CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

APPROVAL LETTER

NDA 20-333/S-002

Roberts Laboratories Inc.
Attention: Richard J. Raffa
4 Industrial Way West
Eatontown, New Jersey 07724-2274

Dear Mr. Raffa:

Please refer to your supplemental new drug application dated December 30, 1997, received January 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Agrylin® (anagrelide hydrochloride) Capsules.

We acknowledge receipt of your submissions dated March 2, April 8, June 25, and November 19, 1998.

This supplemental new drug application provides for the use of Agrylin® (anagrelide hydrochloride) Capsules for treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events.

We have completed the review of this supplemental application, as amended, 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 labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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 "FPL for approved supplement NDA 20-333/S-002." Approval of this submission by FDA is not required before the labeling is used.

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane

Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, contact Ms. Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

FINAL PRINTED LABELING

AGRYLIN®
(anagrelide hydrochloride)
Capsules

DESCRIPTION

Name: AGRYLIN® (anagrelide hydrochloride)

Dosage Form: 0.5 mg and 1 mg capsules for oral administration

Active Ingredient: AGRYLIN® Capsules contain either 0.5 mg or 1 mg of anagrelide base (as anagrelide hydrochloride).

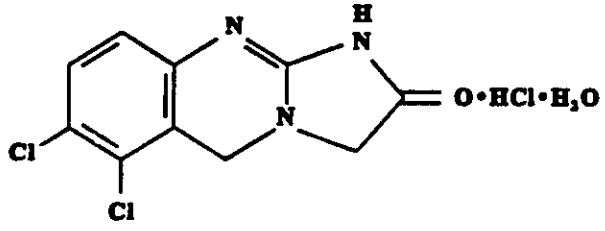
Inactive Ingredients: Povidone USP, Anhydrous Lactose NF, Lactose Monohydrate NF, Microcrystalline Cellulose NF, Crospovidone NF, Magnesium Stearate NF.

Pharmacological Classification: Platelet-reducing agent.

Chemical Name: 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one monohydrochloride monohydrate.

Molecular formula: $C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$
Molecular weight: 310.55

Structural formula:



Appearance: Off-white powder.

Solubility:
Water.....Very slightly soluble
Dimethyl Sulfoxide.....Sparingly soluble
Dimethylformamide.....Sparingly soluble

CLINICAL PHARMACOLOGY

The mechanism by which anagrelide reduces blood platelet count is still under investigation. Studies in patients support a hypothesis of dose-related reduction in platelet production resulting from a decrease in megakaryocyte hypermaturation. In blood withdrawn from normal volunteers treated with anagrelide, a disruption was found in the postmitotic phase of megakaryocyte development and a reduction in megakaryocyte size and ploidy. At therapeutic doses, anagrelide does not produce significant changes in white cell counts or coagulation parameters, and may have a small, but clinically insignificant effect on red cell parameters. Platelet aggregation is inhibited in people at doses higher than those required to reduce platelet count. Anagrelide inhibits cyclic AMP phosphodiesterase, as well as ADP- and collagen-induced platelet aggregation.

Following oral administration of ^{14}C-anagrelide in people, more than 70% of radioactivity was recovered in urine. Based on limited data, there appears to be a trend toward dose linearity between doses of 0.5 mg and 2.0 mg. At fasting and at a dose of 0.5 mg of anagrelide, the plasma half-life is 1.3 hours. The available plasma concentration time data at steady state in patients showed that anagrelide does not accumulate in plasma after repeated administration. The drug is extensively metabolized; less than 1% is recovered in the urine as anagrelide.

When a 0.5 mg dose of anagrelide was taken after food, its bioavailability (based on AUC values) was modestly reduced by an average of 13.8% and its plasma half-life slightly increased (to 1.8 hours), when compared with drug administered to the same subjects in the fasted state. The peak plasma level was lowered by an average of 45% and delayed by 2 hours.

CLINICAL STUDIES

A total of 942 patients with myeloproliferative disorders including 551 patients with Essential Thrombocythemia (ET), 117 patients with Polycythemia Vera (PV), 178 patients with Chronic Myelogenous Leukemia (CML), and 96 patients with other myeloproliferative disorders (OMPD), were treated with anagrelide in three clinical trials. Patients with OMPD included 87 patients who had Myeloid Metaplasia with Myelofibrosis (MMM), and 9 patients who had unknown myeloproliferative disorders.

