers. This ratio did not vary with time

II-PROTEIN BINDING:

The in vitro protein binding measured by ultrafi n ranged from 37 to 46.1 % with a mean value of 41.4 and was independent of concentration in the range of 1.1 to 987 ng/ml.

III-RED BLOOD CELL PARTITIONING:

The sponsor did not report any value for the plasma/red blood cell partition coefficient for ibutilide.

IV-METABOLISM:

82 % of the ^{14}C ibutilide fumarate dose was recovered in the urine while the remaining 18 % was recovered in the feces. 6.7 % of the radioactivity in the urine is due to unchanged ibutilide while the remainder 93 % are due to eight metabolites out of which 6 were also found in the feces.
In vitro studies indicated that the initial metabolite of the primary pathway was the alcohol formed by ω- oxidation of the heptyl side chain of ibutilide (see metabolic scheme in Appendix I page 86). The cytochrome P-450 responsible for this major pathway was not identified. The aldehyde and the acid formed by oxidation of the alcohol were identified in human urine. Further metabolism of the acid metabolite occurs by β-oxidation of the heptyl side chain. Some of the formed acid metabolites are major metabolites identified in urine (Study 7215-94-017).
Initial (ω-1)-oxidation of the heptyl side chain and the associated one carbon loss pathway is a less significant metabolism pathway in humans and is thought to be mediated by CYP2D6. The formation of the N-desheptylated metabolite (which was below the limit of detection in both urine and feces), another minor metabolic pathway of ibutilide, is thought to be mediated by cytochrome 3A4.
Of all the isolated metabolites in humans, the only one that seems to have any activity is the ω-alcohol of ibutilide which results from hydroxylation of the terminal methyl carbon of the aminoheptyl side chain. Preliminary analysis of plasma samples from 4 normal volunteers seem to indicate that systemic exposure to this metabolite is less than 10 % of the corresponding ibutilide exposure based on AUC and less than 1 % based on CMAX (Study 7215-94-032)

V-DOSE AND DOSAGE FORM PROPORTIONALITY:

Study 7215-93-019 showed that the pharmacokinetics of ibutilide is linear with respect to the dose between the dose range of 0.01 mg/kg to 1 mg/kg infused over 8 hours as evidenced by no statistical differences in clearance and volume of distribution. Moreover, both CMAX

and AUC were increased proportionally to the administered dose.

VI-SPECIAL POPULATIONS:

A-Age:

Age did not have any effect on the pharmacokinetics of ibutilide and its 2 enantiomers as evidenced by the fact that elderly and young subjects have similar clearance and volume of distribution.

B-Gender:

Gender does not seem to have any effects on either the pharmacokinetic of ibutilide or its two enantiomers. (Study 7215-94-032)

C-Atrial flutter and atrial fibrillation:

Bayesian estimates of clearance and volume of distribution at steady state obtained from the population analysis of Protocol 14 and 15 (the two pivotal clinical trials) seem to indicate that the pharmacokinetic characteristics of ibutilide in patients with atrial flutter or atrial fibrillation did not differ from those of healthy normal volunteers.

D-Liver impairment:

The effect of liver impairment on the pharmacokinetics of ibutilide could not be determined since patients with liver impairment were excluded from the clinical trials and the sponsor did not perform any pharmacokinetic studies in liver impairment subjects.

E-Renal impairment:

Bayesian estimates of clearance obtained for patients with impaired renal function were not different from the bayesian estimates of patients with normal renal function (Protocol 14 and 15). No significant relationship between creatinine clearance and ibutilide clearance could be observed from these two clinical studies. Moreover, because less than 10 % of the dose is excreted unchanged in the urine and due to the fact this drug will not be administered chronically, the sponsor did not perform any pharmacokinetic studies in patients with severe renal impairment.

F-Patients with decreased left ventricular function:

Study 7215-95-004 showed that in general there was no difference in the pharmacokinetics of ibutilide between patients with LVEF < 35 % and patients with LVEF > 35 %. However, the pharmacokinetics of ibutilide in this study were characterized by atypically high intersubject variability and atypical concentration time profile. Moreover, a correlation

between QTc prolongation and plasma concentrations of ibutilide could not be established. This is contrary to what was found in healthy normal volunteers where the change in QTc was correlated with plasma concentrations via a sigmoidal EMAX model.
This variability in the pharmacokinetic results might be due to the invasive nature of this study.

G-Patients with inducible ventricular tachycardia:

Results of study 7215-95-005 indicated that patients with inducible ventricular tachycardia undergoing electrophysiologic study had atypical plasma concentration time profiles. The intersubject variability was atypically very high. Similarly to the above study, no correlation between QTc prolongation and the ibutilide plasma concentrations could be established. Once again, the variability in the observed results might also be due to the invasive nature of this study.

VIII-DRUG INTERACTIONS:

A-Calcium Channel Blockers:

No formal pharmacokinetic drug interaction studies of ibutilide with calcium channel blockers were undertaken by the sponsor. However, the sponsor calculated the bayesian estimates of the clearance and volume of distribution at steady state of the patients that were on concomitant calcium channel blockers. The estimated clearance and volume of distribution of ibutilide in these patients were found not to be different than in the patients not taking calcium channel blocker. (Protocol 14 and 15).

B-Beta Adrenergic Blockers:

The same approach as with calcium channel blockers was used to study the interaction of ibutilide with beta adrenergic blockers. It was found that the clearance and volume of distribution at steady state of ibutilide was not different in patients taking beta blockers from those that are not.

C-Digoxin:

Ibutilide did not seem to affect the digoxin plasma levels since the digoxin plasma levels were the same prior and 1 hour after ibutilide administration. Moreover the bayesian estimates of the clearance and volume of distribution at steady state of ibutilide were the same for the subjects on digoxin as the patients that were not on digoxin.

IX-PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

A direct correlation seems to exist between dQT and concentration. The sponsor fitted the dQT vs concentration to the sigmoidal EMAX model for the subjects that participated in the

three highest doses in Study 7215-93-019. The estimates of the pharmacodynamic parameters were as follows:

Dose mg/kg	0.03	0.06	0.1
Infusion Duration	10 min	8 hours	8 hours
# Subjects	8	5	7
Emax msec	205 (51)	106 (38)	134 (32)
Ec50 ng/ml	1.4 (0.2)	1.5 (0.5)	2.3 (0.7)
Sigmoidicity	4 (1.5)	5.4 (2.4)	6.1 (3.5)

( )= SD.

The sponsor concluded that the Emax appears to be influenced by the rate of infusion as well as the total dose of ibutilide. The sponsor attributed this finding to the rapid and extensive distribution characteristics of ibutilide. However, a simultaneous fitting of these three doses using a population approach seems to indicate that one of the explanations for the differences in EMAX might be that there is tolerance to the dQT effects of ibutilide. The results of this modelling undertaken by this reviewer will be presented in a separate report. Additionally, the results of Study 7215-94-026 seem to indicate that even though the pharmacokinetics of each enantiomer were similar, the maximum effect differed for each compound dosed. According to the sponsor, this difference was most likely due to a shift in the dose response curve due to a potency difference in enantiomer activity.
The pharmacodynamic parameters of ibutilide and its two enantiomers can be summarized as follows:

Parameter Estimates	Ibutilide fumarate	U-82208E(+)	U-82209F(-)
Emax msec	120 (37)	172 (34)	44 (10)
EC50 ng/ml	0.58 (0.18)	0.55 (0.14)	0.98 (0.69)
Sigmoidicity	5 (3)	4.7 (2.7)	3.9 (2.8)

( ) = SD.

Study 7215-94-032 showed that neither age nor gender seem to affect the QT prolongation of

ibutilide since similar pharmacodynamic values were obtained in these two populations. It is to be noted that even though there was a correlation between QT prolongation and ibutilide plasma concentrations, no relationship between success of treatment (conversion) or proarrhythmia and plasma concentrations could be established in either Protocol 14 or 15.

X-FORMULATION:

Two formulations of ibutilide fumarate injection have been developed:2.5 mg/ml and 0.1 mg/ml solutions. The 2.5 mg/ml solution diluted 25 to 500 fold with either 5 % Dextrose or 0.9 % Sodium Chloride Injection prior to administration has been used for clinical development. The 0.1 mg/ml formulation has been developed for use as a marketed product and was used in later clinical trials. It is equivalent to a 1:25 dilution of the 2.5 mg/ml formulation with 0.9 % Sodium Chloride Injection. The compositional formula of ibutilide fumarate is given in Appendix II as well as the composition of all the formulas that were used in the clinical trials.

XI-ASSAY:

Concentrations of ibutilide fumarate along with both of its enantiomers in plasma and urine were measured with a chiral HPLC method with fluorescence as a detection mode after derivatization.
The concentrations of the ω-1 hydroxy metabolite (U-860-92) and ω hydroxy metabolite (U-107246) from plasma samples were determined using liquid chromatography coupled with mass spectrometry.
Overall, these assays were deemed satisfactory.

Comments to be Sent to the Firm:

1-The sponsor should provide information on the red blood cell partition coefficient of ibutilide.

2-In the ^{14}C ADME study (Study 7215-94-017), data on the recovery of ibutilide and its metabolites in the feces were given only for two subjects. Conclusions on the recoveries in feces were based on the data from these two subjects. Due to the very small sample size (n=2), the conclusions drawn might not be valid. In future studies, the sponsor is asked to provide data from more than 2 subjects. (In such ADME studies, a typical n value would be at least 6 subjects).

3-In protocol 14 and 15, the sponsor collected blood samples up to 3 hours only, yet the terminal half-life of ibutilide is estimated to be 6 hours. This means that the sponsor only covered less than one $t_{1/2}$ of the drug. For this reason, it would be very difficult to develop a population model that will describe adequately the pharmacokinetics of ibutilide from such a

data set. Therefore, the conclusions that can be drawn are very limited and should be viewed within the context of the limitations of these two studies.

4-The model chosen by the sponsor to describe the data obtained from Protocols 14 and 15 is not adequate as evidenced e.g. by a high residual variability (%CV of 95 %). Thus, the data obtained from this analysis might not have the ability or power to detect the effect of the various investigated covariates on the pharmacokinetics of ibutilide. The sponsor should have tried different models to attempt to decrease the % residual variability that was observed with the two compartment model the sponsor chose.

5-The sponsor concludes from the results obtained from Protocol 14 and 15 that liver impairment did not have any effect on the pharmacokinetics of ibutilide. Yet in the inclusion criteria in the protocols, patients with liver impairment were excluded from participation in the studies. In both these clinical trials there was only one patient that could be considered as having liver impairment. Therefore no conclusion can be made on the effect of liver impairment on the pharmacokinetics of ibutilide.

6-Labelling Comments:

a-In the metabolism section of the package insert on page 3: the following statement should be added: "only the ω hydroxy metabolite of ibutilide possesses class III electrophysiologic properties similar to that of ibutilide in an in vitro isolated rabbit myocardium model. However, the concentrations of this active metabolite are less than 10 % of that of ibutilide

In the drug interactions section:

b-Under Digoxin: the statement that **"the pharmacokinetics of Corvert injection are not different in patients treated concomitantly with digoxin when compared with those who were not concomitantly treated."** This statement is based on the population analysis of Protocols 14 and 15. However, due to the reasons outlined in Comments 3 and 4, no conclusions with regard to drug interactions could be drawn from their analysis.

c-The sections on calcium channel blockers and beta adrenergic blocking agents should be replaced by the following statement:
"Coadministration of either calcium channel blockers, adrenergic blocking agents or digoxin did not have any effects on either the safety and efficacy of ibutilide in the clinical trials."

Patrick J Marroum Ph.D.
P Marroum 8/22/1995

Biopharm Day on August 4, 1995 (Ludden, Fleischer, Chen, Hepp, Gillespie, Hussain, Parekh, Gordon and Marroum).

RD/FT initialed by O. Borges Ph.D. 8/22/95

cc: NDA 20-491, HFD 110, HFD 426 (Marroum, Fleischer), Chron, Drug, G , DI, A, HFD 19 (FOI), HFD 340 (Vishwanathan), HFD 427 (M Chen), PkPd.

APPENDIX I

The pharmacokinetics and pharmacodynamics of ibutilide fumarate after intravenous infusions in healthy male volunteers.

Study: 7215-93-019 Volume: 1.45 Pages: 06/04/1-202.

Investigators:

Clinical: Dr. James T. Vanderlugt
The Upjohn Research Clinics-BCIU.
Kalamazoo, MI 49007.

Objectives:

To describe and evaluate the pharmacokinetics of ibutilide in healthy male volunteers in relation to dose and length of infusion and to investigate the pharmacodynamic relationship between QT interval prolongation and ibutilide plasma concentrations.

Formulation

-Ibutilide fumarate sterile solution (2.5 mg/ml). Lot # 25561.
-Placebo lot # 25562.

Study Design:

This single dose, double blind, parallel, placebo-controlled dose escalating study in healthy male volunteers between the ages of 18 and 50 years. The volunteers received either an infusion of ibutilide (n=6 or 8 per dose group) or placebo (n=9 for the 10 minute infusion groups and n=10 for the 8 hour infusion groups). The doses that were investigated were 0.001 mg/kg, 0.003 mg/kg and 0.03 mg/kg ibutilide infused over 8 hours. Originally, the protocol was designed with only 10 minute duration ibutilide infusions with doses up to 0.25 mg/kg. However, the protocol was amended and the 8 hour infusion duration treatments were examined in light of excessive QT interval prolongation observed after the 0.03 mg/kg dose administered over 10 minutes.
Ibutilide sterile solutions (2.5 mg/ml) was diluted in an appropriate amount of D_5W (5% dextrose in water) to acheive the following infusate concentrations for each dose level:

Dose (mg/kg)	Infusate concentrations (mg/ml)
0.001	0.0025
0.003	0.0075
0.010	0.025
0.03	0.075

0.06	0.15
0.1	0.25

Signal averaged electrocardiograms were done twice prior to dosing and at various times after the infusions (usually corresponding to a blood sampling time). Heart rate, PR, QRS and QT intervals were averaged from 25 beats.
Blood samples were collected from subjects receiving the 10 minute infusion at the following times: 0, 10 minutes (at the end of the infusion), 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after the start of the infusion.
Blood samples were collected from subjects receiving the 8 hour infusion at the following times: 0, 1, 2, 4, 6, 7, 8, 8.083, 8.25, 8.5, 9, 9.5, 10, 11, 12, 14, 16 and 24 hours after the start of the infusion.
Saliva samples were collected from the subjects that received 0.1 mg/kg ibutilide infused over 8 hours.

Assay:

Concentrations of ibutilide in plasma were determined using HPLC with fluorescence detection at 345 nm.

-Specificity: satisfactory. Chromatograms presented.
-Linearity: satisfactory. Calibration curves ranging from 0.05 to 20 ng/ml.
-Sensitivity: the limit of quantification which was set to be the upper 95 % confidence limit of the intercept was 0.1295 ng/ml.
-Precision: the between day precision expressed as % CV was 6.3 %.
CV for quality control samples ranged from 8 % at 0.2567 ng/ml to 3 % at 5.13 ng/ml.
-Accuracy: The mean recovery for the quality control samples were 97 +/- 7 %.

Data Analysis:

Pharmacokinetic data analysis:

Pharmacokinetic parameters were calculated using moment analysis methods and also using a three compartment body model.
Pharmacokinetic parameters were not estimated from data from the lower ibutilide doses (0.01 and 0.003 mg/kg infused over 10 minutes and 0.01 mg/kg infused over 8 hours) due to the lack of sufficient concentration time points.

Pharmacodynamic data analysis:

Prolongation of the QT interval (dQT) was calculated as the difference between the measured QT interval and the average of the two pre-dose values for a given subject. The dQT from the lower ibutilide doses (0.001, 0.003 and 0.01 mg/kg ibutilide infused over 10 minutes and 0.01 and 0.03 mg/kg infused over 8 hours) was insufficient in magnitude and/or number of

data points for pharmacodynamic evaluation.
The dQT vs ibutilide concentrations (individual subject) from the larger doses (0.03 mg/kg infused over 10 minutes and 0.06 and 0.1 mg/kg infused over 8 hours) were fitted to the sigmoid EMAX model using the NLIN procedure in SAS. Data from 0 to 8 hours, 0-14 hours and 0-16 hours were used for the 0.03 mg/kg/10 min dose, the 0.06 mg/kg/8 hour dose and the 0.1 mg/kg/8- hour dose respectively.

Results:

-Table 1 shows the mean ibutilide pharmacokinetic parameters for some of the dosing regimens used in this study while Table 2 shows the calculated pharmacodynamics parameters for 2 doses.
-Figures 1 and 2 show the composite plots following the 10 minute and 8 hour infusion respectively. Figure 3 shows the dose proportionality data for AUC and clearance.
-Figures 4 and 5 show the mean ibutilide concentration time profiles for both infusion rates.
-Table 3 gives a summary of the compartmental pharmacokinetic parameters for some of the subjects that were given 0.01 mg/kg infused over 10 minutes.
-Figures 6 and 7 show the mean QT interval vs time for both infusion rates.
-Figures 8 and 9 show mean QT interval vs mean ibutilide concentration for both infusion rates.

The results show that ibutilide half-life was around 6 hours and could be fitted to a tri-exponential. Ibutilide had a high systemic clearance approximating liver blood flow (30 ml/min/kg).The VDss was large and was estimated to be 11 l/kg. The inter subject variability was estimated to be around 25 to 30 %. Ibutilide AUC and Cl did not show any deviation from dose proportionality. A direct correlation between dQT and ibutilide plasma concentration was observed evidenced by a lack of hysteresis in the data during and after the 8 hour infusion.
Ibutilide was characterized by having a steep concentration effect relationship with a relatively consistent EC50 among doses and infusion rates. However, EMAX was influenced by both the dose and rate of ibutilide infusion with the highest EMAX value obtained with the infusion of 0.03 mg/kg over 10 minutes.

TR No.: 7215-93-019

Table 8

Ibutilide Pharmacokinetic Parameter Estimates [Mean (% CV)] and Statistical Analysis

Dose, mg/kg	0.01	0.03	0.03	0.06	0.10	ANOVA
Infusion Duration	10 min	10 min	8 hours	8 hours	8 hours	p-value
No. of Subjects	8	8	6	8	8	---
C_{max}, ng/mL	8.8 (36%)	28.2 (38%)	2.0 (25%)	3.3 (26%)	5.2 (14%)	0.0001
$AUC_{0-\infty}$, ng•h/mL	5.7 (15%)	18.5 (31%)	21.5 (29%)	36.3 (27%)	55.3 (17%)	0.0001
CL, mL min^{-1}/kg	29.8 (17%)	29.7 (32%)	24.5 (22%)	29.1 (22%)	30.9 (16%)	0.4709
V_{ss}, L/kg	11.5 (25%)	13.7 (45%)	9.6 (28%)	11.8 (25%)	10.5 (24%)	0.3339
Half-life, hours	5.9	6.9	6.1	6.7	5.7	0.3108*

* ANOVA p-value from comparison of the elimination rate constant values.

Table 9

Ibutilide Pharmacodynamic Parameter Estimates (Mean ± SD)

Dose, mg/kg	0.03	0.06	0.10
Infusion Duration	10 min	8 hours	8 hours
No. of Subjects	8	5	7
Emax, msec	205 ± 51	106 ± 38	134 ± 32
EC50, ng/mL	1.4 ± 0.2	1.5 ± 0.5	2.3 ± 0.7
Slope Factor	4.0 ± 1.5	5.4 ± 2.4	6.1 ± 3.5

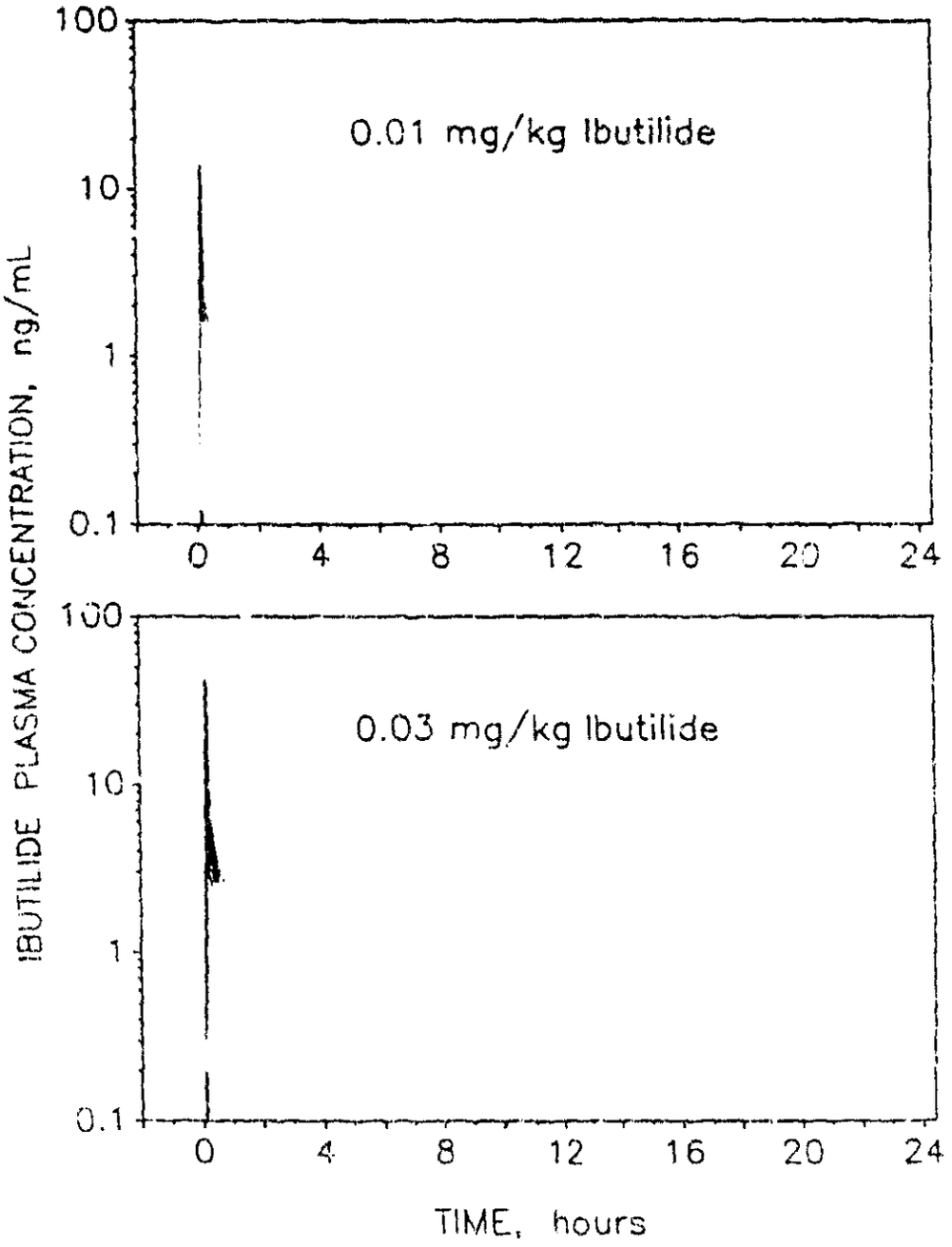
TABLE 3

Summary of Nonlinear Curve Fitting of Ibutilide Protocol P-7550-0001

0.01 mg/kg Ibutilide Dose Infused Over 10 Minutes
(PCNONLIN Triexponential Model 19)

Subject	Parameter Estimate					
	R	S	Q	α	β	γ
17						
24						
25						
28						
30						
31						
32						
33						
Mean	24.8	2.49	1.48	31.1	2.79	0.125
S.D.	6.8	0.70	0.36	6.3	0.47	0.018
%CV	27%	28%	24%	20%	17%	14%

Figure 1 **Composite Plot of Individual Subject Ibutilide Plasma Concentrations Following 10-minute Intravenous Infusion of Ibutilide**



Appendix A

Figure 2 **Composite Plots of Individual Subject Ibutilide Plasma Concentrations Following 8-hour Intravenous Infusion of Ibutilide**

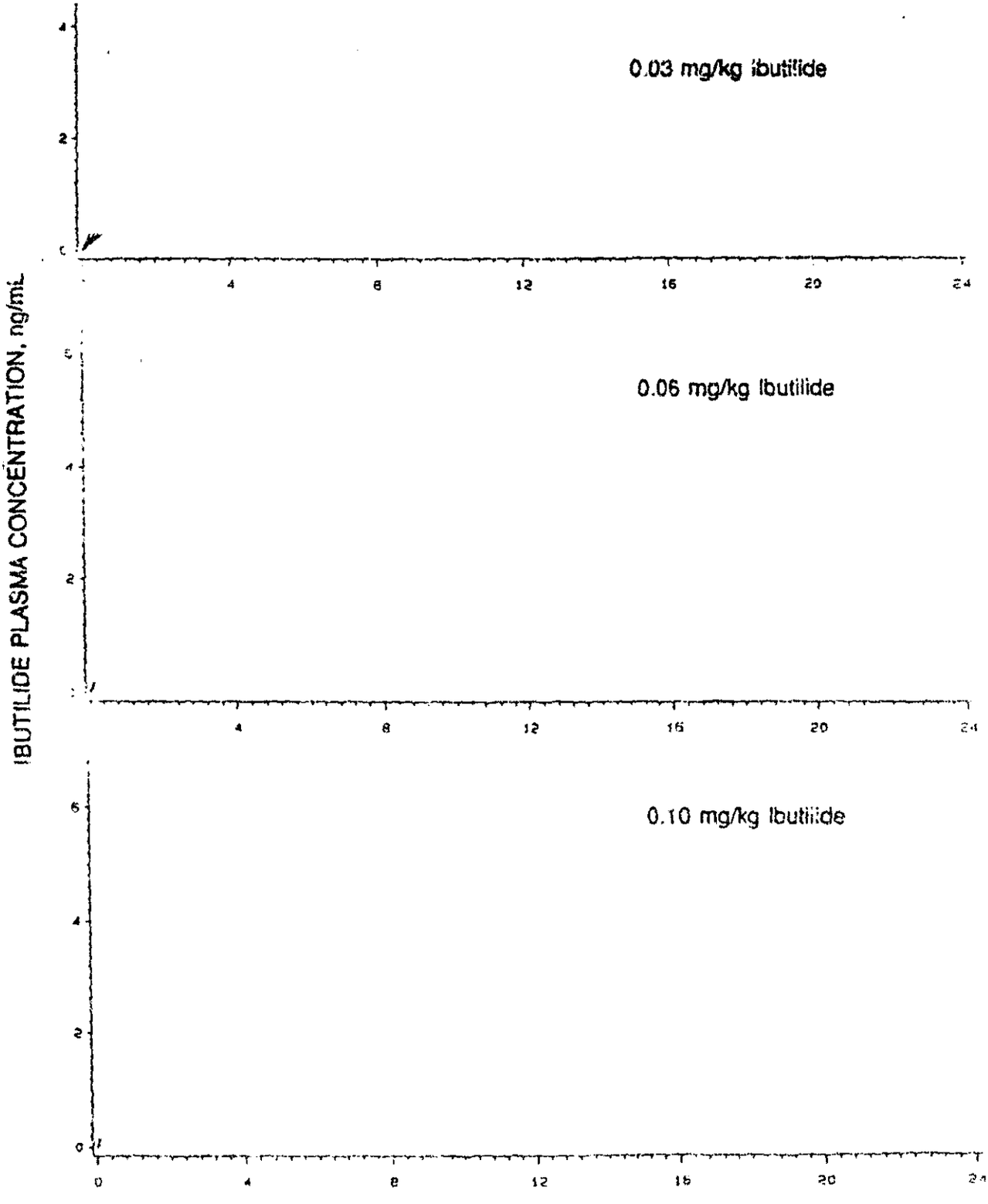


Figure 3. **Dose Proportionality of Ibutilide: AUC and Clearance Data From Individual Subjects and the Mean ± 3D in Relation to Ibutilide Dose**

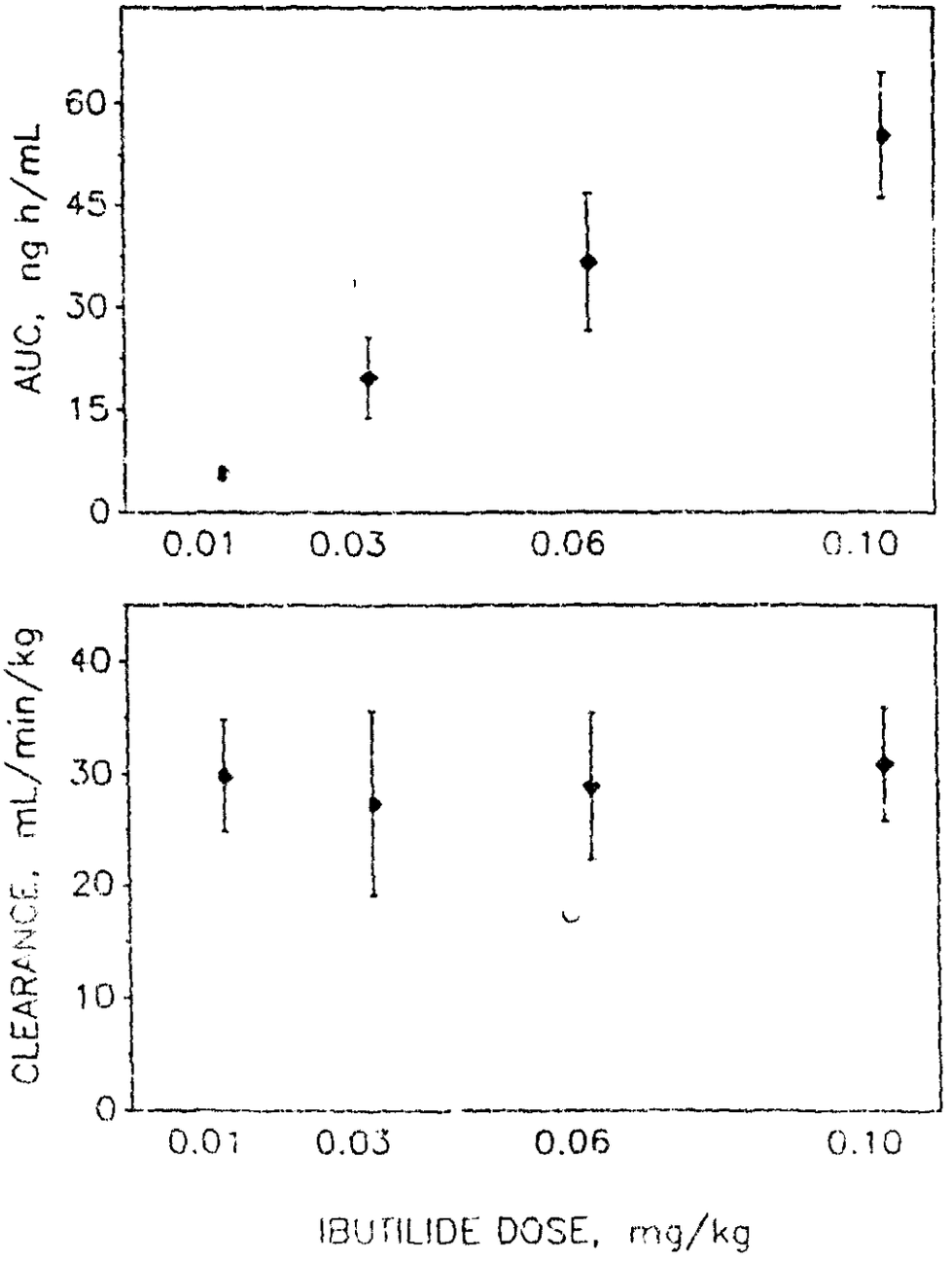


Figure 4. Mean ibutilide plasma concentration versus time after a 10-minute infusion of ibutilide fumarate Protocol P/7550/0001 [NDA reference 6.3]

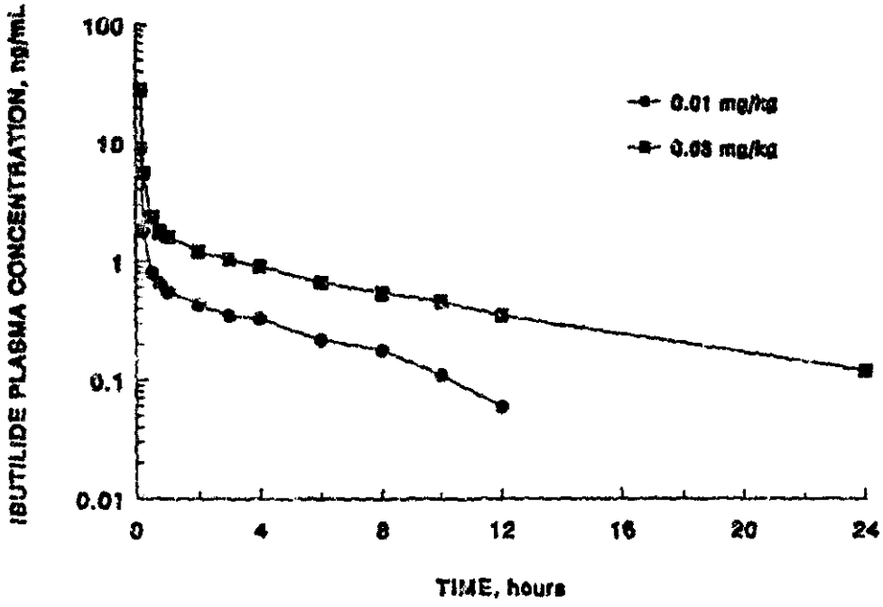


Figure 5. Mean ibutilide plasma concentration versus time after an 8-hour infusion of ibutilide fumarate Protocol P/7550/0001 [NDA reference 6.3]

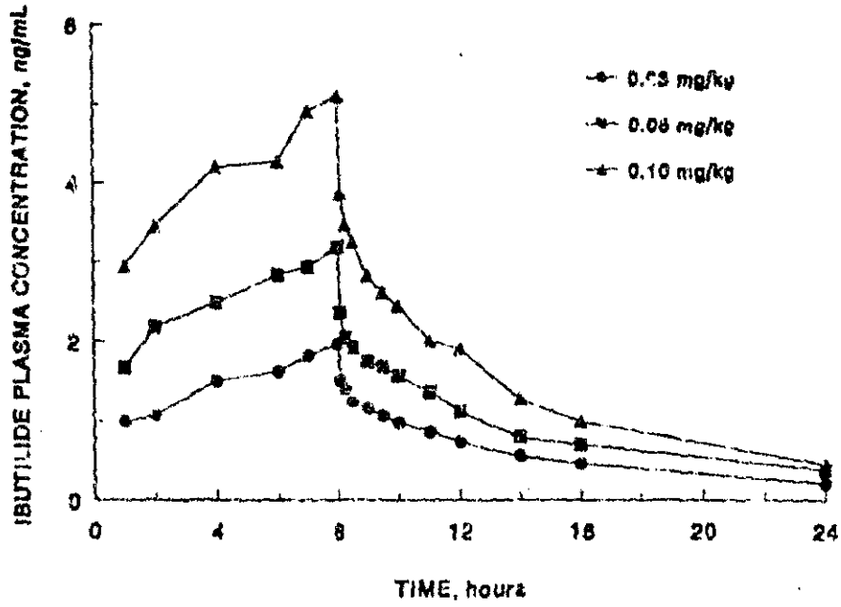


Figure 6 Mean QT interval versus time
after a 10-minute infusion of ibutilide fumarate
Protocol P/7550/0001 [NDA reference 6.3]

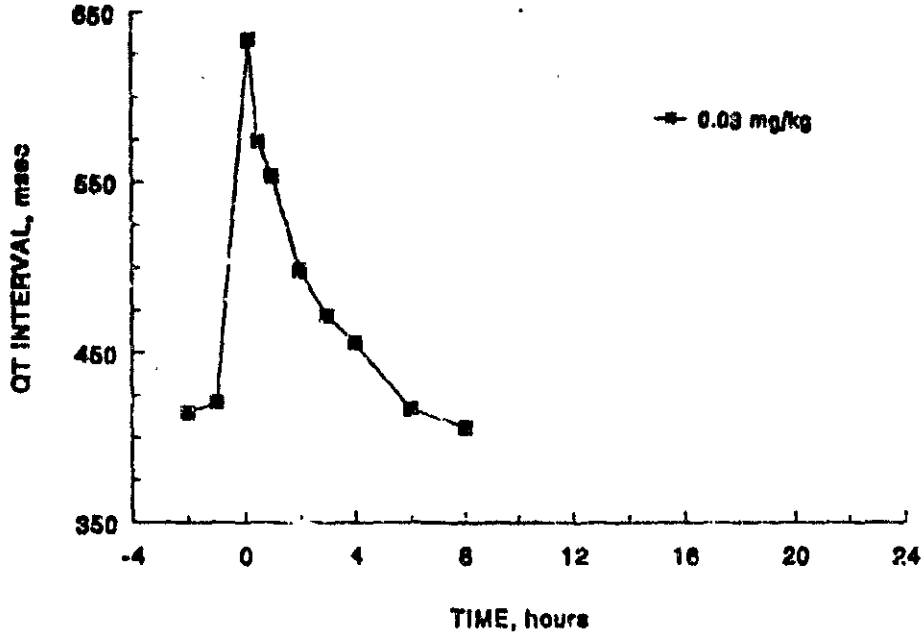


Figure 7 Mean QT interval versus time
after an 8-hour infusion of ibutilide fumarate
Protocol P/7550/0001 [NDA reference 6.3]

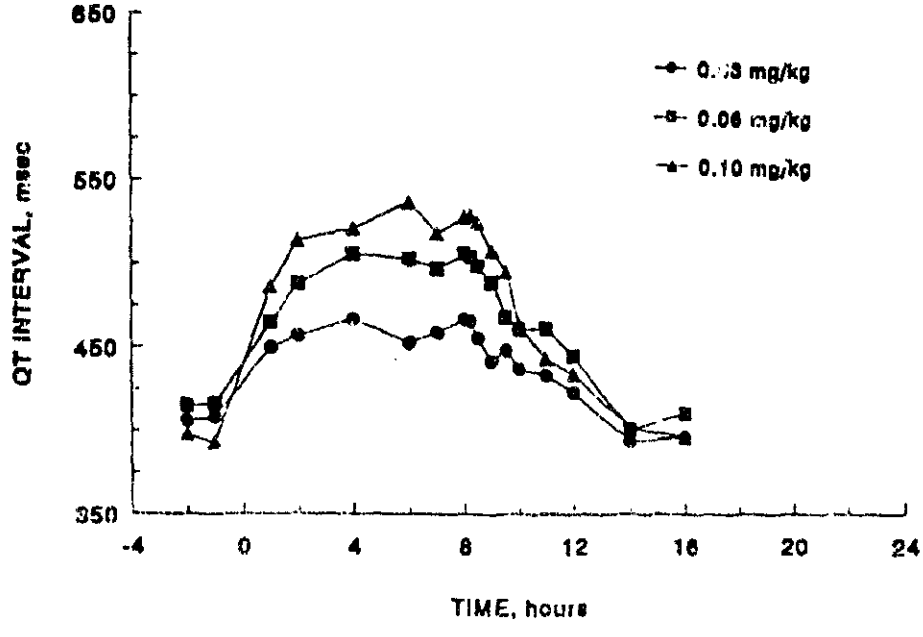


Figure 8 Mean QT interval versus mean ibutilide plasma concentration after a 10-minute infusion of ibutilide fumarate Protocol P/7550/0001 [NDA reference 6.3]