Clinical Studies

Patients with ET, PV, CML, or MMM were diagnosed based on the following criteria:

ET

- Platelet count ≥900,000/μL on two determinations
- Profound megakaryocytic hyperplasia in bone marrow
- Absence of Philadelphia chromosome
- Normal red cell mass
- Normal serum iron and ferritin and normal marrow iron stores.

CML

- Persistent granulocyte count ≥ 50,000/μL without evidence of infection
- Absolute basophil count ≥ 100/μL
- Evidence for hyperplasia of the granulocytic line in the bone marrow
- Philadelphia chromosome present
- Leucocyte alkaline phosphatase ≤ lower limit of the laboratory normal range

PV†

- A1 Increased red cell mass
- A2 Normal arterial oxygen saturation
- A3 Splenomegaly
- B1 Platelet count ≥ 400,000/μL, in absence of iron deficiency or bleeding
- B2 Leucocytosis (≥ 12,000/μL, in the absence of infection)
- B3 Elevated leucocyte alkaline phosphatase
- B4 Elevated serum B_{12}

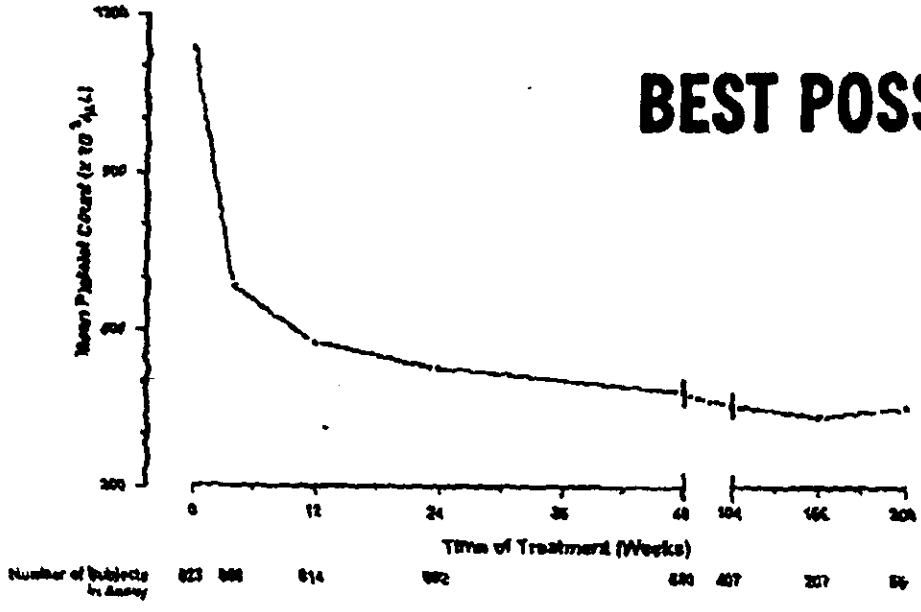
† Diagnosis positive if A1, A2, and A3 present; or, if no splenomegaly, diagnosis is positive if A1 and A2 are present with any two of B1, B2, or B3.

MMM

- Myelofibrotic (hypocellular, fibrotic) bone marrow
- Prominent megakaryocytic metaplasia in bone marrow
- Splenomegaly
- Moderate to severe normochromic normocytic anemia
- White cell count may be variable; (80,000-100,000 per/μL)
- Increased platelet count
- Variable red cell mass: teardrop poikilocytes
- Normal to high leucocyte alkaline phosphatase
- Absence of Philadelphia chromosome

Patients were enrolled in clinical trials if their platelet count was ≥ 900,000/μL on two occasions or ≥ 650,000/μL on two occasions with documentation of symptoms associate with thrombocythemia. The mean duration of anagrelide therapy for ET, PV, CML, and OMPD patients was 65, 67, 40, and 44 weeks, respectively; 23% of patients received treatment for 2 years. Patients were treated with anagrelide starting at doses of 0.5-2.0 mg every 6 hours. The dose was increased if the platelet count was still high, but to no more than 12 mg each day. Efficacy was defined as reduction of platelet count to or near physiologic levels (150,000-400,000/μL). The criteria for defining subjects as "responders" were reduction in platelets for at least 4 weeks to ≤600,000/μL, or by at least 50% from baseline value. Subjects treated for less than 4 weeks were not considered evaluable. The results are depicted graphically below:

Patients with Thrombocytosis Secondary to Myeloproliferative Disorders: Mean Platelet Count During Anagrelide Therapy



		Time on Treatment						
		Weeks				Years		
	Baseline	4	12	24	48	2	3	4
Mean*	1131	683	575	526	484	460	437	457
N	923†	868	814	662	530	407	207	55

*x $10^3/\mu L$

† Nine hundred and forty-two subjects with myeloproliferative disorders were enrolled in three research studies. Of these, 923 had platelet counts over the duration of the studies.