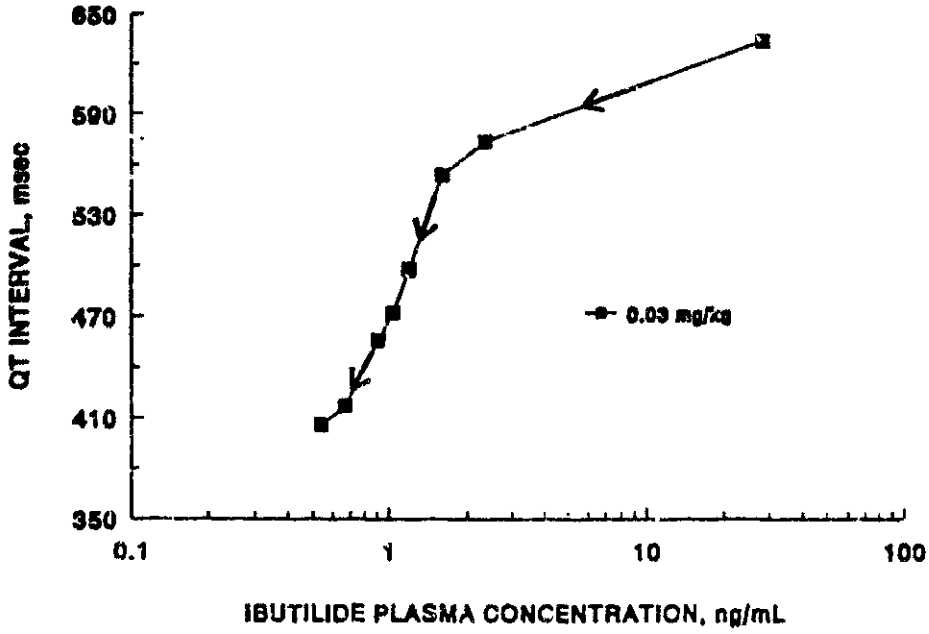
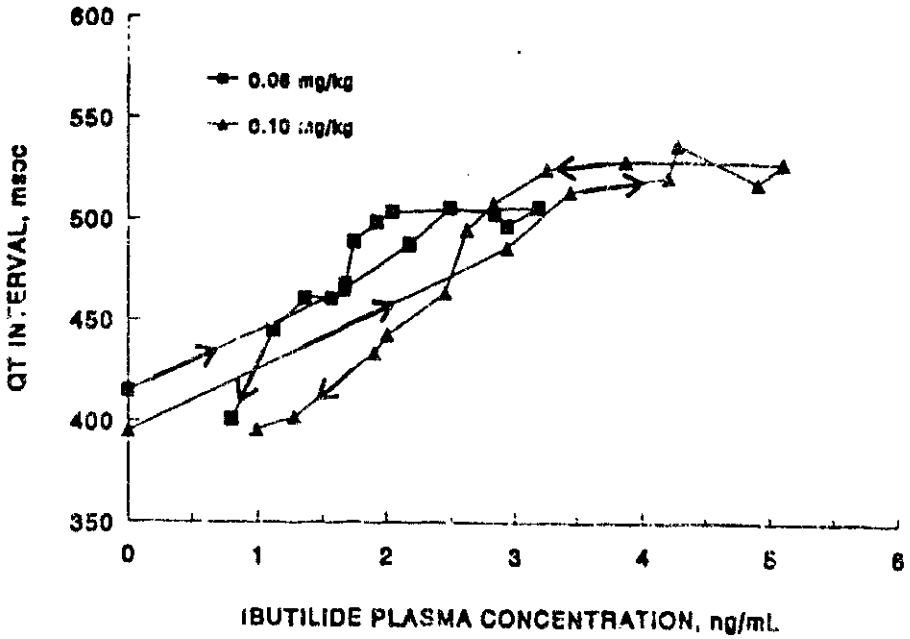


Figure 9. Mean QT interval versus mean ibutilide plasma concentration after an 8-hour infusion of ibutilide fumarate Protocol P/7550/0001 [NDA reference 6.3]



Assay method for U-70226E in saliva and comparison of saliva and plasma U-70226E and enantiomer concentrations after intravenous infusion of ibutilide in healthy male volunteers.

Study #: 7256-93-129. Volume: 1-45 Pages: 06/04/204-233.

Investigator:

Clinical: Dr. James T. Vanderlugt
The Upjohn Research Clinics-BCIU.
Kalamazoo, MI 49007.

Objectives:

The purpose of this portion of this study was to determine whether monitoring of ibutilide in saliva could provide a convenient non invasive means for monitoring concentrations of U-70226E the racemate and its enantiomers U82208E and U82209E.

Formulation:

-Ibutilide fumarate sterile solution (2.5 mg/ml). Lot # 25561.
-Placebo lot # 25562.

Study Design:

The study design was exactly as described in the previous report since this was an extension of the same study. In this portion of the study, saliva was collected from 8 volunteers who received 0.1 mg/kg infused over 8 hours. Extra blank saliva samples were collected from 2 subjects in the placebo group and were used for method development and for preparation of spiked control samples.Saliva samples were collected at the same time when plasma samples were collected by spitting into a small pre-weighed glass scintillation vial.

Assay: HPLC with fluorescence detection at 340 nm emission and 224 nm for excitation.

Ibutilide was derivatized with 0.1 % 1-naphtyl isocyanate and the enantiomers were separated via a D-phenylglycine chiral analytical column The enantiomers were detected with fluorescence at 290 nm excitation and 345 nm for emission.

Saliva:

-Specificity:satisfactory. Chromatograms presented in Figure 1 and 2 respectively showing the racemate and the separation of the two enantiomers in saliva respectively.
-Linearity: satisfactory. Calibration curves from 0.1384 to 13.84 ng/ml.

-Accuracy: the overall % recovery ranged from 84.8 to 92 %.
-Precision: the overall % precision ranged from 2.7 % to 5 %.

No validation data was presented for the enantiomeric assay in either plasma or saliva.

Data Analysis:

There was no pharmacokinetic analysis of the data.

Results:

-Figure 3 shows the mean plasma and saliva profile for the subjects where both plasma and saliva were assayed for ibutilide concentrations while Figure 4 shows the composite profiles in both matrices for some of the subjects where ibutilide concentrations were measured.
-Table 1 gives some of the plasma and saliva data for ibutilide and its enantiomers.
-Table 2 gives a summary of the some of the pk parameters in plasma and saliva.

The results show that there was a lag time of 4 hours before saliva acheived the same concentrations as plasma. The terminal half-life estimated from saliva was the same as plasma (4.8 hr vs 5.8 hr for plasma). However, the data that was obtained from saliva was much more variable (CVs as high as 59 %).
The data show that the % of each enantiomer did not vary with time in either plasma or saliva. However, the ratio of the two enantiomers were different in the two matrices. In plasma, 52.8 % was U-82208E (+) while it was 61.9 % in saliva. This suggests that the two enantiomers do not distribute similarly in the two matrices.

Comments:

The sponsor should submit assay validation data for the racemic assay and for both the two enantiomers.

Comparative pharmacokinetics and pharmacodynamics of ibutilide fumarate and its enantiomers following single 10 minute intravenous infusions in healthy male volunteers.

Study: 7215-94-026 Volume: 1.46 Pages: 06/05-1-368.

Investigators:

Clinical: Dr. James T. Vanderlugt
The Upjohn Research Clinics-BCIU.
Kalamazoo, MI 49007.

Objectives:

1-Evaluate and compare the pharmacokinetics and pharmacodynamics of ibutilide, U-82208 and U-82209 following a single intravenous infusion of ibutilide, U-82208E and U-82209E in healthy volunteers.

2-Determine if the enantiomers are interconverted in vivo following dosing with a single enantiomer of ibutilide.

3-Determine if one enantiomer affects the disposition of the other.

Investigate the relationship between QT interval prolongation and plasma concentration.

Formulation:

-Ibutilide fumarate lot# 25735.
-U-82208E (+ ibutilide) lot# 25736.
-U-82209E (- ibutilide) lot# 25737.

Study Design:

6 healthy male volunteers between the ages of 22 and 50 years participated in this double blind 3 way crossover study. In all the three phases of the study, a single dose (0.01 mg/kg) of ibutilide fumarate, U-8220E or U-82209E was administered by a 10 minute IV infusion. There was a 7 day washout period between treatments.
Blood samples were collected (pre-dose), at the end of infusion (0.167 hours) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours.
Signal-averaged ECGs for the assessment of QT intervals were obtained at the times of blood sampling.
Urine was collected at the following time intervals: -12-0, 0-2, 2-4, 4-8, 8-12 and 12-24 hours.

Assay: HPLC with fluorescence detection 224 nm excitation and 340 nm emission wavelength.
Plasma:

-Specificity: satisfactory. Chromatograms of ibutilide and its enantiomers are presented in Figure 1 and 2.
-Linearity: satisfactory. Standard Curves from 0.0175 to 17.55 ng/ml for both enantiomers.
-Precision: interassay precision was 6 % for both enantiomers.
-Accuracy: interassay accuracy as indicated by % recovery was 97 % for U-82208E and 96 for U-82209E.
-Sensitivity: The limit of quantification was 0.0351 ng/ml for both enantiomers.
No Quality control samples for intraday assays were available.

Urine:

-Specificity:satisfactory. Chromatograms of ibutilide and its enantiomers are presented in Figure 1.
-Linearity: satisfactory. Standard calibration curves from 0.1755 to 351 ng/ml for both enantiomers.
-Sensitivity: the limit of quantification was 0.702 ng/ml for each enantiomer.
-Precision: the between day precision was 12 % for both enantiomers.
-Accuracy: the between day accuracy expressed as % recovery was 107 % for U-82208E and 98 % for U-82209E.
No quality control samples for intraday assays were available.

Data Analysis:

-Data analysis was exactly the same as described in the previous study.

Results:

-Table 1 Shows the pharmacokinetic parameters for ibutilde and its two enantiomers .
-Table 2 shows the pharmacodynamic parameters for ibutilide and its two enantiomers.
-Figure 3 shows the mean plasma concentrations for ibutilide and its two enantiomers
-Figures 4 and 5 show the mean QT interval vs time and the mean QT interval vs the mean plasma concentrations of ibutilide and its two enantiomers respectively.
The results show that nearly equal cocentrations of the (+) and (-) isomers were achieved after dosing with the racemate and each enantiomer. No concentrations of the other enantiomer were observed after dosing with U-82208E or U-82209E indicating no significant in vivo interconversion. However, the CMAX that was acheived after infusion of U82208E was higher than CMAX acheived after infusion of U82209E (11.1 vs 7.91 ng/ml). It is to note that there was no difference in any of the other pharmacokinetic parameters between the two enantiomers.
The same could not be said about the pharmacodynamic parameters for the two enantiomers.

Ibutilide fumarate (the racemate) as well as the (+) isomer had a much steeper concentration effect relationship compared to the (-) isomer. The EC_{50} for both the racemate and the (+) isomer was around 0.55 ng/ml while it was almost double the value 0.98 ng/ml for the (-) enantiomer. EMAX was estimated to be 120 msec for the racemate, 172 for the (+) enantiomer and only 44 msec for the (-) enantiomer.

Conclusion:

This study shows that there are no pharmacokinetic differences between the two enantiomers of ibutilide. When the racemate is administered, they are present in almost equal amounts. No in vivo interconversion takes place. However, the (+) enantiomer seems to have increased ability for QT prolongation compared to the (-) enantiomer (3 times more active).

Metabolism and excretion of ibutilide following an intravenous infusion ^{14}C ibutilide fumarate in healthy male volunteers.

Study: 7215-94-017. Volume: 1.47 Pages: 06-1-06-194.

Investigators:

Clinical: Dr. Kirsteen M. Donaldson.
Brighton Upjohn Clinical Research Unit.
Brighton General Hospital,
Elm Grove, Brighton England BN2 3EW.

Objectives:

The objective of the study was to determine quantitatively the disposition (metabolism and excretion) of ^{14}C ibutilide in healthy male volunteers after IV administration in a manner similar to that recommended for antiarrhythmic therapy. The quantitative analysis of blood and plasma was used to evaluate the distribution and clearance of ibutilide and related metabolites. Analysis of urine and fecal specimens was included to yield information on the rates and routes of excretion of the ibutilide related materials, as well as information on the chemical structures of the excreted metabolites. Metabolite profiles were compared to the metabolic pathways which have been established in animal models for the purposes of identifying metabolites and establishing the relevance of the animal species used in toxicological studies.

Formulation:

^{14}C ibutilide fumarate sterile solution lot # 26657.

Study Design:

Six healthy nonsmoking male volunteers between the ages of 37 and 49 years participated in this study. 0.8 ml of a 2.5 mg/ml solution were diluted up to 60 ml with 5 % dextrose in water. 30 mls of this solution was infused at a constant rate (3 ml/min) over 10 minutes. Solutions were mixed no earlier than 4 hours before dosing.
Blood samples were taken at 0, 10, 15, 30 and 45 minutes and 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours after drug administration. An extra 15 mls of blood was obtained at 15 and 30 minutes and 1 and 6 hours after dosing.
All urine and faeces were collected during the time interval up to 96 hours.
Breath samples were collected prior to dosing and at 20 minute intervals after dosing for the next 8 hours (1 mM of CO_2 was trapped in the hyamine:ethanol).

Assay:

Analysis of total radioactivity in urine, faeces, expired air, plasma and blood was done by liquid scintillation counting.

Identification of ibutilide possible metaboli[illegible]lasma, urine and fecal samples was performed using 3 HPLC methods.

The plasma concentrations of the two enantiomers of ibutilide were measured using an HPLC method with fluorescence as a detection method. The excitation wavelength was 290 nm while the emission wavelength was 345 nm.

Specificity: satisfactory. Chromatograms of the two separated enantiomers were presented.
Linearity: satisfactory. Calibration curves from 0.03 to 3 ng/ml.
Precision: betweeen day precision ranged from 2.4 % at 2.52 ng/ml to 6 % at 0.0504 ng/ml for U-82208E. For U-82209E the between day precision ranged from 2.7 % at 2.52 ng/ml up to 5 % at 0.0504 ng/ml.
Accuracy: between day accuracy expressed as % recovery for U-82208E ranged from 99.1 % at 2.52 ng/ml up to 102 % at 0.054 ng/ml. For U-82209E, the between day accuracy ranged from 99.1 % at 2.52 ng/ml to 102 % at 0.252 ng/ml.

Data Analysis:

The data analysis was performed using standard pharmacokinetic techniques.

Results:

The results of this study showed that 70.5 % of all the given dose was recovered in 24 hours. Urinary excretion of radioactivity was complete by 96 hours and acounted for 82 % of the dose. The terminal half-life of radioactivity estimated from urine was 11 hours. Fecal excretion accounted for the remainder of the administered dose (19.3 %) with the half-life estimated from the fecal route to be 12.9 hours.
No radioactivity was measured in the expired air samples.
-Table 1 shows the % of the dose recovered in urine and faeces as a function of time while Figure 1 shows the corresponding profile for the recovered radioactivity.
-Table 2 gives a summary of the most important pharmacokinetic parameters for ibutilide and its two enantiomers.
-Tables 3 and 4 show the % of each metabolite recovered in the urine and fecal pool respectively.
-Figure 2 shows the mean concentration of radioactivity in plasma and blood while Figure 3 shows the blood/plasma ratio of radioactivity as a function of time.
-Figure 4 shows the plasma concentration time profile for the two enantiomers for ibutilide.
-Figure 5 shows the plasma concentration profiles of total radioactivity and unchanged ibutilide fumarate measured by HPLC vs time.

-Scheme 1 shows the proposed metabolic pathways for ibutilide in the human.

Metabolite identification:

Metabolite E was the most abundant metabolite recovered in urine accounting for almost 30 % of the administered dose. It is resulting from the ω oxidation of the heptyl side chain of ibutilide. 6.7% of intact ibutilide was recovered in the urine. The % of each metabolite recovered in the urinary pool is given by Table 3.

Conclusion:

82 % of the total radioactive dose was recovered in the urine while the remaining 18 % were recovered in faeces. Ibutilide as well as 8 previously identified metabolites in animals accounted for the total radioactivity administered.
The metabolism of ibutilide in humans appear to proceed primarily through a pathway consisting of ω oxidation of the heptyl side chain followed by a β oxidation of the heptyl side chain.
(ω-1)-oxidation of the heptyl side chain and the associated one carbon loss pathway is a less significant metabolism pathway in humans.

Pharmacokinetics and pharmacodynamics of ibutilide fumarate in healthy male and female volunteers.

Study: 7215-94-032 Volume: 1.47. Pages: 06-196-06-495.

Investigators:

Clinical: Dr Albert J. Dietz.
Upjohn Research Clinics
Kalamazoo, MI.

Objectives:

The objective of the study was to evaluate potential sex-related differences in the pharmacokinetics of ibutilide fumarate. Potential differences between males and females in pharmacodynamic response to ibutilide fumarate infusion as measured by QT interval prolongation was also evaluated.

Formulation:

-0.01 mg/kg of ibutilide fumarate (Research lot 27127) given as a single intravenous infusion over 10 minutes.

Study Design:

Eight healthy male volunteers and 8 healthy female volunteers between the ages of 45 and 80 years participated in this open-label, single dose parallel group study. The subjects were age matched.
Plasma samples and ECG measurements were obtained prior to dosing and at the end of infusion (10 minutes) and at 15, 30, 45 minutes and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours.

Assay:

Plasma concentrations of the enantiomers of ibutilide were measured using an HPLC method with fluorescence as a detection mode.

-Specificity: satisfactory. Chromatograms for the 2 enantiomers are presented.
-Linearity: calibration curves between 0.0302 to 30.2 ng/ml for both enantiomers.
-Precision: inter-assay precision expressed as % CV ranged from 0.16 % to 12 % at 0.0504 ng/ml for U-82208E. As for U82209E, the inter-assay precision ranged from 0.16 % at 2.52 ng/ml to 6 % at 0.0504 ng/ml.
-Accuracy: inter-assay accuracy expressed as % recovery ranged from 91.9 % to 101 % at

0.054 ng/ml for U-82208E. As for U82209E, the inter-assay accuracy ranged from 95.1 % at 0.252 ng/ml to 102 % at 0.0504 ng/ml.

Data Analysis:

Data analysis was exactly the same as described in the previous studies.

Results:

-Table 1 summarizes the main pharmacokinetic parameters for ibutilide and its enantiomers in males and females while Figure 1 shows the corresponding plasma profiles.
-Table 2 summarizes the pharmacodynamic parameters for both populations.
-Figure 2 shows the mean QTc vs time and Figure 3 shows the mean plasma concentration vs QTc for both males and females.
-Figure 3 shows the mean plasma concentrations for ibutilide fumarate and U-107246 (the active metabolite) vs time while Table 3 gives the corresponding plasma concentration values.
The results show that there was neither a pharmacokinetic nor a pharmacodynamic difference between males and females.

Conclusion:

Gender does not seem to have any effects on either the pharmacokinetics or the pharmacodynamic effects of either ibutilide or its 2 enantiomers.

The pharmacokinetics of ibutilide after one or two intravenous infusions of ibutilide fumarate in patients with atrial flutter or atrial fibrillation

STUDY # P/7550/14 P/7550/15 VOLUME: 1-44 PAGEs: 06/03/335.

INVESTIGATOR: Dr James T. Vanderlugt.
Multi Center Trials.

PHARMACOKINETIC ANALYSIS:

OBJECTIVES:

This portion of the study was designed to describe and evaluate the pharmacokinetics of ibutilide in patients with atrial flutter or atrial fibrillation. This was an initial exploratory analysis to develop the poulation pharmacokinetic model and begin the assessment of the influence of patient characteristics on ibutilide diposition.

STUDY DESIGN:

In both multicenter, double-blind, randomized placebo controlled dose response studies, patients were stratified based on diagnosis of atrial flutter or atrial fibrillation.
The single dose study was conducted according to Protocol 14. The repeated dose study was conducted according to Protocol 15 and its two amendments.
Briefly, 466 patients (200 in Protocol 14 and 266 in Protocol 15) with a rhythm of sustained atrial flutter (duration 3 hours or greater) or atrial fibrillation (duration greater than 3 hours and less than 90 days; less than 45 days in Protocol 15) aged 25 to 90 years, participated in these studies. In protocol 14, the patients were randomiz[illegible] to receive a 10 minute IV infusion of either placebo (n=20 per arrhythmia) or ibutilide fumarate (n=20 per arrhythmia per dose group). The doses investigated in Protocol 14 were 0.005, 0.01, 0.015 and 0.025 mg/kg ibutilide fumarate. In Protocol 15, the patients were randomized to receive a 10 minute infusion of either placebo (n=40 per arrhythmia)or 1 mg ibutilide fumarate (n=40 per arrhythmia) or 1 mg ibutilide (n=40 per arrhythmia). If the patient's arrhythmia did not terminate during the infusion or within the 10 minutes following, the patients in the placebo group received a second infusion of placebo while the patients in the ibutilide fumarate group received a second infusion of 1 mg ibutilide fumarate or an infusion of 0.5 mg ibutilide fumarate depending upon the group to which they had been randomized. Patients enrolled in Protocol 15 who weighed less than 60 kg were dosed based on body weight:0.01 mg/kg rather than 1 mg, and 0.05 mg/kg rather than 0.5 mg ibutilide fumarate.
When possible, venous blood samples were collected at the following time points:
For Protocol 14 prior to dosing (-10 minutes), immediately following infusion (10 minutes) and at 15, 30, 60, 90, 120 and 180 minutes after infusion began.
For Protocol 15, prior to dosing (-10 minutes) at minutes 20 and 40 and at hour 1.5. When termination of atrial flutter or fibrillation occurred within 1 hour after the end of the infusion

(Protocol 14), prior to hour 1.5 (Protocol 15) or if a significant change in rhythm occurred prior to 1.5 hours after the start of the first infusion, a blood sample was also drawn at this time. The actual time of sample collection was recorded and was used in the pharmacokinetic analysis.

ASSAY:

Plasma samples collected in both studies were quantitated for racemic ibutilide fumarate using a sensitive and specific HPLC with fluorescence as detection mode.
-Specificity: satisfactory. Chromatograms presented.
-Linearity: satisfactory. Calibration curves between 0.1 and 20.2 ng/ml.
-Sensitivity: the limit of quantification was 0.1 ng/ml.
-Precision: between day precision averaged 11.1 % at 0.204 ng/ml, 6.2 % at 1.02 ng/ml and 3.9 % at 10.2 ng/ml.
-Accuracy: between day accuracy averaged 2 % at 0.204 ng/ml, 3.4 % at 1.02 ng/ml and 1.5 % at 10.2 ng/ml.

DATA ANALYSIS:

The data were fit to a 2 compartment model using the NONMEM program (ADVAN3 TRANS 3 subroutines). Interindividual variability in clearance and volume of the central compartment were modelled using a proportional error model. Residual variability for the pharmacokinetic analysis was modelled using a proportional error model. The development of the basic method was performed using the first order conditional estimation method
In order to perform initial exploratory analyses, empiric bayesian estimates of clearance and volume of distribution at steady-state were obtained for each subject using the POSTHOC option with NONMEM. Scatterplots and frequency distributions for the bayesian estimates of clearance and Vss for age, gender, estimated creatinine clearance, SGOT, SGPT, success/failure, an indicator variable for whether proarrhythmia occurred, and indicator variables for concomitant digoxin, calcium channel blockers, and beta blockers were generated.
Because several patients had missing information for one or more of the laboratory values measured, the mean value of these measurements in the remaining patients was assigned to replace the missing values.
To estimate creatinine clearance in this population, the Jellife method was used.

RESULTS:

In total, the sponsor deemed 285 subjects out of the 339 that were treated with ibutilide to be suitable for the NONMEM analysis. 1298 plasma ibutilide concentrations were measured in these subjects.
In general the patients were elderly with a mean age of 66 years. Their mean weight was 83.1 kg and the mean estimated creatinine clearance was 54.7 ml/min. 82 % were male and only 39.3 % of the patient population included in the NONMEM analysis had a successful

response to therapy. Approximately, 60 % of patients received concomitant digoxin, 40 % received concomitant calcium channel blockers and approximately 19 % received concomitant beta blockers. Table 1 summarizes the demographic characteristics of this patient population while Table 2 gives a summary of the results of the analysis that were undertaken.
The results show that there was a great deal of varibility in the plasma concentrations specially in the time around the termination of the 10 minute infusion. The residual variability after deletion of 28 patients who were considered to have large weighted residuals (>4) was still 46.7 % which might indicate that there might be a model mispecification.
-Figures 1 and 2 show the concentration time profiles from Protocol 14 and Protocol 15 respectively.
-Figure 3 shows the measured vs predicted ibutilide concentrations for the 285 patients (analysis A).
-Figure 4 shows the weighted residuals vs predicted ibutilide concentrations.

Comments:

1-In these two protocols, the sponsor collected blood samples up to 3 hours only, yet the terminal half-life of ibutilide is estimated to 6 hours. This means that the sponsor only covered less than one $t_{1/2}$ of the drug. For this reason, it would be very difficult to develop a population model that will describe adequately the pharmacokinetics of ibutilide from such a data set. Therefore, the conclusion that can be drawn are very limited and should be viewed within the context of the limitations of these two studies.

2-The plasma levels that were obtained in these studies were characterised by a high degree of intersubject variability. Therefore the data obatined from this analysis might not have the ability or power to detect the effect of the various covariates that were investigated on the pharmacokinetics of ibutilide.

3-The sponsor concludes from the results obtained from this study that liver impairment did not have any effect on the pharmacokinetics of ibutilide. Yet in the inclusion criteria in the protocol, patients with liver impairment were excluded from participation in the study. In both these clinical trials there was only one patient that could be considered as having liver impairment. Therefore no conclusion can be made on the effect of liver impairment on the pharmacokinetics of ibutilide.

The pharmacokinetics of ibutilide after intravenous infusion of ibutilide fumarate in patients with normal or decreased left ventricular function.

Study: 7215-94-004 Volume: 1 Pages: 06/05-1-368.

Investigators:

Clinical: Dr. James T. Vanderlugt
Multicenter trial.

Objectives:

The overall purpose of this study was to evaluate the effects of intravenous ibutilide fumarate on standard electrophysiologic and hemodynamic parameters assessed during invasive study. The objectives of this portion of the study were to determine the pharmacokinetics of ibutilide in patients undergoing invasive electrophysiologic study and to investigate a potential correlation between ibutilide serum or plasma concentrations and electrophysiologic effects after treatment with ibutilide fumarate.

Formulation:

-Ibutilide fumarate lot# 26416, 26206, 25735.
-Placebo lot# 26436, 26207,25674.

Study Design:

This multicenter, randomized, placebo-controlled, dose-ranging study in patients undergoing invasive electrophysiologic study was conducted at five centers in the US and two centers in Europe.
2 groups (strata) of patients were studied concurrently: those patients with left ventricular ejection fraction (LVEF) greater than or equal to 35 % and those with LVEF less than 35 %. In each stratum, patients were randomized to receive active drug (6 patients) or placebo (2 patients). The low dose (0.01/0.002 mg/kg) was evaluated first in both strata and the data were reviewed by both the medical monitor and the investigators before proceeding to the higher doses (0.02/0.004 mg/kg and 0.03/0.006 mg/kg). Dosing consisted of a 10 minute infusion (loading dose) followed by a 30 minute maintenance infusion.
Briefly, 47 patients between the age of 21 and 80 years participated in this study. Of these patients, 12 received placebo and 35 received ibutilide.
The rationale for these infusion regimens were based on targeted increases in the QT interval (from very slight increases at the low dose to QTc values at approximately 530 msec at the highest dose) and the desire to maintain the prolonged QT interval for about 30 minutes during which the clinical assessment would occur as described in the protocol.
Venous blood samples were drawn prior to dosing (-10 minutes), immediately following the

loading dose (10 minutes), at the midpoint of the maintenance infusion (25 minutes), and immediately following the maintenance infusion (40 minutes). Blood sasmples were also determined at 5, 15, 30 minutes and at 1, 2, 4, and 6 hours at the end of the infusion.

Assay: HPLC with fluorescence detection 224 nm excitation and 340 nm emission wavelength.

-Specificity: satisfactory. A small number of samples exhibited peaks that coeluted with ibutilide fumarate. These peaks were present in the pre-dose samples for the test subject and are attributed to co-administered drugs. No endogenous plasma peak interference was noted.
-Linearity: satisfactory. Standard Curves from 0.1 to 20.6 ng/ml for ibutilide.
-Precision: precision ranged from 7.8 % at 0.204 ng/ml to 2.3 % for the 10.2 ng/ml QC pool.
-Accuracy: accuracy as indicated by % recovery was 99.1 %.

Data Analysis:

-Data analysis was done using standard pharmacokinetic methods.

Results:

-Table 1 Shows the pharmacokinetic parameters for the different dose levels of ibutilide
-Figures 1 to 3 show the individual patient ibutilide concentration time profile for the different dose levels respectively.
-Figure 4 shows the individual patient QTc interval vs ibutilide plasma concentrations at the end of the first infusion (loading dose)
-Figure 5 shows the individual patient change in QTc interval (from predose) vs ibutilide plasma concentration at the end of the first infusion (loading dose).

The results show that there was no difference in the pharmacokinetics of ibutilide between patients with LVEF > 35 % and patients with LVEF < 35 %.
The plasma concentrations time profiles were characterized by very high interindividual variability with some profiles being erratic . This might be due to the fact that these patients are undergoing invasive clinical measurements which might have an impact on the hemodynamic status of these patients.
A similar correlation to that obtained in healthy volunteers between ibutilide concentration and QTc interval prolongation was to be expected. However, Figures 4 and 5 showed that there was no correlation between QTc change and the levels of ibutilide concentrations observed in this patient population.

Conclusion:

This study shows that there was no discernable pharmacokinetic differences between patients of LVEF> 35 % and LVEF < 35 %. Moreover, contrary to expectations, QTc prolongation did not correlate with ibutilide plasma concentrations. The reason for this lack of correlation is not known and was not explained by the sponsor.

The pharmacokinetics of ibutilide after intravenous infusion of ibutilide fumarate in patients with inducible ventricular tachycardia undergoing electrophysiologic study.

Study: 115-94-005 Volume: 1 Pages: 239-397.

Investigators:

Clinical: Dr. James T. Vanderlugt
Multicenter trial.

Objectives:

The overall purpose of this study was to evaluate whether the administration of ibutilide fumarate would prevent induction of ventricular tachycardia by programmed electrical stimulation as well as to investigate the effects of ibutilide on various electrophysilogic parameters. The objectives of this portion of the study were to determine the pharmacokinetics of ibutilide in patients undergoing invasive electrophysiologic study and to investigate a potential correlation between ibutilide plasma concentrations and electrophysiologic effects after treatment with ibutilide fumarate.

Formulation:

-Ibutilide fumarate lot# 26416, 26206, 25735.

Study Design:

This multicenter, dose-ranging study in patients with inducible ventricular tachycardia undergoing invasive electrophysiologic study was conducted by 16 investigators in the US.
Dosing consisted of a 10 minute infusion (loading dose) of ibutilide fumarate (0.005, 0.01 or 0.02 mg/kg) followed by a 30 minute maintenance infusion of ibutilide fumarate (0.001, 0.002 or 0.004 mg/kg respectively). The rationale for these infusion regimens were based on targeted increases in the QT interval (from very slight increases at the low dose to QTc values of approximately 530 msec at the highest dose) and the desire to maintain the prolonged QT interval for about 30 minutes during which the clinical assessment would occur. Ventricular tachycardia was induced by programmed ventricular stimulation prior to treatment. Induction of ventricular tachycardia was attempted during the maintenance infusion (between 20 and 40 minutes).
55 patients between the ages of 40 to 83 years with a history of coronary artery disease with inducible ventricular tachycardia participated in this study.
Venous blood samples were withdrawn prior to dosing (-10 minutes) and immediately following the loading dose (10 minutes), at the midpoint of the maintenance infusion (25 minutes) and immediately following the maintenance infusion (40 minutes). Plasma concentrations were also

determined at 5, 15 and 30 minutes and at 1, 2, 4, and 6 hours after the end of the infusion.

Assay: HPLC with fluorescence detection 224 nm excitation and 340 nm emission wavelength.

-Specificity: satisfactory. A small number of samples exhibited peaks that coeluted with ibutilide fumarate. These peaks were present in the pre-dose samples for the test subject and are attributed to co-administered drugs. No endogenous plasma peak interference was noted.
-Linearity: satisfactory. Standard Curves from 0.1 to 20.6 ng/ml for ibutilide.
-Precision: precision ranged from 2.1 % at 0.309 ng/ml to 3.5 % for the 8.24 ng/ml QC pool.
-Accuracy: accuracy as indicated by % recovery ranged from 91.7 to 98.7 %.

Data Analysis:

-Data analysis was done using standard pharmacokinetic methods.

Results:

-Table 1 Shows the pharmacokinetic parameters for the different dose levels of ibutilide.
-Figures 1 to 3 show the individual patient ibutilide concentration time profile for the different dose levels respectively.
-Figure 4 shows the individual patient QTc interval vs ibutilide plasma concentrations at the end of first infusion (loading dose)
- . 5 shows the individual patient change in QTc interval (from predose) vs ibutilide plasma concentration at the end of the first infusion (loading dose).

The plasma concentrations time profiles were characterized by very high interindividual variability with some profiles being erratic . This might be due to the fact that these patients are undergoing invasive clinical measurements which might have an impact on the hemodynamic status of these patients.
A similar correlation to that obtained in healthy volunteers between ibutilide concentration and QTc interval prolongation was to be expected. However, Figures 4 and 5 showed that there was no correlation between the Qtc prolongation and the levels of ibutilide concentrations observed in this patient population.

Attempts to identify the major isoenzymes of cytochrome P450 involved in the metabolism of[^{3}H]-ibutilide in human liver microsomes.

Study: 1425-95-007 Volume: Amendment 2. Pages: 1-41.

Investigators:

G. Scott and J. N. Duncan
Upjohn Laboratories -Europe.
Fleming Way Crawley, W Sussex
UK RH102LZ.

Objectives:

The objectives of the current work were to demonstrate that human liver microsomes were a useful model in vitro for the major routes of metabolism of ibutilide in vivo, and to establish the role of cytochrome P450 in the microsomal metabolism of the drug. Studies were designed to attempt to identify the specific isoenzymes of cytochrome P450 involved in the formation of metabolites in microsomal incubates.

Study Design and Results:

A tabulated summary of the study along with the results is presented in the attached table.

TABULATED STUDY REPORT

Name of company The Upjohn Company Name of finished product Ibutilide fumarate Name of active ingredient U-70226E	Tabulated Study Report III.G.410	. . . . .
Pharmacokinetics	Biotransformation	
Report 1425-95-007 Page 1 of 2	Study 94-830	Study Period July 94-March 95

Species/Strain	Human	Formulation:	Aqueous solution 2.5 mg ml^{-1} or 1.1 $\mu g\ ml^{-1}$
Metabolism *in vitro*	human liver microsomes	Nuclide:	^3H
		Specific radioactivity:	4.066 MBq μg^{-1}

Correlation of formation of metabolites with specific P450 enzyme activities

Metabolite	Isoenzyme	R^2
U-86092	CYP2D6	0.59
U-88465	CYP3A4	0.95
U-107246	No correlation observed	

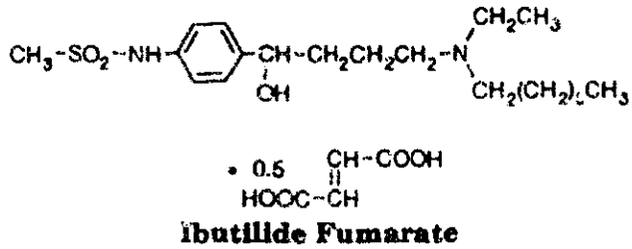
Additional information: Three major metabolites were observed on radio-HPLC of incubates of [^{3}H]-Ibutilide with human microsomes (see supplementary sheet for structures). On the basis of chromatographic retention times these metabolites appear to be U-107246 (ω-hydroxylation on the heptyl side chain), U-86092 (ω-1-hydroxylation on the heptyl side chain) and U-88465 (N-desheptyl Ibutilide). Formation of these metabolites was demonstrated to be NADPH dependent and was inhibited by selected known P450 inhibitors (aminobenzotriazole, n-octylamine and SKF 525A). Formation of U-88465 correlated with 6-β-hydroxylation of testosterone and inhibition studies with troleandomycin confirmed CYP3A4 as the isoenzyme responsible for this metabolism. Formation of the ω-1-OH (U-86092) metabolite correlated with dextromethorphan O-demethylase (CYP2D6) and further evidence for involvement of this isoenzyme was provided from inhibition studies with quinidine and studies utilizing microsomes prepared from yeast engineered to express CYP2D6. The major route of metabolism of Ibutilide (to the ω-OH metabolite, U-107246) did not appear to be mediated by any of the isoenzymes of cytochrome P450 characterised in our liver bank and none of the probe substrates used in the study affected the microsomal production of this metabolite.

Study conducted by Upjohn Laboratories-Europe, Fleming Way, Crawley, W Sussex, UK. RH10 2LZ

Study in compliance with GLP Yes ( ) No ( ) Not required (✓)

ANNOTATED PROPOSED PACKAGE INSERT

The proposed package insert has been annotated to the submission volume and page of the application summary and technical sections (eg, volume 1.18, page 5/1/10). References to individual study reports appear within brackets in bold print in the text (eg, **[5.3]** in the Clinical Pharmacology section refers to reference no. 3 in Item 5).