Agrylin was effective in phlebotomized patients as well as in patients treated with other concomitant therapies including hydroxyurea, aspirin, interferon, radioactive phosphorus, and alkylating agents.

INDICATIONS AND USAGE

AGRYLIN® Capsules are indicated for the treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events (see CLINICAL STUDIES, DOSAGE and ADMINISTRATION).

WARNINGS

Cardiovascular

Anagrelide should be used with caution in patients with known or suspected heart disease. and only if the potential benefits of therapy outweigh the potential risks. Because of the positive inotropic effects and side-effects of anagrelide, a pre-treatment cardiovascular examination is recommended along with careful monitoring during treatment. In humans, therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations. and congestive heart failure.

Renal

It is recommended that patients with renal insufficiency (creatinine ≥ 2 mg/dL) receive anagrelide when, in the physician's judgment, the potential benefits of therapy outweigh the potential risks. These patients should be monitored closely for signs of renal toxicity while receiving anagrelide (see ADVERSE REACTIONS, Urogenital System).

Hepatic

It is recommended that patients with evidence of hepatic dysfunction (bilirubin, SGOT, or measures of liver function >1.5 times the upper limit of normal) receive anagrelide when, in the physician's judgment, the potential benefits of therapy outweigh the potential risks. These patients should be monitored closely for signs of hepatic toxicity while receiving anagrelide (see ADVERSE REACTIONS, Hepatic System).

PRECAUTIONS

Laboratory Tests: Anagrelide therapy requires close clinical supervision of the patient. While the platelet count is being lowered (usually during the first two weeks of treatment), blood counts (hemoglobin, white blood cells), liver function (SGOT, SGPT) and renal function (serum creatinine, BUN) should be monitored.

In 9 subjects receiving a single 5 mg dose of anagrelide, standing blood pressure fell an average of 22/15 mm Hg, usually accompanied by dizziness. Only minimal changes in blood pressure were observed following a dose of 2 mg.

Cessation of AGRYLIN® Treatment: In general, interruption of anagrelide treatment is followed by an increase in platelet count. After sudden stoppage of anagrelide therapy, the increase in platelet count can be observed within four days.

Drug Interactions: Bioavailability studies evaluating possible interactions between anagrelide and other drugs have not been conducted. The most common medications used concomitantly with anagrelide have been aspirin, acetaminophen, furosemide, iron, ranitidine, hydroxyurea, and allopurinol. The most frequently used concomitant cardiac medication has been digoxin. Although drug-to-drug interaction studies have not been conducted, there is no clinical evidence to suggest that anagrelide interacts with any of these compounds.

There is a single case report which suggests that sucralfate may interfere with anagrelide absorption.

Food has no clinically significant effect on the bioavailability of anagrelide.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been

performed to evaluate carcinogenic potential of anagrelide hydrochloride. Anagrelide hydrochloride was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, $TK^{-/-}$) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Anagrelide hydrochloride at oral doses up to 240 mg/kg/day (1,440 mg/m^2/day, 195 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male rats. However, in female rats, at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher, it disrupted implantation when administered in early pregnancy and retarded or blocked parturition when administered in late pregnancy.

Pregnancy: Pregnancy Category C.

(i) Teratogenic Effects

Teratology studies have been performed in pregnant rats at oral doses up to 900 mg/kg/day (5,400 mg/m^2/day, 730 times the recommended maximum human dose based on body surface area) and in pregnant rabbits at oral doses up to 20 mg/kg/day (240 mg/m^2/day, 32 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to anagrelide hydrochloride.

(ii) Nonteratogenic Effects

A fertility and reproductive performance study performed in female rats revealed that anagrelide hydrochloride at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher disrupted implantation and exerted adverse effect on embryo/fetal survival.