DRAFT PACKAGE INSERT	Location in Summary and Technical Sections
CORVERT™ Injection (brand of ibutilide fumarate injection) For intravenous infusion only	
DESCRIPTION	
CORVERT Injection is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.087 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection.	1.16, 5/1/109; 1.1, 2/1/57 1.2, 3/1/7
CORVERT Injection is an isotonic, clear, colorless aqueous solution.	1.2, 3/1/9
Ibutilide fumarate has one chiral center, and exists as a racemate of the (+) and (-) enantiomers.	1.2, 3/1/2
The chemical name for ibutilide fumarate is N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is $C_{22}H_{36}N_2O_5S$ and its molecular weight is 442.62.	1.2, 3/1/2
Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower.	1.2, 3/1/3
The structural formula is represented below:  **Ibutilide Fumarate**	1.2, 3/1/2

CLINICAL PHARMACOLOGY **Mechanism of Action**: CORVERT Injection prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness in vivo **[5.3-5.5, 5.13-5.15, 5.17-5.20, 5.23-5.28]**. Voltage clamp studies indicate that CORVERT Injection, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which most other class III antiarrhythmics act **[5.6-5.10, 5.12]**. The antiarrhythmic effects of CORVERT Injection are thought to be primarily due to these class III electrophysiologic properties, i.e., prolongation of atrial and ventricular action potential duration and refractoriness. **[5.17-5.20, 5.23, 5.26-5.28]**. In humans, the predominant electrophysiologic property of CORVERT Injection is demonstrated by prolongation of effective refractory periods in atrial and ventricular muscle.	1.18, 5/1/109; 1.1, 2/1/57 1.18, 5/1/109; 1.1, 2/1/59
Hemodynamics: When CORVERT Injection was given intravenously to animals at doses greater than ten times the human dose, mild, negative inotropic effects were observed (less than 8% decrease in left ventricular contractility) **[5.28]**. A study of hemodynamic function in patients stratified for ejection fractions (greater than or equal to 35% and less than 35%) demonstrated no significant effects on cardiac output, mean pulmonary arterial pressure, or capillary wedge pressure at doses up to 0.03 mg/kg.	1.18, 5/1/184; 1.1, 2/1/60 1.52, 8/1/469; 1.1, 2/1/112
Pharmacology: CORVERT Injection produces mild slowing of the sinus rate and atrioventricular conduction. CORVERT Injection produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship of plasma concentration to antiarrhythmic effect, CORVERT Injection produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity **[6.3, 8.11, 8.12]**. (See WARNINGS for relationship between QTc prolongation and torsades de pointes-type arrhythmias.) In a study in healthy volunteers, **[6.3, 6.4, 8.12]** intravenous infusions of CORVERT Injection resulted in prolongation of the QT intervals that were directly correlated with ibutilide plasma concentrations during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was demonstrated. The maximum effect was a function of both the dose of CORVERT Injection and the infusion rate **[6.3]**.	1.52, 8/1/474 1.52, 8/1/461; 1.1, 2/1/141 1.42, 6/1/40, 1.1, 2/1/91 1.42, 6/1/40 1.42, 6/1/40

Pharmacokinetics: After intravenous infusion, ibutilide plasma concentrations *rapidly decrease in a multi-exponential fashion. The pharmacokinetics of ibutilide* are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg) and a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers **[6.3, 6.5, 6.6, 6.7]**. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation **[6.1, 6.2, 8.15, 8.16]**. The elimination half-life averages about 6 hours (typically ranges from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT Injection *over the dose range of 0.01 mg/kg to 0.10 mg/kg* **[6.1, 6.3]**. The enantiomers of ibutilide fumarate have pharmacokinetic properties similar to each other and to ibutilide fumarate **[6.5, 6.6, 6.7]**. The pharmacokinetics of CORVERT Injection in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, patient age, sex, or the concomitant use of digoxin, calcium channel blockers, or beta blockers **[6.1, 6.2]**.	1.42, 6/1/19; 1.1, 2/1/90 1.42, 6/1/25 1.42, 6/1/31 1.42, 6/1/19 1.42, 6/1/38 1.42, 6/1/36 1.42, 6/1/37 1.42, 6/1/39
Elimination: In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [^{14}C]ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (19%) was recovered in the feces **[6.6]**. **Metabolism**: Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω-oxidation followed by sequential β-oxidation of the heptyl side chain of ibutilide. These metabolites have no activity or weak class III activity relative to ibutilide **[6.6]**. **Distribution**: Ibutilide exhibits moderate plasma protein binding (41% bound) over the concentrations achieved in clinical studies, and, therefore is not expected to displace other drugs bound to plasma proteins **[5.130]**. Ibutilide is rapidly and extensively distributed extravascularly as evidenced by the large volume of distribution **[6.1–6.7, 8.15, 8.16]**.	1.42, 6/1/34; 1.1, 2/1/90 1.42, 6/1/31; 1.1, 2/1/90 1.42, 6/1/35 1.1, 2/1/90 1.42, 6/1/19 1.42, 6/1/25

Clinical Studies: A multicenter, placebo-controlled study of 242 non-postsurgical patients was conducted to assess the response to a single 1-mg dose of CORVERT Injection versus placebo and to allow a second infusion (either 0.5 or 1 mg) to be administered to those who did not convert following the initial dose. These results are discussed below **[8.14]**.	1.52, 8/1/227; 1.1, 2/1/116
Atrial Flutter: Following administration of placebo, 1 of 41 (2.4%) patients with atrial flutter cardioverted to sinus rhythm. In contrast, 19 of 80 (24%) patients with atrial flutter converted within 20 minutes of starting a single, 10-minute, 1-mg infusion of CORVERT Injection. Administration of a second dose of 0.5 mg to those patients who did not respond to the first dose resulted in an overall cumulative conversion rate of 54% (21 of 39 patients), while administration of a second dose of 1 mg resulted in an overall cumulative conversion rate of 71% (29 of 41 patients). Consequently, the sequential administration of 1 mg followed by 0.5 mg, started 20 minutes apart, results in an overall conversion rate in patients with atrial flutter that is not statistically different than the sequential administration of two 1-mg doses of CORVERT Injection (54% and 71%, respectively) **[8.14]**.	1.52, 8/1/227; 1.1, 2/1/116
Atrial Fibrillation: Following administration of placebo, 1 of 40 (2.5%) patients with atrial fibrillation cardioverted to sinus rhythm. In contrast, 16 of 81 (20%) patients with atrial fibrillation converted within 20 minutes of starting a single, 10-minute, 1-mg infusion of CORVERT Injection. Administration of a second 10-minute infusion of 0.5 mg to those patients who did not respond to the first dose resulted in an overall cumulative conversion rate of 35% (14 of 40 patients), while administration of a second 1-mg dose resulted in an overall cumulative conversion rate of 27% (11 of 41 patients). Accordingly, the sequential administration of 1 mg followed by 0.5 mg, started 20 minutes apart, results in an overall conversion rate in patients with atrial fibrillation that is not statistically different from the sequential administration of two 1-mg doses (35% and 27%, respectively) **[8.14]**.	1.52, 8/1/227; 1.1, 2/1/116
INDICATIONS AND USAGE CORVERT Injection is indicated for the rapid conversion of atrial fibrillation or atrial flutter to sinus rhythm.	1.52, 8/1/240; 1.1, 2/1/126; 1.1, 2/1/152
CONTRAINDICATIONS CORVERT Injection is contraindicated in patients who have previously demonstrated hypersensitivity to ibutilide fumarate or any of the other product components CORVERT Injection is contraindicated in patients who have previously demonstrated torsades de pointes.	1.52, 8/1/220

WARNINGS Proarrhythmia:	
Like other antiarrhythmic agents, CORVERT Injection can induce or worsen ventricular arrhythmias in some patients. This may have potentially fatal consequences. Torsades de pointes, a polymorphic ventricular tachycardia that develops in the setting of a prolonged QT interval, may occur because of the effect CORVERT Injection has on cardiac repolarization. In general, with drugs that prolong the QT interval, the risk of torsades de pointes is thought to increase progressively as the QT interval is prolonged and may be worsened with bradycardia and a varying heart rate. Also, the frequency of proarrhythmia is higher in women than men [8.30]. In the more recent clinical trials conducted in patients with atrial fibrillation and atrial flutter, those with QTc intervals > 440 msec were not allowed to participate [8.14].	1.52, 8/1/484-91; 1.1, 2/1/151 1.52, 8/1/220; 1.1, 2/1/143 1.52, 8/1/200 1.52, 8/1/202
During clinical trials, 2.4% of patients with atrial flutter or atrial fibrillation treated with CORVERT Injection developed sustained polymorphic ventricular tachycardia requiring cardioversion; 4.0% experienced nonsustained polymorphic ventricular tachycardia. In these clinical trials, all initial episodes of polymorphic ventricular tachycardia occurred during or within 30 minutes of an infusion. Management of the polymorphic ventricular tachycardia included magnesium sulfate infusions and cardiac pacing. Nonsustained monomorphic ventricular tachycardias occurred in 4.0% of the patients treated with CORVERT Injection 2.7% were possibly related to drug. (See Adverse Reactions.)	1.52, 8/1/449; 1.1, 2/1/135 1.52, 8/1/490
Proarrhythmic events must be anticipated and proper equipment, such as a defibrillator, and medication for treatment of sustained ventricular tachycardias must be available during administration of CORVERT Injection. Before treatment with CORVERT Injection, plasma hypokalemia and hypomagnesemia should be corrected to reduce the potential for proarrhythmia.	1.52, 8/1/220; 1.1, 2/1/152
PRECAUTIONS **General Precautions:** Antiarrhythmics: Class Ia antiarrhythmic drugs (Vaughan Williams Classification), such as disopyramide, quinidine, and procainamide, and other class III drugs, such as amiodarone and sotalol, should not be given concomitantly with CORVERT Injection because of their potential to prolong refractoriness.	1.59, 8/8/116 1.68, 8/17/133; 1.1, 2/1/151
Other Drugs that prolong the QT interval: The potential for proarrhythmia may increase with the administration of CORVERT Injection to patients who are being treated with drugs that prolong the QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, and antihistamine drugs (H1 receptor antagonists). **Laboratory Test Interactions**: None known.	1.52, 8/1/487; 1.1, 2/1/143

Drug Interactions: Digoxin: Supraventricular arrhythmias may mask the cardiotoxicity associated with excessive digoxin levels. Therefore, cardioversion with CORVERT Injection may be hazardous in patients whose plasma digoxin levels are above the usual therapeutic range. Acute dosing with CORVERT Injection does not affect serum digoxin levels [8.13, 8.15, 8.16]. The pharmacokinetics of CORVERT Injection are not different in patients treated concomitantly with digoxin when compared with those who were not concomitantly treated [6.1, 6.2]. Calcium channel blocking agents: The pharmacokinetics of CORVERT Injection are not different in patients treated concomitantly with calcium channel blocking agents when compared with those who were not concomitantly treated [6.1, 6.2]. Beta Adrenergic Blocking Agents: The pharmacokinetics of CORVERT Injection were not different in patients treated concomitantly with beta adrenergic blocking agents when compared with those who were not concomitantly treated [6.1, 6.2].	1.52, 8/1/254; 1.1, 2/1/131 1.42, 6/1/39; 1.1, 2/1/91 1.42, 6/1/39 1.42, 6/1/39
Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been conducted to determine the carcinogenic potential of CORVERT Injection; however, it was not mutagenic in a battery of mutagenicity assays including the Ames assay, mammalian cell forward gene mutation assay, unscheduled DNA synthesis assay, and mouse micronucleus assay [5.77–5.81]. Similarly, no drug-related effects on fertility or mating were noted in a reproductive study in rats [5.69].	1.18, 5/1/380; 1.1, 2/1/69 1.18, 5/1/76; 1.1, 2/1/67 1.18, 5/1/75 1.18, 5/1/321; 1.1, 2/1/68
Pregnancy, Labor, and Delivery: Pregnancy Category CORVERT Injection was teratogenic and embryocidal in reproduction studies in rats. These findings indicate that the potential risk to the fetus must be considered when anticipating treatment of pregnant women or women of child-bearing potential.	1.18, 5/1/75; 1.1, 2/1/67 1.18, 5/1/324
Nursing Mothers: The excretion of ibutilide into breast milk has not been studied; accordingly, breastfeeding should be discouraged during CORVERT Injection therapy. **Pediatric Use:** Clinical trials with CORVERT Injection in patients with atrial fibrillation and atrial flutter did not include anyone under the age of 18.	

Use in Elderly Patients: No age-related pharmacokinetic differences were observed in a Phase II dose-response trial conducted in patients 25 to 82 years old (mean = 64) in which pharmacokinetic parameters were compared for patients less than 65 with those of patients 65 years and older **[6.1]**.	1.42, 6/1/36; 1.1, 2/1/91
Use in Patients with Hepatic or Renal Dysfunction: The safety, effectiveness, and pharmacokinetics of CORVERT Injection have not been established in patients with hepatic or renal dysfunction. However, it is unlikely that dosing adjustments would be necessary in patients with compromised renal or hepatic function based on the following considerations: 1) CORVERT Injection is indicated for rapid intravenous therapy (duration ≤ 30 minutes) and is dosed to a known, well-defined pharmacologic action (termination of arrhythmia) or to a maximum of two 10-minute infusions; 2) less than 10% of the dose of CORVERT Injection is excreted unchanged in the urine; 3) the hepatic metabolic clearance of ibutilide is perfusion-rate limited **[6.5, 6.6]**; and 4) drug distribution appears to be one of the primary mechanisms responsible for termination of the pharmacologic effect.	1.42, 6/1/31 1.42, 6/1/19
In 285 patients with atrial fibrillation or atrial flutter who were treated with CORVERT Injection, the clearance of ibutilide was independent of renal function as measured by creatinine clearance (range 21 to 140 mL/min), and also independent of hepatic function, as measured by serum ALT and AST **[6.2]**.	1.42, 6/1/38; 1.1, 2/1/91 1.42, 6/1/37
ADVERSE REACTIONS CORVERT Injection was generally well tolerated in clinical trials. Of the 375 patients who received CORVERT Injection, 86 (23%) reported medical events related to the cardiovascular system, including sustained polymorphic ventricular tachycardia (2.4%) and nonsustained polymorphic ventricular tachycardia (4.0%).	1.52, 8/1/448; 1.1, 2/1/136
Other clinically important adverse events with uncertain relationship to CORVERT Injection include the following (0.3% represents 1 patient): sustained monomorphic ventricular tachycardia (0.3%), nonsustained monomorphic ventricular tachycardia (4.0%), A-V block—1st degree (1.6%), A-V block—2nd degree (0.5%), A-V block—3rd degree (0.3%), A-V block—variable (0.3%), ventricular/bigeminal extrasystoles (3.5%), hypotension/postural hypotension (2.9%), bradycardia/sinus bradycardia (1.1%), nodal arrhythmia (0.8%), congestive heart failure (0.5%), supraventricular tachycardia (0.5%), idioventricular rhythm (0.3%), syncope (0.3%), and renal failure (0.3%). Although no cause-effect relationship has been established, the incidence of these events, except for syncope, was greater in the CORVERT Injection group than in the placebo group.	1.52, 8/1/485 1.52, 8/1/527
Other adverse reactions that may be associated with the administration of CORVERT Injection were nausea and headache, both of which occurred with a frequency greater than 1% more in ibutilide-treated patients than those treated with placebo.	1.52, 8/1/449; 1.1, 2/1/134

Gender Differences in Frequency of Proarrhythmia: As with other class III antiarrhythmic agents, the incidence of proarrhythmia in patients treated with CORVERT Injection is greater in women than men **[8.30]**. This was borne out in clinical trials conducted in patients with atrial fibrillation and atrial flutter, in which more women than men developed polymorphic ventricular tachycardia **[8.14]**. Also, the pharmacokinetics of CORVERT Injection are similar in men and women with atrial fibrillation and atrial flutter **[6.1, 6.2]**. In studies in healthy volunteers, there were no gender differences in the pharmacokinetics of ibutilide **[6.7]**, or with respect to prolongation of the QTc interval **[6.7]**.	1.52, 8/1/487; 1.1, 2/1/143 1.42, 6/1/37; 1.1, 2/1/91 1.42, 6/1/37 1.42, 6/1/40
Details of the gender distribution of the different ventricular tachycardias in the 38 patients treated with CORVERT Injection are provided in the following table.	1.52, 8/1/487 1.52, 8/1/508

Percentage of Patients With New or Worsened Ventricular Tachycardia

Sex	N	Polymorphic VT		Monomorphic VT		Total No. of Patients	
		Sustained	Nonsustained	Sustained	Nonsustained	n	%
Male	312¶	2.2	2.9	0.3	2.9	25	8.0
Female	63*	3.2	9.5	0	9.5	13	20.6

¶ One male patient had a sustained polymorphic VT and a sustained monomorphic VT.
* One female patient had a sustained and a nonsustained polymorphic VT.

The medical events reported for more than 1% of the patients are shown in the following table.

Treatment-Emergent Medical Events with Frequency of More Than 1% Protocols 0003, 0005, 0014, 0015

Event	Placebo N=127		All Ibutilide N=375	
	Patients		Patients	
	n	%	n	%
CARDIOVASCULAR				
Nonsustained Monomorphic VT	1	0.8	15	4.0
Nonsustained Polymorphic VT	--	--	15	4.0
Ventricular Extrasystoles	1	0.8	13	3.5
Hypotension	2	1.6	11	2.9
AV Block	1	0.8	9	2.4
Sustained polymorphic VT	--	--	9	2.4
Chest Pain	2	1.6	6	1.6
Hypertension	--	--	5	1.3
Tachycardia	1	0.8	4	1.1
GASTROINTESTINAL				
Nausea	1	0.8	10	2.7
Vomiting	2	1.6	6	1.6
Diarrhea	3	2.4	6	1.6
LABORATORY VALUES				
Increased Serum Creatinine	1	0.8	4	1.1
RESPIRATORY				
Dyspnea	3	2.4	7	1.9
CENTRAL NERVOUS SYSTEM				
Headache	4	3.1	18	4.8
Dizziness	2	1.6	7	1.9
UROGENITAL				
Urinary Retention	2	1.6	--	--
MISCELLANEOUS				
Back Pain	6	4.7	7	1.9
Fever	4	3.1	5	1.3
Localized Pain	1	0.8	4	1.1

[1.52, 8/1/449; 1.1, 2/1/134]

OVERDOSAGE **Acute Experience in Animals:** Acute overdose in animals results in CNS toxicity; notably, CNS depression, rapid gasping breathing, and convulsions. The intravenous median lethal single dose is more than 50 mg/kg but less than 100 mg/kg in two species; this dose is at least 1500 times more than the maximum recommended therapeutic dose.	1.18, 5/1/78; 1.1, 2/1/65 1.18, 5/1/227; 1.1, 2/1/71
Human Experience: In the clinical trials with CORVERT Injection, four patients were unintentionally overdosed. The largest dose was 3.4 mg administered over 15 minutes. One patient developed increased ventricular ectopy and monomorphic ventricular tachycardia, another patient developed A-V block—3rd degree and nonsustained polymorphic VT, and two patients had no medical event reports. Based on known pharmacology, the clinical effects of an overdosage with ibutilide could exaggerate the expected prolongation of repolarization seen at usual clinical doses. Medical events (eg, proarrhythmia, A-V block) that occur after the overdosage should be treated with measures appropriate for that condition.	1.52, 8/1/543; 1.1, 2/1/145
DOSAGE AND ADMINISTRATION The recommended dose of CORVERT Injection for patients 60 kg (132 lb) or more is 1 mg administered by intravenous infusion over a 10-minute period. For patients less than 60 kg, administer 0.01 mg/kg over a 10-minute period. If the arrhythmia does not terminate within 10 minutes after the end of the initial infusion, a second 10-minute infusion of equal strength may be administered. More rapid infusion is not recommended. CORVERT Injection may be administered undiluted or diluted in 50 mL of diluent (see Dilution). If new or worsened ventricular arrhythmia develops during administration of CORVERT Injection, the infusion should be stopped immediately. Additional doses are not recommended because of the risk of adverse events associated with QT interval prolongation.	1.52, 8/1/258; 1.1, 2/1/129
Dilution: CORVERT Injection may be added to 0.9% Sodium Chloride Injection or 5% Dextrose Injection before infusion. The contents of one 10-mL vial (0.1 mg/mL) may be added to a 50-mL infusion bag to form an admixture of approximately 0.017 mg/mL ibutilide fumarate.	1.3, 3/2/1
Compatibility and Stability: The following diluents are compatible with CORVERT Injection (0.1 mg/mL): 5% Dextrose Injection 0.9% Sodium Chloride Injection The following intravenous solution containers are compatible with admixtures of CORVERT Injection (0.1 mg/mL): polyvinyl chloride plastic bags polyolefin bags	1.3, 3/2/422
Storage: Store the product at controlled room temperature (15° to 30°C or 59° to 86°F). Keep the product in its original carton until used. When kept at controlled room temperature, CORVERT Injection can be stored for 24 months. Admixtures of the product, with approved diluents, are chemically and physically stable for 24 hours at room temperature (15° to 30°C or 59° to 86°F) and for 48 hours at refrigerated temperatures (2° to 8°C or 36° to 46°F). Strict adherence to the use of aseptic technique during the preparation of the admixture is recommended in order to maintain sterility.	1.3, 3/2/415 1.3, 3/2/422
HOW SUPPLIED CORVERT Injection is supplied as an acetate-buffered isotonic solution at a concentration of 0.1 mg/mL that has been adjusted to approximately pH 4.6 in 10-mL clear glass flip-top vials.	1.3, 3/2/1 1.3, 3/2/47
Caution: Federal law prohibits dispensing without prescription. **The Upjohn Company** • Kalamazoo, Michigan 49001, USA Revised: **October 1994**	

Table 6.H-1. Comparison of clinical and registered formulations of ibutilide fumarate injection

Ingredient	Clinical Formulation (2.5 mg/mL)		Registered Formulation (0.1 mg/mL)
	Amount / mL (Formulation)	Amount / mL (1:25 Admixture with 0.9% NaCl)	Amount / mL (Formulation)
Ibutilide Fumarate	2.5 mg	0.1 mg	0.1 mg
Sodium Acetate USP Granular (Trihydrate)		0.169 mg	0.169 mg
Sodium Chloride USP to adjust tonicity		8.89 mg	8.90 mg
10% Solution Sodium Hydroxide* or 10% Hydrochloric Acid† to adjust pH to 4.6	qs		qs
Water for Injection USP qs to 1 mL	1 mL		1 mL

* Prepared from Sodium Hydroxide NF and Water for Injection USP.
† Prepared from Hydrochloric Acid NF and Water for Injection USP.

The quantity of ibutilide fumarate is specified in terms of the hemifumarate salt form.

The 0.1 mg/mL formulation is stable for at least 24 months when stored at controlled room temperature (15-30°C).

The purpose of each component in Ibutilide Fumarate Injection 0.1 mg/mL is listed below:

Table 6.H-2. Components of ibutilide fumarate injection 0.1 mg/mL

Components	Function
Ibutilide Fumarate	Active ingredient
Sodium Acetate Granular Trihydrate USP	pH buffer
10% Sodium Hydroxide USP* and 10% Hydrochloric Acid USP†	To adjust pH to 4.6
Sodium Chloride USP	Tonicity modifying agent
Water for Injection USP	Solvent

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ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CORVERT™

(IBUTILIDE FUMARATE)

INJECTION

NDA 20-491

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-491

CORVERT

(Ibutilide Fumarate)

Injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **CORVERT, The UpJohn Company** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Ibutilide Fumarate injection, a synthetic drug, is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. The drug substance and drug product will be produced, formulated, and packaged at The UpJohn Company's main pharmaceutical and chemical manufacturing complex in Kalamazoo, Michigan. The finished drug product will be used in hospitals and clinics located throughout the United States, especially in major metropolitan centers.

Ibutilide Fumarate may enter the environment from manufacturing waste, disposal of unused and off specification product, and from patient excretion.

Chemical and physical test results indicate that the drug substance will most likely be restricted to the aquatic environmental compartment. Tests have shown that there is little likelihood that the substance will bioaccumulate.

Scientific tests have shown that the environmental degradation

mechanisms include aquatic photodegradation and microbial degradation.

Microbial Inhibition was not seen in five test organisms at a concentration that might obtain in the environment.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at licensed incineration and landfill facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the site of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/21/95
DATE

PREPARED BY
Carl J. Berninger, Ph.D.
Chemist
Center for Drug Evaluation and Research

11/22/95
DATE

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

Copies:

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ENVIRONMENTAL ASSESSMENT REPORT (EA)

This Amended Environmental Assessment is submitted in compliance with 21 CFR Part 25.31a to accompany the New Drug Application (NDA) #20-491for Ibutilide Fumarate Injection.

1. DATE

October 5, 1995 (revision)

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address of The Upjohn Company's headquarters is:

7000 Portage Road
Kalamazoo, Michigan 49001

telephone number (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval - Need for the Action

This environmental assessment is necessary for the approval of New Drug Application (NDA) #20-491 for CORVERT™ Injection. CORVERT Injection is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.067 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection. CORVERT Injection is supplied in 10mL clear glass vials with butyl rubber serum closures.

4.2 Location Where the Product will be Produced

The drug substance and drug product will be produced, formulated, and packaged at The Upjohn Company's main pharmaceutical and chemical manufacturing complex in Kalamazoo, Michigan.

4.3 Location Where the Product will be Used

The expected locations of use are hospitals and clinics located throughout the United States, especially in major metropolitan centers.

4.4 Locations Where Product will be Disposed

Disposal of drug substance or drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers. The present infrastructure at the proposed manufacturing site provides for the following recovery and/or ultimate disposal mechanisms:

4.4.1 Off-Specification Lots of Drug Substance

Off-specification lots of drug substance, ibutilide fumarate, may be either recrystallized or recycled back to free base and then converted to ibutilide fumarate.

4.4.2 Off-Specification Lots of Drug Product and Returned Goods

It is not appropriate to make final disposal decisions this far in advance of having off-specification formulated lots or returned goods for disposal. However, if the company were to dispose of such material at the present time, it would use:

- Westside Landfill in Three Rivers, MI (Waste Management of Michigan, Inc.) operating under State of Michigan Solid Waste Disposal License No. 8147 for bulk, uncrushed material;
- Orchard Hills Landfill in Watervliet, MI, operating under State of Michigan Solid Waste Disposal License No. 8113 for any finished drug product;
- or a comparable facility.

Upjohn has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The underlying agreements with the sanitary landfills affirm compliance status. All facilities must be audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site. In addition, Upjohn personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

4.4.3 Discarded Product in Hospital Setting

Any discarded product or product containers generated in a hospital or clinic setting would typically be disposed in accordance with applicable Federal, State and local regulations. Only minute traces of the active ingredient, ibutilide fumarate, would be expected to remain with empty product containers.

4.5 Type of Environment Present at and Adjacent to Manufacturing Locations

Ibutilide Fumarate Injection will be processed, formulated, and packaged at The Upjohn Company's Portage site facility, located in the northern portion of the City of Portage in Kalamazoo County, Michigan. Kalamazoo County is in the southwest corner of the State Approximately 140 miles equidistant from Chicago and Detroit. The facility is approximately 1.7 miles northeast of the center of the City of Portage, approximately 5.4 miles south of the center of the City of Kalamazoo, and directly to the south of the Kalamazoo/Battle Creek International Airport.

The area in the immediate vicinity of the Upjohn facility is a mix of zoning including heavy and light industry, general business, and single- and multiple-family residences. Upjohn is on land zoned for heavy industry. The site is directly bordered by airport property, residences, and undeveloped land. The climate is temperate. In terms of the Universal Transverse Mercator Coordinate System (UTM), the plant is located in Zone 16 at 619.1 Km east and 4674.1 Km north, which corresponds to latitude 42°12'42" north and longitude 85°33'25" west.

This complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (see Appendices 2 and 3). The plant site occupies a portion of approximately 810 hectares lying south of Bishop Road, east of Portage Road, north of Centre Street, and west of Sprinkle Road in Portage, Michigan.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

5.1 Chemical Process

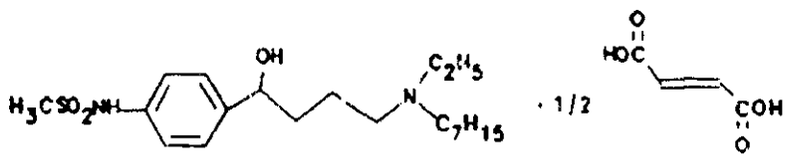
The following summarizes the materials used in the manufacture of the drug substance, ibutilide fumarate, including CAS No., molecular weight, molecular formula, and brief description. The material safety data sheet (MSDS) for the drug substance, ibutilide fumarate, is enclosed (see Appendix 4).

The specifications for ibutilide fumarate stipulate not more than 1.0% of the labeled amount of ibutilide fumarate as decomposition product U-87473, and not more than 178 Endotoxin Units per mg ibutilide fumarate. All inert ingredients used in the formulation are listed in the USP-NF and are tested to meet current requirements of that pharmacopeia.

Table 1: Materials Used in the Manufacture of Ibutilide Fumarate

Name	CAS No.	Molecular Wt.	Formula	Physical Appearance
Acetone	67-64-1	58.08	C_3H_6O	Colorless liquid
Methyl-tert-butyl ether	109-60-4	102.13	$C_5H_{12}O_2$	Water-white liquid
Ethyl acetate	141-78-6	88.11	$C_4H_8O_2$	Clear, colorless liquid
N-Ethylheptylamine	106-39-8	158.24	$C_9H_{19}O_2$	Colorless liquid
Fumaric acid	110-17-8	16.07	$C_4H_4O_4$	White crystals
Isobutyl chloroformate	543-27-1	136.6	$C_5H_9ClO_2$	Clear, colorless liquid
Lactic acid	63-42-3	342.30	$C_{12}H_{22}O_{11}$ H_2O	Fine white powder
Lithium aluminum hydride, 1M in tetrahydrofuran	16853-85-3	37.95	$AlH_4 \cdot Li$	White to light-grey powder
4-[(Methane-sulfonyl)amino]-γ-oxobenzene-butanoic acid (U-68849)	122647-32-9	271.29	$C_{10}H_{13}NSO_5$	Off-white powder
Sodium chloride	7647-14-5	58.44	NaCl	White crystals
Sodium hydroxide 50% solution	1310-73-2	40.0	NaOH	Clear liquid
Tetrahydrofuran	109-99-9	72.11	C_4H_8O	Clear, colorless liquid
Triethylamine	121-44-8	101.19	$C_6H_{15}N$	Colorless liquid

Figure 1: Chemical structure for ibutilide fumarate



Ibutilide Fumarate

5.2 Pharmaceutical Formulation

The following summarizes the ingredients used in the formulation of the drug product, Ibutilide Fumarate Injection:

Table 2: Ingredients Used in the Formulation of Ibutilide Fumarate Injection

Ingredients Used in the Formulation of Ibutilide Fumarate Injection				
Name	CAS No.	M.W.	Formula	Appearance
Ibutilide fumarate	122647-32-9	442.62	$C_{20}H_{36}N_2O_3S \cdot 0.5\ C_4H_4O_4$	White amorphous powder
Sodium chloride	7647-14-5	58.44	NaCl	White crystals
Sodium Acetate Trihydrate	6131-90-4		$C_2H_4O_2$	White crystals
Water	7732-18-5	18.0	H_2O	Clear liquid
HCl (10%) to adjust pH to 4.6	7647-01-0	36.47	HCl	Corrosive, toxic, colorless liquid

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Ibutilide fumarate is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

Portions of the materials listed in Part 5 will be released to the environment as a result of the proposed action. The manufacturing of the product will result in waste in the form of air emissions, liquid waste streams, and solid wastes.

6.1 Chemical Process

6.1.1 Air/Solvent Emissions

The Upjohn Company is operating under an air consent judgment with the Michigan Department of Natural Resources (MDNR) dated March 15, 1991, which has required that an inventory be taken of all equipment with the potential to emit or control contaminants by July 1, 1991 and that completed permits be in place for this equipment in accordance with the schedule set forth in the consent judgment. That inventory was submitted to MDNR on July 1, 1991. Where applicable, LAER (lowest

achievable emission rate) controls must be installed on the VOC (volatile organic compound) portion of the process by September 1, 1995. The ibutilide fumarate production facility is part of Region IV of the Chemical Division. The permit application for all subject equipment in this region was submitted to the MDNR on October 1, 1992, in compliance with the submittal date within the air consent judgment.

Solvent emissions from the equipment used in the production of ibutilide fumarate will be controlled through the use of vent condensers with an efficiency rating of approximately 90% , dependent on the vapor pressure of the solvent. Any solvent emissions from this process not condensed by the vent condensers would go into the regional control system, a thermal oxidizer system, which is scheduled for start-up in 1995. The regional thermal oxidizer system has a removal efficiency of at least 98%.

Particulate emissions may result during the introduction of raw materials into the process and during packaging of the product at the end of the process. Particulate emissions from raw material charging are removed via an exhaust fan. Particulate emissions from material packaging are controlled by a HEPA filter with an efficiency of 99.9%.

Table 3: Substances Which May be Emitted

Acetone	67-64-1	Chemical Process Wastewater Management (CPWM). Converted in process to potassium chloride; remainder is discharged to the CPWM (deep well) with the aqueous process waste.	Chemical Process Water Management (CPWM) injection system (Class 1 wells) Underground Injection Control (UIC) Permits MI-077-1W-0001 MI-077-1W-0002 eff. 7/9/93-10/27/96	U.S. EPA, Region 5, Safe Drinking Water Act
Methyl-tert-butyl ether	109-60-4	Fuels blending	- TWI, Sauget, IL, No. ILD098642424 or - Systech Environmental Corp, Alpena, MI, No. MID981200835 (haz. waste facility permit) and 587-93 (air permit); - Systech Environmental Corp., Paulding, OH, No. OHD008048947 (haz. waste facility permit) and 0363000002P016 and 0363000002P017 (air permit); or - Continental Cement, Hannibal, MO, No. MOD054018288 (haz. waste facility permit) and 1086-004A (air permit) or - a comparable facility	EPA EPA State of Michigan EPA State of Ohio EPA State of Missouri
Ethyl acetate	141-78-6	see CPWM permit/data info listed above		
N-Ethylheptylamine	106-30-6	see CPWM permit/data info listed above		

Fumaric acid	110-17-8	see fuels blending info listed above		
Isobutyl chloroformate	543-27-1	see CPWM permit/data info listed above		
Lactic acid	63-42-3	see CPWM permit/data info listed above		
Lithium aluminum hydride, 1M in tetrahydrofuran	16853-85-3	see CPWM permit/data info listed above		
4-(Methane-sulfonyl)amino)-γ-oxobenzene-butanoic acid (U-68849)	122647-32-9	see CPWM permit/data info listed above		
Sodium chloride	7647-14-5	see CPWM permit/data info listed above		
Sodium hydroxide 50% solution	1310-73-2	see CPWM permit/data info listed above		
Tetrahydrofuran	109-99-9	As aqueous filtrate: CPWM As organic distillate: fuels blending	see CPWM permit/data info listed above see fuels blending info listed above	
Triethylamine	121-44-8	see CPWM permit/data info listed above		

6.1.2 Aqueous Waste Streams

Aqueous waste streams resulting from chemical processes will be disposed either to the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant or through the chemical process water management (CPWM) injection system in accordance with this facility's Underground Injection Control permits granted pursuant to the Safe Drinking Water Act.

Only those aqueous streams not permitted to be discharged directly to the sanitary sewer are sent to the CPWM.

6.1.2.1 *Industrial Pretreatment Program (IPP).* In response to Federal and State requirements governing the City of Kalamazoo's Industrial Pretreatment Program (IPP), The Upjohn Company has been issued a discharge permit in the form of an Industrial Control Document (ICD) dated March 25, 1994 through March 31, 1999. In addition, incorporated by reference are The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations Nos.

- 1-89 (dated December 5, 1989), detailing penalties for noncompliance;
- 91-1 (dated April 29, 1991), providing pollutant discharge limits for metals;
- and 94-1 (dated February 9, 1994) providing pollutant discharge limits for petroleum hydrocarbons.

These documents detail additional specific discharge requirements and regulations. Projecting to the fifth year of production, all discharges from the production of ibutilide fumarate are permitted and will not impact the limits imposed under the ICD and accompanying Sewer Use Regulations.

6.1.2.2 *Chemical Process Water Management (CPWM).* Our CPWM injection operations are conducted in accordance with this facility's Underground Injection Control permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency pursuant to the Safe Drinking Water Act. Both permit Nos. are active through October 27, 1996.

With respect to our permits to dispose of liquid waste by the CPWM system, our Federal Underground Injection Control Permits restrict the types and concentrations of contaminants in the injected fluid. The contaminants are the same contaminants which we are allowed to handle under our hazardous waste permit application. These permits require that the concentration and type of contaminants listed in the permits to be monitored on a monthly basis and reported to the USEPA, Region 5. In addition, groundwater is protected through the construction and design of the CPWM injection system, the operating procedures employed and the continuous monitoring program, all of which are described in the permit. Major production of volatile contaminants are now removed from this waste stream by steam stripping and recovered by our solvent recycling and distribution process.

All chemicals listed in Section 5 may be expected to be included in the injected wastes either through direct discharge of spent materials or as trace contaminants in equipment washing.

With respect to the permit application terminology, The Upjohn Company wells are identified as "class 1" by U.S. EPA. Class 1 wells are used to inject hazardous wastes below the deepest underground source of drinking water or aquifer. A confining formation consisting of an impermeable geologic strata prevents any upward migration of injected fluids into underground sources of drinking water. The Upjohn Company has completed and received approval of a no-migration petition and demonstration for both UIC wells. The no-migration petition is a requirement of the USEPA Land Ban Restrictions which state that wastes may not be placed in a land disposal unit unless an approved petition is in place. The petition must show that there will be no migration of any waste constituent from the injection zone for as long as the waste remains hazardous or for 10,000 years. A containment system called a pressurized annulus prevents the leakage of injected fluids from the injection wells into any formation outside of the injection zone.

A further description of EPA's requirements for the issuance of UIC permits is contained in 40 CFR Part 144.

Following is a listing of the types of liquid waste streams generated from the ibutilide fumarate process:

Table 4: Liquid Waste Streams Resulting from Ibutilide Fumarate Process

Type of Stream	Major Components	Disposition
Aqueous filtrate	Water Ethyl Acetate Tetrahydrofuran Dissolved solids	CPWM
Aqueous filtrate	Water Acetone Salts (sodium/aluminum) Dissolved solids	Chemical process water management (CPWM)
Aqueous filtrate	Water Ethyl Acetate Tetrahydrofuran Dissolved solids	CPWM
Organic distillate	Acetone	Sent to an approved off-site facility as part of a waste-derived fuels program
Organic filtrate	Acetone Water Dissolved solids	Sent to an approved off-site facility as part of a waste-derived fuels program

Organic filtrate	Acetone	Sent to an approved off-site facility as part of a waste-derived fuels program
Organic distillate	Ethyl Acetate Tetrahydrofuran Water Dissolved solids	Sent to an approved off-site facility as part of a waste-derived fuels program
Organic distillate	Acetone Methyl t-butyl ether Water Dissolved solids	Sent to an approved off-site facility as part of a waste-derived fuels program
Organic distillate	Ethyl Acetate Dissolved solids	Sent to an approved off-site facility as part of a waste-derived fuels program

6.1.3 Spent Solvents

Used solvent mixtures are either directed to the solvent recycling and distribution (SRD) unit for recycling and reuse within the Portage manufacturing facility, used as a fuel in an on-site incinerator (interim status treatment storage and disposal facility, see 6.1.3.2, *Incinerator*) at the Portage manufacturing site, or are sent to an approved off-site facility as part of a waste-derived fuels program where the waste is blended at permitted facilities with other solvents for incineration or directly injected for incineration.

6.1.3.1 *SRD.* Used solvents at The Upjohn Company are collected at the production areas and conveyed via pipeline to a SRD facility within the plant site.

The SRD system receives the various solvents into dirty tanks and then feeds them into one of five distillation/reclamation columns that fractionate the constituents through the application of heat. At the different temperatures, various solvent species are recovered and sent to a clean tank where they are then distributed to the various production operations located throughout the plant site.

Those portions of the fractionation process that do not result in a product that is usable in our production operations are sent off site for disposal. The vast majority of this material is used as a waste-derived fuel that replaces or enhances other fossil fuels burned for energy. Other disposal options are the local waste water treatment plant and high temperature incineration, dependent upon the chlorine and water content of an individual stream.

6.1.3.2 *Incinerator.* The on-site incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264 Subpart O

requirements. A hazardous waste RCRA Part B/Michigan Act 64 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (MDNR) and is pending issuance.

The Air Quality Division of the MDNR revised and reissued Permit to Install No. 242-80 on May 26, 1993, to allow operation of the incinerator in accordance with Michigan Act 64 requirements.

This incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

Ash generated as a result of the incineration process is sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management of Indiana, Inc., 4636 Adams Center Road, Fort Wayne, IN, operating license listed under Indiana Dept. of Environmental Management (IDEM) Permit No. IND 078911146;
- Environmental Quality Co., 1349 South Huron Street, Ypsilanti, MI: Michigan Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (treatment) operating license listed under EPA ID No. MID 000 724 831; Wayne Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (disposal) operating license listed under EPA ID No. MID 048 090 633;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and are properly permitted.

We have identified hazardous waste as well as air permits given to us by these facilities, but there may be other permits and licenses applicable which are currently held by the facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

6.1.3.3 *Off-site Spent Solvents.* Waste spent solvents sent off-site are transported to permitted facilities using the Uniform Hazardous Waste Manifest form. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;
- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and properly permitted.

Following is a table showing solvents used in the ibutilide fumarate process that are recycled through SRD and the disposition of the remainder:

Table 5: Solvent Disposition

Solvent	Solvent Disposition from Ibutilide Generic Process Through SRD				
	% SRD Recovery	% Upjohn Distillation	% Fuel Blending	% Other	% Sanitary Sewer
Acetone	48		27		25
Ethyl Acetate	39.6	38.2	4.7	11.0 chlorinated solvent tanks (methylene chloride is removed and remaining solvent hauled off-site for fuels blending)	
Tetrahydrofuran	53	39	8		

6.1.4 Solid Waste

- Any Magnesol 400/10 cartridge grade used in the process would be treated and then disposed in a permitted hazardous waste landfill (see Section 6.1.3.2 for a listing of permitted facilities Upjohn uses).