A perinatal and postnatal study performed in female rats revealed that anagrelide hydrochloride at oral doses of 60 mg/kg/day (360 mg/m^2/day, 49 times the recommended maximum human dose based on body surface area) or higher produced delay or blockage of parturition, deaths of nondelivering pregnant dams and their fully developed fetuses, and increased mortality in the pups born.

Five women became pregnant while on anagrelide treatment at doses of 1 to 4 mg/day. Treatment was stopped as soon as it was realized that they were pregnant. All delivered normal, healthy babies. There are no adequate and well-controlled studies in pregnant women. Anagrelide hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Anagrelide is not recommended in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of child-bearing potential should be instructed that they must not be pregnant and that they should use contraception while taking anagrelide. Anagrelide may cause fetal harm when administered to a pregnant woman.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reaction in nursing infants from anagrelide hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of anagrelide in patients under the age of 16 years have not been established. Myeloproliferative disorders are uncommon in pediatric patients. Anagrelide has been used

successfully in 12 pediatric patients (age range 6.8 to 17.4 years; 6 male and 6 female), including 8 patients with ET, 2 patients with CML, 1 patient with PV, and 1 patient with OMPD. Patients were started on therapy with 0.5 mg qid to a maximum daily dose of 10 mg. The median duration of treatment was 18.1 months with a range of 3.1 to 92 months. Three patients received treatment for greater than three years.

ADVERSE REACTIONS

Analysis of the adverse events in a population consisting of 942 patients diagnosed with myeloproliferative diseases of varying etiology (ET: 551; PV: 117; OMPD: 274) has shown that all disease groups have the same adverse event profile. While most reported adverse events during anagrelide therapy have been mild in intensity and have decreased in frequency with continued therapy, serious adverse events were reported in these patients. These include the following: congestive heart failure, myocardial infarction, cardiomyopathy, cardiomegaly, complete heart block, atrial fibrillation, cerebrovascular accident, pericarditis, pulmonary infiltrates, pulmonary fibrosis, pulmonary hypertension, pancreatitis, gastric/duodenal ulceration, and seizure.

Of the 942 patients treated with anagrelide for a mean duration of approximately 65 weeks, 161 (17%) were discontinued from the study because of adverse events or abnormal laboratory test results. The most common adverse events for treatment discontinuation were headache, diarrhea, edema, palpitation, and abdominal pain. Overall, the occurrence rate of all adverse events was 17.9 per 1,000 treatment days. The occurrence rate of adverse events increased at higher dosages of anagrelide.

The most frequently reported adverse reactions to anagrelide (in 5% or greater of 942 patients with myeloproliferative disease) in clinical trials were:

Headache	43.5%
Palpitations	26.1%
Diarrhea	25.7%
Asthenia	23.1%
Edema, other	20.6%
Nausea	17.1%
Abdominal Pain	16.4%
Dizziness	15.4%
Pain, other	15.0%
Dyspnea	11.9%
Flatulence	10.2%
Vomiting	9.7%
Fever	8.9%
Peripheral Edema	8.5%
Rash, including urticaria	8.3%
Chest Pain	7.8%
Anorexia	7.7%
Tachycardia	7.5%
Pharyngitis	6.8%
Malaise	6.4%
Cough	6.3%
Paresthesia	5.9%
Back Pain	5.9%
Pruritus	5.5%
Dyspepsia	5.2%

Adverse events with an incidence of 1% to < 5% included:

Body as a Whole System: Flu symptoms, chills, photosensitivity.

Cardiovascular System: Arrhythmia, hemorrhage. cardiovascular disease, angina pectoris, heart failure, postural hypotension, thrombosis, vasodilatation, migraine, syncope.

Digestive System: Constipation, GI distress, GI hemorrhage, gastritis, melena, aphthous stomatitis, eructation.

Hemic & Lymphatic System: Anemia, thrombocytopenia, ecchymosis, lymphadenopathy.
Platelet counts below 100,000/μL occurred in 84 patients (ET: 35; PV: 9; OMPD: 40), reduction below 50,000/μL occurred in 44 patients (ET: 7; PV: 6; OMPD: 31) while on anagrelide therapy. Thrombocytopenia promptly recovered upon discontinuation of anagrelide.

Hepatic System: Elevated liver enzymes were observed in 3 patients (ET: 2; OMPD: 1) during anagrelide therapy.

Musculoskeletal System: Arthralgia, myalgia, leg cramps.