- Particulate is captured in the recirculating HEPA filtration system. HEPA filters which become loaded are sealed in plastic bags and sent off-site to a permitted incinerator (see Section 6.1.3.3 for a listing of permitted facilities Upjohn uses).

- Rough-in filters (approximately 30% efficiency) are disposed in an approved on-site incinerator. (For description of the incinerator and related permits, see Section 6.1.3.3)

6.2 Pharmaceutical Formulation and Packaging

6.2.1 Air Emissions

The Upjohn Company is operating under an air consent decree with the MDNR dated March 15, 1991, which requires that all manufacturing and production facilities operate within a specified set of parameters according to the environmental air permit-to-install for each plant. This includes the definition of all air emitting and control equipment.

An air use permit application for this equipment was approved by the MDNR on March 29, 1994 for the Sterile Injectable Operations where this product will be manufactured. All materials in the formulation for Ibutilide Fumarate Injection are included in this approved air permit. In this permit it is assumed that 0.4% of the dry materials handled would be lost to the exhaust systems serving the manufacturing modules. Of this 0.4%, 75% is removed by a recirculating HEPA filtration system, and 25% is handled by a rotoclone wet dynamic precipitator with a 92.2% removal efficiency (Rotoclone v-4). This rotoclone was inventoried on the equipment inventory also required under the air consent judgment.

The process to manufacture Ibutilide Fumarate Injection does not use any VOCs, although the preparation and testing of filtration equipment does use isopropyl alcohol. The emission of this compound is discussed in the above-mentioned MDNR application.

Ibutilide Fumarate Injection will be packaged and labeled using on-line printers with VOC-based inks. Because these printers emit small amounts of VOCs, they are exempt from permitting under MDNR rules.

6.2.2 Liquid Waste Streams

Liquid waste streams resulting from the pharmaceutical formulation and packaging facility will consist of residue waste waters from sanitary use and washing operations which will be discarded to the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant (see Section 6.1.2.1, p. 8).

Projecting to the fifth year of production, the pharmaceutical formulation and packing of Ibutilide Fumarate Injection will not impact the limits imposed under the ICD and accompanying Sewer Use Regulations.

6.2.3 Solid Waste

All unused, discarded, or returned product will be incinerated in an approved on-site incinerator (see Section 6.1.3).

Solid wastes will result as particulate is captured in the recirculating HEPA filtration system. HEPA filters which become loaded are sealed in plastic bags and sent off-site to a permitted incinerator.

6.3 Applicable Regulations and Laws at the Site

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended.
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
   a. National Electrical Code Standards
   b. Life Safety Requirements
10. Act #348 of 1965, Michigan Air Pollution Act, as amended.
11. Act #245 of 1929, Michigan Water Resource Commission Act, as amended.
12. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
13. Act #136 of 1969, Michigan Liquid Industrial Waste Disposal Act, as amended.
14. Act #315 of 1969, Michigan Mineral Well Act, as amended.
15. Act #641 of 1978, Michigan Solid Waste Management Act.
16. Act #64 of 1979, Michigan Hazardous Waste Management Act, as amended.
17. Act #368 of 1978, Public Health Code.
18. Chapter 28 of the Kalamazoo City Code (Services and Waste water) as amended by ordinance No. 1190.
19. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

Permits and other actions covering specific environmental regulations in force at the The Upjohn Company's main pharmaceutical and chemical manufacturing complex in Kalamazoo, Michigan, including permit numbers and expiration dates where applicable, are summarized in the table attached (see Appendix 5).

6.4 Statement of Compliance

6.4.1 Emission Requirements

The Upjohn Company states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the manufacture of Ibutilide Fumarate Injection at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of Ibutilide Fumarate Injection at its facilities in Kalamazoo, Michigan.

6.4.2 OSHA Requirements

The Upjohn Company certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.5 Effect of the Approval of the Proposed Action

Ibutilide Fumarate Injection will be produced on the current filling line in the manufacturing facility. No new capital equipment will be required.

Based on information outlined in Sections 6.1 and 6.2, approval of the proposed action will not modify or have an effect upon the Upjohn Kalamazoo site existing facilities.

6.6 Use and Disposal of Products

The amount of drug left-in containers over a year's use of the product at hospital or clinic settings is estimated to be very minute and would not result in significant introductions from use of the product into the environment.

Ibutilide Fumarate Injection will be administered by intravenous infusion to patients in hospitals or clinics. The small amounts of parent compound excreted in urine or feces would be discharged into sanitary sewer and/or septic systems. Only minute traces of the active ingredient, ibutilide fumarate, would be expected to remain with empty product containers.

Marketing forecasts in terms of amounts of ibutilide fumarate required per year for the first through fifth years of production are shown below in grams.

Table 6: Five-Year Market Figures

	140	455	805	1050	1120

These amounts represent the theoretical maximum amounts that could be released to the environment through accidental release, end-use and disposal.

6.7 Maximum Expected Environmental Concentration (MEEC)

Estimations of theoretical maximum environmental concentrations (MEECs) can be made using the following equation:

MEEC (ppm) = lbs/yr x 8.9 E^{-6}

= (A)(B)(C)(D)(E)(F)

where:

A	=	pounds per year production
B	=	year/365 days
C	=	day person/150 gallons
D	=	1/264 million person (U.S. population)
E	=	gallons/8.34
F	=	1 million

Utilizing the first year production forecast of 140 grams, the maximum environmental concentration that could be achieved is 2.7 x $10E^{-6}$ ppm. Utilizing the fifth-year production forecast of 1120 grams, the maximum environmental concentration that could be achieved is 2.1 x $10E^{-4}$ ppm. These concentrations assume complete and instantaneous release of the entire year's production with no degradation.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Fate of Emitted Substances in the Environment

Ibutilide fumarate occurs as a white crystalline powder with a melting point range of 115-119°C. Its aqueous solubility at room temperature is greater than 100 mg/mL at any pH less than 7. Between pH 7 and 9.4 aqueous solubility decreases rapidly. A minimum solubility of 6 mg/mL occurs at pH 9.4. Above pH 9.5, solubility rapidly increases and is greater than 100 mg/mL above pH 10.5 (Amidon and DeMulder, 1989).

Ibutilide is the active form of ibutilide fumarate. In healthy male volunteers, about 82% of a 0.01mg/kg dose of [^{14}C]ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (19%) was recovered in the feces. Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω-oxidation followed by sequential β-oxidation of the heptyl side chain of ibutilide. These metabolites have no activity or weak class III activity relative to ibutilide.

It is anticipated that ibutilide fumarate will be administered primarily in hospital settings. Discharges to air or waste water are not expected as a consequence of the use or disposal of this product, other than for possible disposal of small amounts of unused drug formulation to local publicly owned treatment works. Unused product returned to The Upjohn Company would be subject to final disposal via government-permitted mechanisms and not released to the environment.

7.2 Studies

A series of studies were conducted in accordance with Good Laboratory Practices at ABC Laboratories, Columbia, Missouri, to better understand the fate of ibutilide fumarate if released to one or more environmental compartments.

7.2.1 Vapor Pressure

The vapor pressure of ibutilide fumarate was presumed to be negligible (< 10 E-7 torr), because the compound occurs as a solid with a melting point in excess of 100°C. A negligible vapor pressure means that the compound does not have a tendency to vaporize, and therefore would not enter the air compartment, or be transported in air. Experimental measurement of vapor pressure confirms this assumption.

7.2.2 Microbial Inhibition

Microbial inhibition was studied by the agar plate dilution technique with ibutilide fumarate incorporated into the agar medium, at nominal concentrations of 1000, 250, 62.5, 15.6, and 3.91 mg/L. Test organisms included *Aspergillus flavus*, *Chaetomium globosum*, *Nostoc sp.*, *Pseudomonas acidovorans*, and *Azotobacter chroococcum*.

These organisms are present in various environmental media and contribute to ecosystem balance. For example, *Pseudomonas* plays a role in degradative and transformation processes. *Azotobacter* fixes nitrogen from the atmosphere. *Chaetomium* is known to degrade cellulose, thus converting a complex organic molecule into more readily assimilable material in soil and other media.

Growth inhibition was not seen in *Psuedomonas*, *Aspergillus*, *Nostoc*, or *Chaetomium* at the highest concentration (1000 ppm) tested. Growth inhibition was seen in *Azotobacter*, and a minimum inhibitory concentration of 1000 mg/L was calculated for this microorganism.

7.2.3 Aerobic Biodegradation

Carbon-14 labeled ibutilide fumarate was tested for biodegradability in an aqueous aerobic medium at a test concentration of approximately 10 mg carbon/liter. Significant biodegradation was not seen during the 29-day incubation period in darkness at 22 ± 3° C.

7.2.4 Hydrolysis

A hydrolysis study was conducted with C-14 labeled ibutilide fumarate, in aqueous buffered solutions, in darkness, at a nominal test concentration of one ug/mL. Significant degradation of the compound was not seen after a five-day incubation period at 50° C. Therefore, ibutilide fumarate was considered to be hydrolytically stable with a half-life equal to or greater than one year.

7.2.5 Aquatic Photodegradation

Photodegradation is a process whereby chemicals are altered as a result of irradiation. The process involves absorption of light in the ultraviolet-visible region by a molecule with a resultant increase in the molecular energy level; the increased energy level then transforms the molecule into one or more products. Ibutilide fumarate showed a 10 % potency loss when exposed to high intensity fluorescent light for 7 days, and a 25 % loss in potency when exposed to high intensity ultraviolet light for 7 days. These results indicate that ibutilide fumarate is subject to rapid aqueous photolysis.

An aqueous photodegradation study was conducted at 25 ± 1° C by exposing 14C-ibutilide fumarate in pH 5, 7, and 9 buffers to a xenon arc light source. The study was conducted at a nominal test chemical concentration of 1.0 ug/mL. The study demonstrated that ibutilide fumarate undergoes photodegradation in aqueous media with experimentally measured half lives of 16.8, 5.8, and 0.4 days for pH 5, 7, and 9, respectively.

7.2.6 Partition Coefficient

The logarithm of the n-octanol/water partition coefficient was found to be between 0.65 and 0.86 at pH 7 (DeMulder, PJ. 1992). This range does not suggest a potential for ibutilide fumarate to bioccumulate in living systems.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

The manufacture of ibutilide fumarate is not expected to present significant risks to public health or the environment since releases which may be associated with drug synthesis or product manufacture are governed by federal, state and local regulations. The use of ibutilide fumarate is not expected to present a risk to public health or the environment because the theoretical maximum amounts that could be released would be less than those found toxic in aquatic systems. The theoretical maximum environmental concentration that could result from the complete and instantaneous release of the entire fifth year production is 2.1 x $1CE^{-3}$ ppm. Inhibition of representative environmental microorganisms was not seen at concentrations 10 orders of magnitude greater that the MEEC of ibutilide fumarate as calculated from the projected fifth-year production volume. As previously noted, ibutilide fumarate is unstable in the presence of light with a half-life from 0.4 days to 16.8 days in aquatic systems. Because of its low partition coefficient, ibutilide fumarate would not

bioaccumulate in living systems. Therefore, based on a worst-case analysis, amounts of ibutilide fumarate which might reach an environmental compartment may reasonably be anticipated to be non-toxic according to the definition found at 21 CFR 25.15(b)(6).

9. USE OF RESOURCES AND ENERGY

Following is a table detailing production volume and utility usage:

Table 7: Production Volume

	140	455	805	1050	1120
	1.8	5.8	10.3	13.2	14.1
	.16	.47	1.14	1.46	1.57

No effects on endangered or threatened species are anticipated as a result of drug approval.

A preliminary ecological assessment was conducted to fulfill the requirements of the pending U.S. EPA-administered Hazardous Solid Waste Amendment (HSWA) permit, which is issued under RCRA authority. Results of this preliminary ecological assessment for The Upjohn Company's manufacturing headquarters did not reveal the presence of endangered or threatened species and did not demonstrate adverse impacts of manufacturing operations on aquatic or terrestrial biota including plants and waterfowl (Downey, 1993).

The use of natural resources and energy for the manufacture of this product will be less than 2% (at the fifth year) of present total plant usage and can be handled by the existing infrastructure. The resources committed will be the materials listed in Section 5, the utilities used in manufacturing, and minor miscellaneous support materials.

Under the authority of the National Historic Preservation Act of 1966, as amended, The Upjohn Company has received an opinion letter from the State Historic Preservation Officer that, since this activity does not involve the alteration, demolition or construction of building or any earth-disturbing projects, historic property determination is not required (see Appendix 6).

The amount of emissions from this formulation at the manufacturing site in Kalamazoo will be controlled in accordance with Federal, State and local standards in order to prevent adverse effects on the environment or to any wildlife.

10. MITIGATION MEASURES

Measures taken at the manufacturing site to avoid potential adverse environmental impacts associated with the proposed action include:

Adherence to all applicable Federal, State and local regulations as outlined in Section 6.3 above shall be followed to avoid potential adverse impact associated with the proposed action.

Measures taken at the formulation site to avoid potential adverse environmental impacts associated with the proposed action include:

- use of equipment systems to prevent emission levels from exceeding limits established by Federal, State and local regulations;

- disposal of aqueous waste streams into the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant or through an on-site CPWM system conducted in accordance with this facility's permit granted by the U.S. EPA pursuant to the Safe Drinking Water Act;

- solvent recovery through the SRD unit; waste solvents not recovered in SRD are manifested to our outside brokers, where these solvents are blended for fuel use; and

- an extensive spill control plan to protect employees and environmental compartments is in place at The Upjohn Company Portage Road facility to mitigate any adverse effects of inadvertent releases to the environment.

Material Safety Data Sheets (MSDSs) are available on site. Employees associated with the manufacture of Ibutilide Fumarate Injection have appropriate training. Employee protective clothing (e.g., gloves, uniforms, and safety shoes) and protective equipment (e.g., safety glasses and approved respirators) are used during manufacture to assure compliance with applicable occupational safety requirements.

The Upjohn Company has a comprehensive occupational health and safety program. This includes conduct of preplacement physical examinations of employees and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the course of employment. The above procedures will serve to monitor employees for the development of conditions attributable to exposure.

Employees observe written standard operating procedures detailing handling, precautions, and use of personal protective equipment.

In addition, all employees in Pharmaceutical Manufacturing are required to take basic safety training on an annual basis, which includes:

- Hazard communication and hazardous materials,
- Personal protective equipment and production equipment, and
- Standard Operating Procedures and personal safety practices.

Reference is made to item 6 above for additional information.

11. ALTERNATIVES TO THE PROPOSED ACTION

Resources and facilities are being used effectively to produce a quality product with minimal environmental impact. The alternative of no action resulting with the deprivation to mankind of potentially beneficial therapy is not anticipated.

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

J. S. Mehring	Environmental Quality and Safety Division Manager, Environmental Health Sciences Ph.D., Agriculture Professional experience: 23 years
S. I. Shedore	Environmental Quality and Safety Division Environmental Technician A.A., Liberal Arts Corporate experience: 23years
A.S.Pandrangi	Chemical Engineering Support Production Engineer M.S., Chemical Engineering Professional experience: 27 years
V.G.Kalthod	Chemical Process R&D Research Scientist B.S., Chemical Engineering Professional experience: 3 years

N.J.Tuit	Worldwide Pharm. Mfg. Operations Environmental & Safety Administrator B.S., Industrial Engineering Professional Experience: 16 years
M. A. Parks	Environmental Compliance Engineering Environmental Compliance Engineer B.S., Engineering Professional experience: 5 years
W.F.Oberheu	Chemical Division Environmental Group Environmental Engineer B.S., Natural Resources Professional experience: 8 years
R.F.Tolbert	Environmental Compliance Engineering Environmental Compliance Engineer B.S., Mechanical Engineering Professional experience: 6 years
T.E.Nicholson	Pharmaceutical Mfg. Project & Regulatory Management Senior Industrial Engineer M.B.A., Industrial Management Professional experience: 24 years
K. B. Eckert	Acting State Historic Preservation Officer Bureau of History Michigan Department of State Lansing, Michigan

13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

Randal S. Senger, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

10-4-95
Date

Jeffrey S. Mehring, Manager
Environmental Health Sciences
(telephone 616/323-4746)

5 OCT 95
Date

14. REFERENCES

Amidon GE, DeMulder PJ. Aqueous solubility profile of U-70226E. Upjohn Technical Report 7230-89-008, July 13, 1989. [attached as Appendix 7]

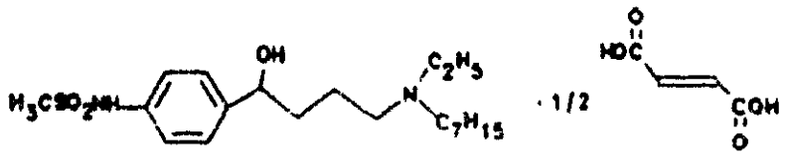
DeMulder PJ. The Upjohn Company. Personal Communication. September 22, 1992.

Downey RG. Preliminary ecological assessment for The Upjohn Company, Portage Road facility. June 25, 1993.