Nervous System: Depression, somnolence, confusion, insomnia, hypertension, nervousness, amnesia.

Nutritional Disorders: Dehydration.

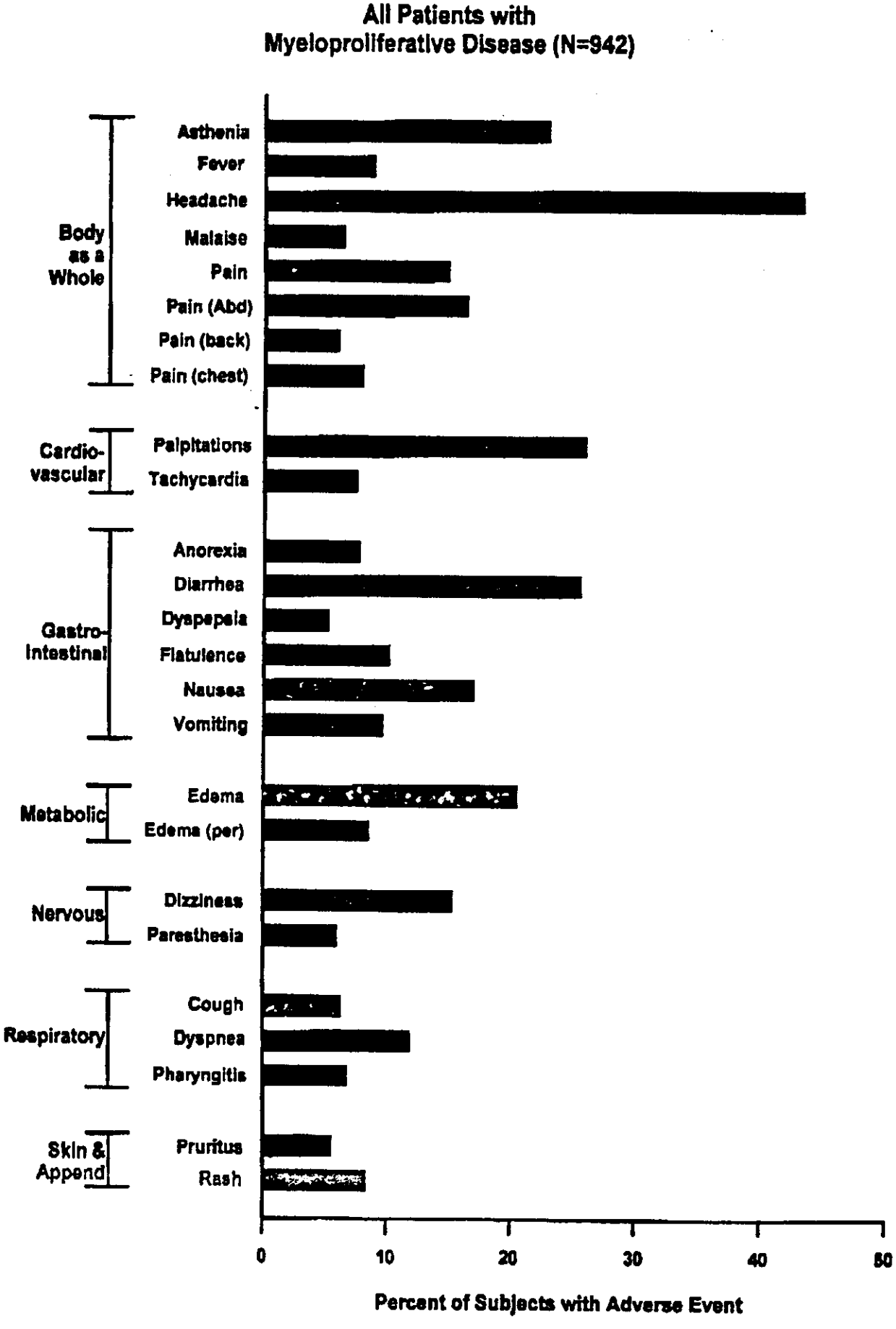
Respiratory System: Rhinitis, epistaxis, respiratory disease, sinusitis, pneumonia, bronchitis, asthma.

Skin and Appendages System: Skin disease, alopecia.

Special Senses: Amblyopia, abnormal vision, tinnitus, visual field abnormality, diplopia.