15. APPENDICES

APPENDIX 1: SUMMARY

Chemical name	N-{4-{ethylheptylamino}-1 hydroxybutyl}phenyl}methane sulfonamide, (E)-2-butenedioate (2:1) salt
CAS Registry number	122647-32-9
Upjohn U-number	70226E
USAN approved generic name	ibutilide fumarate
Structure	



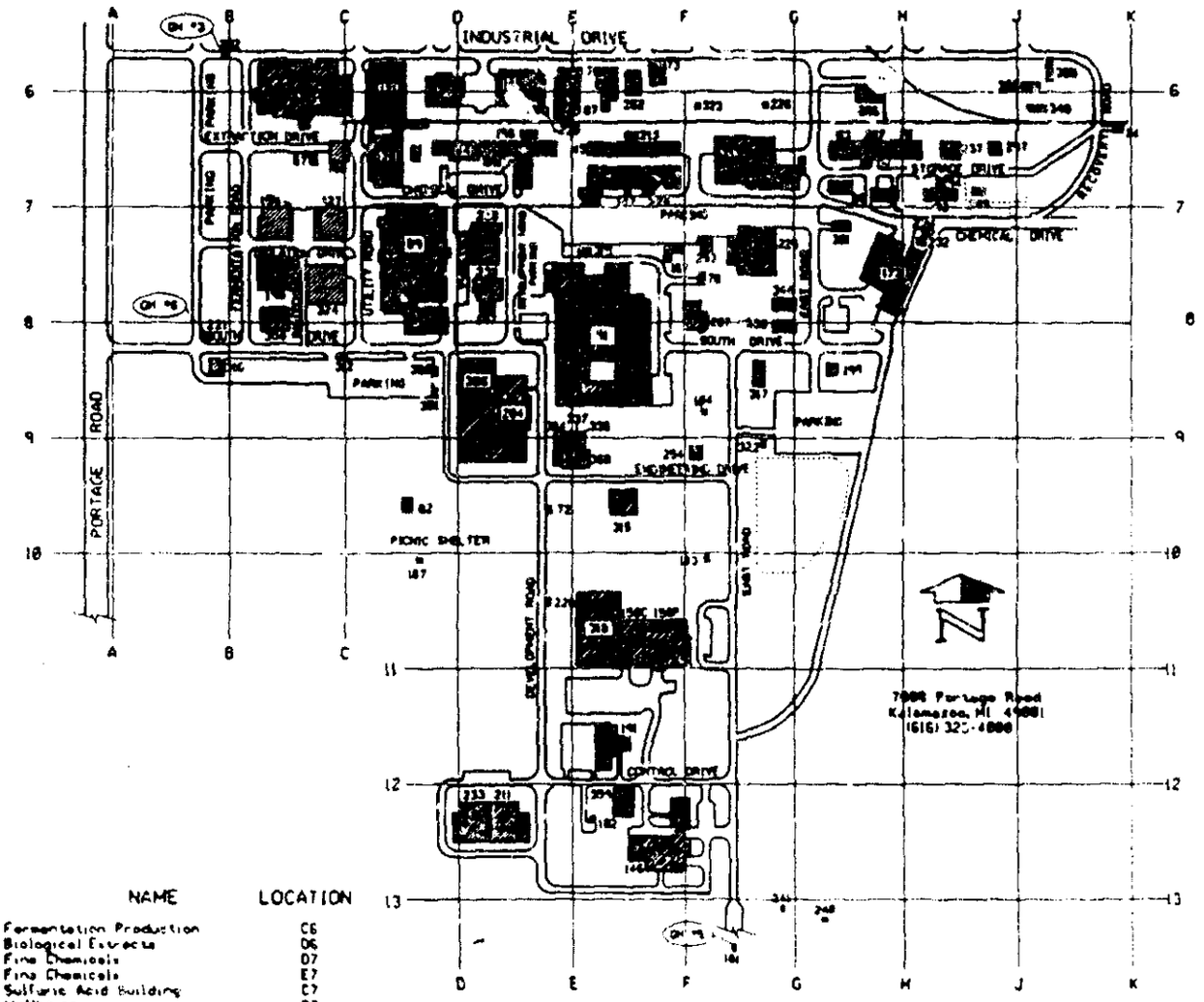
Ibutilide Fumarate

Empirical formula	$C_{22}H_{36}N_2O_6N$
Molecular weight	442.61
Melting point	116-119°C
Appearance	white crystalline powder
Solubility (mg/mL)	> 100 at pH < 7 6 at pH 9.4 > 100 at pH > 10.5
Dissociation constants (pKa)	8.4 (sulfonamide) and 9.6 (tertiary amine)
Vapor pressure (mmHg)	< 5 X 10E-10
Partition coefficient (Log P)	0.65 to 0.86
aerobic biodegradation half-life (days)	> 365
hydrolysis half-life (years)	≥ 1

APPENDIX 1: SUMMARY (continued)

photodegradation half-life (days)	16.8 at pH 5 5.8 at pH 7 0.4 at pH 9
MIC (ppm), *Pseudomonas acidovorans*	> 1000
MIC (ppm), *Aspergillus flavus*	> 1000
MIC (ppm), *Azotobacter chroococcum*	1000
MIC (ppm), *Nostoc sp.*	> 1000
MIC (ppm), *Chaetomium globosum*	> 1000

PORTAGE ROAD BUILDINGS
EAST SIDE
South of Industrial Drive

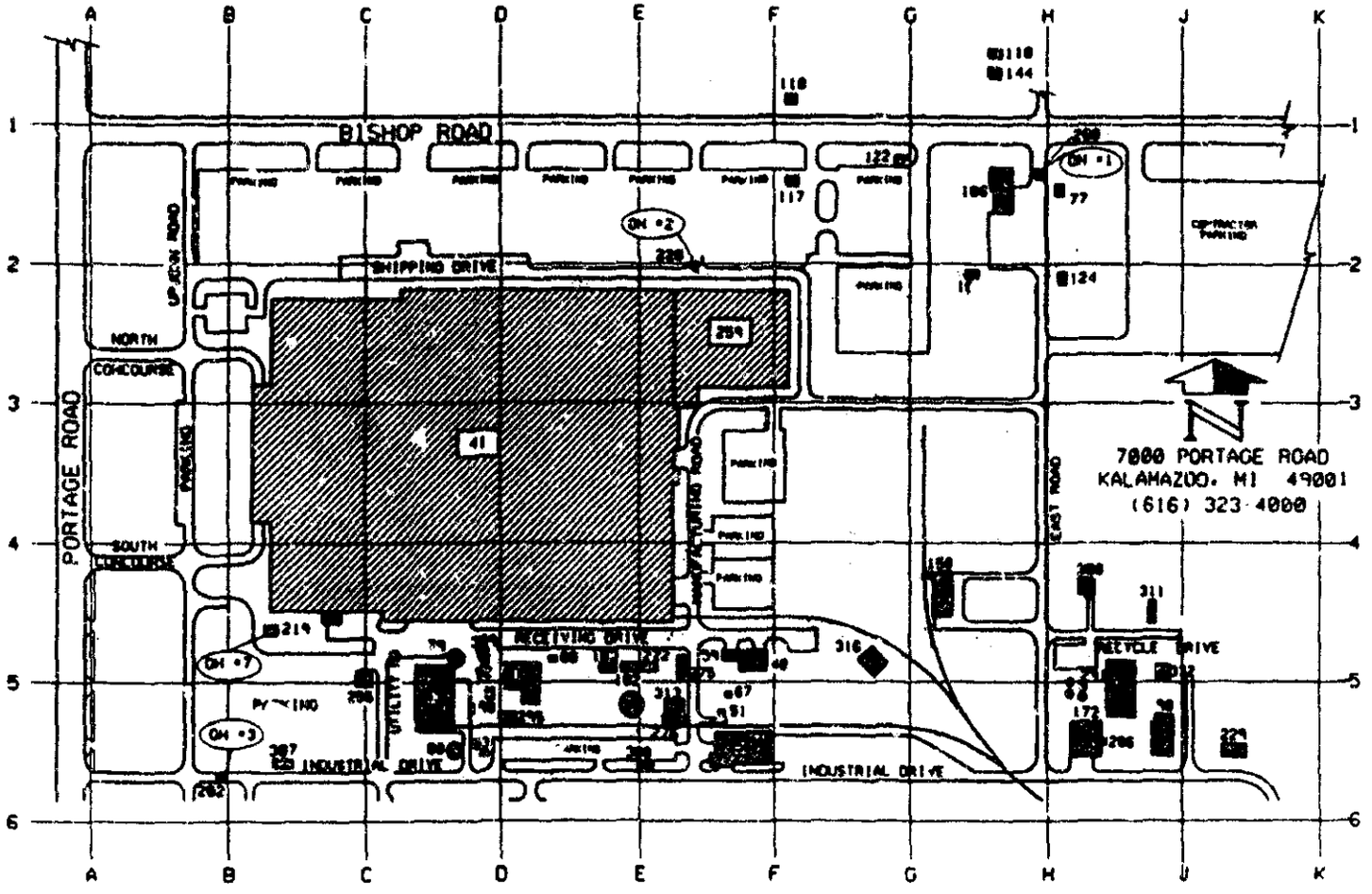


BLDG.#	NAME	LOCATION
38	Fermentation Production	C6
39	Biological Extracts	D6
44	Fine Chemicals	D7
45	Fine Chemicals	E7
57	Sulfuric Acid Building	C7
61	Wellhouse	D7
63	Solvent Storage	G6
66	Specialty Chemical Production	D7
68	Fine Chemicals	E7
69	Fine Chemicals	F7
70	Solvent Storage	H7
72	Pumphouse Well #16	E10
73	Solvent Recovery	F6
74	Incinerator	K6
76	Fine Chemical Waste Disposal	F8
78	Fine Chemicals	E6
82	Picnic Shelter	D10
86	Chemical Dev. Storage Building	D7
87	Fine Chemicals	E6
91	Fermentation Development	D7
91	Chemical Development	E8
92	Chemical Storage	H7
93	Chemical Storage	H7
94	LAW Storage	H7
182	Pumphouse Well #21	E12
183	Pumphouse Well #22	F10
184	Pumphouse Well #23	F9
120	Fermentation Warehouse	C7
121	Fermentation Structure	C6
127	Fermentation Production	C7
146	Animal Rearing Building	F13
147	Scale House-Dibal	E7
149	Fine Chemicals	E6
155	Ferm. Prod. Crystallization	B7
156c	Cephalosporin Processing	F11
156p	Penicillin Processing	F11
166	Rotary Filter Building	C7
167	Chlorine Storage	F7

BLDG.#	NAME	LOCATION
173	Specialty Chemical Production	H8
181	Guard House #5	F13
187	Picnic Area Rest Room	D10
191	Animal Quarantine Facilities	E12
195	Ferm. Prod. Crystallization	B8
196	Fine Chemicals Office	D6
199	Fire Reservoir #2 Pumphouse	G8
202	Guard House #3	B6
204	Welding Shop	D9
205	Fine Chem. Office & Classroom	E7
207	Chemical Production	F8
208	Pharmaceutical Chem. Cafeteria	D7
211	Chronic Toxicology Building	D12
213	Portable Office Unit	F6
221	Guard House #6	B8
224	Mechanical Brine Chiller Bldg.	F7
225	Pharm. Chem. Prod. Facility	G7
226	Sodium Hydroxide Pumphouse	G6
228	Chlorinator House Well #18	E10
230	Analytical Laboratory Building	D8
232	Emergency Generator Building	H7
233	Biological Control Facilities	D12
236	Chiller Bldg. OPGII	E6
237	Cyanide storage Building	H7
238	Acetylene Storage & Supply Bldg.	H7
240	Pumphouse Well #39	G13
241	Pumphouse Well #40	G13

BLDG.#	NAME	LOCATION
253	Wellhouse for Disposal Well #3	F7
254	Wellhouse for Disposal Well #4	F9
283	Chemical Receiving Barn	H6
297	Cooler Bldg. for Minocidil	J7
299	Freezer Building	J7
301	Maintenance Shop Building	G7
306	Chemical Engineering Building	D9
310	Backflow Preventer Bldg. #4	B9
312	Instrumentation Building	C8
315	Chilled Water General Facility	E10
317	Instrument Shop	G8
318	Cephalosporin Building	E11
321	Brine Building	E7
322	Instrumentation Building	C9
323	Motor Control Building	F9
324	RBST	C6
335	Office Trailer	F7
337	Office Trailer	E9
338	Office Trailer	G8
344	Office Trailer	G8
350	Office Trailer	D8
351	Office Trailer	D6
358	Refrigerated Equipment Building	B6
359	Airco Nitrogen Plant	E12
362	IB/mcc Room	E6
363	Office Trailer	E9
364	Office Trailer	E9

PORTAGE ROAD BUILDINGS
EAST SIDE
North of Industrial Drive



BLDG.	•	NAME	LOCATION
40		GROUND SERV. & WATER UTILITIES	F5
41		PHARMACEUTICAL MANUFACTURING	C4
43		POWER HOUSE	C5
51		SWITCHGEAR HOUSE	F5
52		PUMPHOUSE •1	D5
53		PUMPHOUSE •2	D6
56		GARAGE	F6
59		YARD CREW & WATER DEPT. OFFICE	F5
60		PUMPHOUSE •4	D5
67		METER HOUSE	F5
77		PUMPHOUSE •17	H1
79		WATERSPHERE	D5
80		WATERSPHERE	D6
90		CONSTRUCTION CONTRACTORS SHOP	J5
109		WELLHOUSE	G2
110		PUMP HOUSE WELL •25	H1
117		CHLORINATED WELL •7	F1
118		CHLORINATED WELL •8	F1
122		CHLORINATED WELL •19	G1
124		FIRE TRAINING BUILDING	H2
144		PUMPHOUSE WELL •27	H1
150		PRE-MIX PRODUCTS	G4
172		INCINERATOR BUILDING	H5
182		CENTER RELOCATABLE CLASSROOM	E5
183		WEST RELOCATABLE CLASSROOM	E5

BLDG.	•	NAME	LOCATION
186		FIRE STATION	H1
188		CENTRAL UTILITIES FACILITY	D5
198		COOLING TOWER FIRE PROT. BLDG.	D5
202		GUARDHOUSE •3	B6
219		GUARDHOUSE •7	B5
220		GUARDHOUSE •2	E2
222		EAST RELOCATABLE CLASSROOM	E5
229		ENGINEERING STORAGE BUILDING	J5
255		OIL PUMPHOUSE FOR BOILERS	C5
259		LAB & TECHNICAL SERV. FACILITY	F3
260		GUARDHOUSE •1	H1
275		OFFICE TRAILER	E5
276		OFFICE TRAILER	E5
286		POLE BARN	H5
291		WASTE CONTROL BUILDING	H5
295		METAL BUILDING	D5
307		BACKFLOW PREVENTER BLDG •1	B6
308		BACKFLOW PREVENTER BLDG •2	E6
309		BACKFLOW PREVENTER BLDG •3	D5
311		INSTRUMENTATION BUILDING	J4
313		WATER BOOSTER PUMP STATION	E5
316		STORAGE GARAGE	G5
332		UTILITY STORAGE	J5
388		HAZARDOUS SOLVENT WASTE STORAGE	H4

Upjohn

Print Date: October 03, 1995
Revision Date: February 08, 1995
Agent Id#: 41140

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: IBUTILIDE FUMARATE

SYNONYMS: 122647-32-9 - CAS NUMBER
Methanesulfonamide,N-[4-(4-(ethylheptylamino)-1-hydroxybutyl) phenyl]-, (E)-2-butenedioate (2:1) salt
200219 - EDP NUMBER
U-70,226E - UPJOHN U#
MOLECULAR FORMULA: C20-H36-N2-O3-S . 0.5 C4-H4-O4
CHEMICAL FAMILY: No information found
MANUFACTURER/SUPPLIER: THE UPJOHN COMPANY
7171 PORTAGE RD.
KALAMAZOO, MI 49001-0199

TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Ibutilide Fumarate
CHEMICAL NAME: Methanesulfonamide,N-[4-(4-(ethylheptylamino)-1-hydroxybutyl) phenyl]-, (E)-2-butenedioate (2:1) salt
% BY WEIGHT: < 100 %
CAS NUMBER: 122647-32-9
EXPOSURE LIMIT(S): Not established.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation.
EFFECTS OF OVEREXPOSURE: Overexposure may cause vomiting, ataxia, body tremors and rapid eye blinking or twitching and bobbing of head and convulsions. Repeated overexposure may cause testicular degeneration/atrophy or mammary gland proliferation and mucification of the vaginal epithelium.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Not established.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.
SKIN: Wash with soap and water. Remove contaminated clothing.
INHALATION: Remove from exposure.
INGESTION: Contact a physician or poison control center.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable.
LOWER EXPLOSION LIMIT (LEL): Not applicable.

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[redacted]

UPPER EXPLOSION LIMIT (UEL): Not applicable.
EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.
FIRE-FIGHTING PROCEDURES: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.
UNUSUAL FIRE OR EXPLOSION HAZARDS: None.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove ignition sources; control the generation of dust/vapors; provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Vacuum (with HEPA-filtered and explosion-proof equipment) or scoop spilled material and place in container.

7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: Avoid generating dust/vapors and contact with skin, eyes and clothing. Use with adequate ventilation. Wash thoroughly after handling. Launder contaminated clothing before reuse. Store at room temperature. Do not get in eyes, on skin or clothing. Avoid breathing dust or mist. Use adequate dust/vapor control.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator.
VENTILATION: Local exhaust.
PROTECTIVE GLOVES: Rubber.
EYE PROTECTION: Safety glasses with side shields.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: White amorphous powder.
MELTING POINT: > 100 degrees C.
MOLECULAR WEIGHT: 442.62
ODOR: No information found.
SOLUBILITY IN WATER: No information found.
VAPOR PRESSURE: Not applicable.

10. STABILITY AND REACTIVITY

STABILITY: Stable.
PHYSICAL CONDITIONS TO AVOID: None.
INCOMPATIBILITY WITH OTHER MATERIALS: None.
HAZARDOUS DECOMPOSITION PRODUCTS: None.
HAZARDOUS POLYMERIZATION: Does not occur.

Upjohn

[redacted]

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
EYE IRRITATION (RABBIT): Moderately to severely irritating.
SKIN IRRITATION (RABBIT): Non-irritating to intact skin; moderately irritating to abraded skin.
INTRAVENOUS TOXICITY: The no-observed-adverse-effect level (NOAEL) in a 14-day study in rats was 12.5 mg/kg. The NOAEL in a 14-day study conducted in dogs was less than 2.5 mg/kg/day.
ORAL TOXICITY (RAT): The single oral no-observed-adverse-effect level (NOAEL) of ibutilide fumarate in rats is between 160 and 500 mg/kg.
ORAL LD50 (RAT): > 500 MG/KG
SUBCHRONIC/CHRONIC STUDIES: In a 90-day oral study in rats, a reversible increase in body weight was seen in females receiving 10 to 63 mg/kg/day. A reversible decrease in estrous cycling was also noted in females fed 63 mg/kg/ day during the last 30 days of the 90-day trial.
OTHER STUDIES:
GENOTOXICITY: Ibutilide fumarate was negative when tested in the micronucleus assay, the Ames assay, the mammalian cell mutation assay and the unscheduled DNA synthesis assay.
REPRODUCTION/FERTILITY: The oral no-observable-adverse-effect level (NOAEL) in the rat for maternal, paternal, reproductive and developmental toxicity was 5 mg/kg/day.
TERATOGENICITY: The oral no-observed-adverse-effect level (NOAEL) for teratogenicity in the rat was 5 mg/kg/day and 2 mg/kg/day in the rabbit (highest level tested). Some evident of teratogenicity was observed in rabbits tested at higher levels.
CARCINOGENICITY: Ingredient(s) are not listed as carcinogenic by IARC, NTP or OSHA.

12. ECOLOGICAL INFORMATION

ENVIRONMENTAL FATE:
MOBILITY: The vapor pressure of ibutilide fumarate is presumed to be negligible (<10E-7 torr) because the compound occurs as a solid with a melting point in excess of 100 degrees C. A negligible vapor pressure means that the compound does not have a tendency to vaporize, and therefore, would not be anticipated to enter the air compartment or to be transported in air.
BIOACCUMULATIVE POTENTIAL: The logarithm of the n-octanol/water partition coefficient was found to be between 0.65 and 0.86 at pH 7. This range does not suggest a potential for ibutilide fumarate to bioaccumulate in living systems.
ABIOTIC POTENTIAL: Ibutilide fumarate may have mild to no inhibition of growth in several types of microbes present in various environmental media.
ECOTOXICITY: No information found.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

14. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport

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[redacted]

Association (IATA). May be subject to state and/or local transportation requirements.

15. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.
DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. The Upjohn Company disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

16. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): K-1
HAZARD: TOXIC. IRRITANT.
SIGNAL WORD: WARNING!
STATEMENT OF HAZARD/RISK PHRASE: May be harmful if swallowed, inhaled or absorbed through skin. May cause skin, eye, or respiratory tract irritation.
PRECAUTIONARY MEASURES: Do not get in eyes, on skin, on clothing. Avoid breathing dust, vapor, mist or gas. Keep container closed. Use with adequate ventilation. Wash thoroughly after handling.

APPENDIX 5
THE UPJOHN COMPANY: PERMIT INDEX

Air Consent Judgment Air Use Permit	Michigan Department of Natural Resources, Air Quality Division MDNR, Air Quality Division	 923-92	03/15/91 03/29/94	03/01/96
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90	10/01/95
RCRA/Michigan Hazardous Waste Management Act 64 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000620381 pending action on Part B/Act 64 permit app'n.		
Michigan Air Pollution Act 348 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

MICHIGAN DEPARTMENT OF STATE
RICHARD H. AUSTIN SECRETARY OF STATE
LANSING
MICHIGAN 48918

September 3, 1991

Ms. Susan I. Shedore
Environmental Technician
The Upjohn Company
Kalamazoo, MI 49007

RE: ER-910587 Environmental Assessment for the Formulation and Packaging of Drugs, Various Locations, Kalamazoo County (FDA)

Dear Ms. Shedore:

We have reviewed the above-cited project at the location noted above, under the authority of the National Historic Preservation Act of 1966, as amended. It is the opinion of the State Historic Preservation Officer (SHPO) that the project does not require a historic property determination since the activity does not involve the alteration, demolition or construction of buildings, or any earth disturbing projects.

Please maintain a copy of this letter with your environmental review record for this project. If you have any questions, please contact William Rutter, the Environmental Review Coordinator for the Bureau of History, at (517) 335-2721.

Thank you for this opportunity to review and comment.

Sincerely,

Kathryn B. Eckert
Acting State Historic Preservation Officer
Bureau of History

KBE:ER:br

END

J.H.M. RESEARCH &DEVELOPMENT, INC. 5776 SECOND STREET.N.E. WASH. DC 20011