Urogenital System: Dysuria, Hematuria.
Renal abnormalities occurred in 15 patients (ET: 10; PV: 4; OMPD: 1). Six ET, 4 PV and 1 with OMPD experienced renal failure (approximately 1%) while on anagrelide treatment; in 4 cases, the renal failure was considered to be possibly related to anagrelide treatment. The remaining 11 were found to have pre-existing renal impairment. Doses ranged from 1.5-6.0 mg/day, with exposure periods of 2 to 12 months. No dose adjustment was required because of renal insufficiency.

The adverse event profile for patients in clinical trials on anagrelide therapy (in 5% or greater of 942 patients with myeloproliferative diseases) is shown in the following bar graph:


All Patients with
Myeloproliferative Disease (N=942)
Body as a Whole
Asthenia
Fever
Headache
Malaise
Pain
Pain (Abd)
Pain (back)
Pain (chest)
Cardio-vascular
Palpitations
Tachycardia
Gastro-Intestinal
Anorexia
Diarrhea
Dyspepsia
Flatulence
Nausea
Vomiting
Metabolic
Edema
Edema (per)
Nervous
Dizziness
Paresthesia
Respiratory
Cough
Dyspnea
Pharyngitis
Skin & Append
Pruritus
Rash
0
10
20
30
40
50
Percent of Subjects with Adverse Event

OVERDOSAGE

Acute Toxicity and Symptoms

Single oral doses of anagrelide hydrochloride at 2,500, 1,500 and 200 mg/kg in mice, rats and monkeys, respectively, were not lethal. Symptoms of acute toxicity were: decreased motor activity in mice and rats and softened stools and decreased appetite in monkeys.

There are no reports of overdosage with anagrelide hydrochloride. Platelet reduction from anagrelide therapy is dose-related; therefore, thrombocytopenia, which can potentially cause bleeding, is expected from overdosage. Should overdosage occur, cardiac and central nervous system toxicity can also be expected.

Management and Treatment

In case of overdosage, close clinical supervision of the patient is required; this especially includes monitoring of the platelet count for thrombocytopenia. Dosage should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

DOSAGE AND ADMINISTRATION

Treatment with **AGRYLIN®** Capsules should be initiated under close medical supervision. The recommended starting dosage of **AGRYLIN®** is 0.5 mg qid or 1 mg bid, which should be maintained for at least one week. Dosage should then be adjusted to the lowest effective dosage required to reduce and maintain platelet count below 600,000/μL, and ideally to the normal range. The dosage should be increased by not more than 0.5 mg/day in any one week. Dosage should not exceed 10 mg/day or 2.5 mg in a single dose (see PRECAUTIONS). The decision to treat asymptomatic young adults with thrombocythemia secondary to myeloproliferative disorders should be individualized.

To monitor the effect of anagrelide and prevent the occurrence of thrombocytopenia, platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until the maintenance dosage is reached.

Typically, platelet count begins to respond within 7 to 14 days at the proper dosage. The time to complete response, defined as platelet count $\leq$ 600,000/μL, ranged from 4 to 12 weeks. Most patients will experience an adequate response at a dose of 1.5 to 3.0 mg/day. Patients with known or suspected heart disease, renal insufficiency, or hepatic dysfunction should be monitored closely.

HOW SUPPLIED

AGRYLIN® is available as:

0.5 mg, opaque, white capsules imprinted "ROBERTS 063" in black ink: NDC 54092-063-01 = bottle of 100.

1 mg, opaque, gray capsules imprinted "ROBERTS 064" in black ink: NDC 54092-064-01 = bottle of 100.

Store from 15° to 25°C (59° to 77°F), in a light-resistant container.

Rx only

Manufactured for Roberts Laboratories Inc.
a subsidiary of
ROBERTS PHARMACEUTICAL CORP.
Eatontown, NJ 07724-2274, USA
by MALLINCKRODT INC.
Hobart, NY 13788

12/97 063 0117 002
Printed in USA

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-333/SE1-002

Name of Drug: Agrylin® (anagrelide hydrochloride) Capsules

Sponsor: Roberts Laboratories Inc.

DEC 16 1998

Material Reviewed

Submission Date(s): December 30, 1997

Receipt Date(s): January 2, 1998

Background and Summary Description: This supplemental application contains two proposed package inserts. One package insert states the indication as follows: [redacted] A second package insert states the indication as follows: "... treatment of patients with thrombocytosis, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms...." Based on conclusions of the December 11, 1998, Medical Officer review, the latter package insert was compared to the currently approved labeling.

Review

The submitted package insert identified as "0630117002, 12/97" was compared to the package insert approved March 14, 1997, identified as [redacted] The package inserts are identical except for the following:

A. The CLINICAL STUDIES section has many revisions. See Attachment 1A for the currently approved CLINICAL STUDIES section and Attachment 1B for the firm's proposed CLINICAL STUDIES section.

See Attachment 1C for revisions to the proposed CLINICAL STUDIES section made by the Medical Officer, Dr. Lilia Talarico, in the November 24, 1998, and December 11, 1998, team meetings and agreed to in the November 24, 1998, and December 11, 1998, teleconferences with the firm. See Attachment 3 for faxes by the firm regarding confirmation of these changes.

B. In the INDICATION AND USAGE section:

1. The following words have been changed from: [redacted] to: "[redacted] secondary to myeloproliferative disorders, ..."

This change reviewed by the MEDICAL OFFICER, Dr. Lilia Talarico, should be further revised as follows: "...thrombocythemia, secondary to myeloproliferative disorders, ... including thrombo-hemorrhagic events (see CLINICAL STUDIES, DOSAGE and ADMINISTRATION)." See Attachment 3 for faxes by the firm regarding confirmation of this change.

2. The firm proposes the addition of the following two sentences at the end of this section (see Attachment 3, fax dated November 30, 1998):

This addition reviewed by the Medical Officer, Dr. Lilia Talarico, should be revised as follows and moved to the end of the clinical studies section: "Agrylin was effective in phlebotomized patients as well as in patients treated with other concomitant therapies including hydroxyurea, aspirin, interferon, radioactive phosphorus, and alkylating agents." The firm agreed with this revision in the December 11, 1998, teleconference.

C. In the PRECAUTIONS section:

In the Pediatric Use subsection: The following paragraph should be changed from:

to: "The safety and efficacy of anagrelide in patients under the age of 16 years have not been established. Myeloproliferative disorders are uncommon in pediatric patients. Anagrelide has been used successfully in 12 pediatric patients (age range 6.8 to 17.4 years; 6 male and 6 female), including 8 patients with ET, 2 patients with CML, 1 patient with PV, and 1 patient with OMPD. Patients were started on therapy with 0.5 mg qid to a maximum daily dose of 10 mg. The median duration of treatment was 18.1 months with a range of 3.1 to 92 months. Three patients received treatment for greater than three years." (See December 11, 1998, Medical Officer review).

D. The ADVERSE REACTIONS section has many revisions. See Attachment 2A for the currently approved ADVERSE REACTIONS section and Attachment 2B for the firm's proposed ADVERSE REACTIONS section.

See Attachment 2C for revisions to the proposed ADVERSE REACTIONS section made by the Medical Officer, Dr. Lilia Talarico, in the November 24, 1998, team meeting and agreed to in the November 24, 1998, teleconference with the firm. See

Attachment 3 for faxes by the firm regarding confirmation of these changes.

E. In the DOSAGE AND ADMINISTRATION section:

1. The last sentence in the first paragraph has been changed from:

This revision reviewed by the Medical Officer, Dr. Lilia Talarico, should be further revised as follows: "The decision to treat asymptomatic young adults with thrombocythemia secondary to myeloproliferative disorders should be individualized."

2. **In the December 11, 1998, team meeting, Dr. Lilia Talarico requested that the following sentence be inserted between the first and second sentences in the last paragraph of this section: "The time to complete response, defined as platelet count ≤ 600,000/μL, ranged from 4 to 12 weeks." This addition was agreed to in the December 11, 1998, teleconference with the firm. See Attachment 3 for faxes by the firm regarding confirmation of this addition.**

F. In the HOW SUPPLIED section:

The manufactured by statement has been changed from: to: "MALLINCKRODT INC."

This revision is ACCEPTABLE because it is a name change only. According to the firm, facilities, personnel, manufacturing procedures, and controls remain the same. (See Y-001, submitted 4/24/98, received 4/30/98, page 42).

G. Additional Comments:

1. **The following statement located at the end of the package insert should be changed from: to: "Rx only" as required under Section 126 of the Food and Drug Administration Modernization Act of 1997.**

2. The identification number and revision date at the end of the package insert have been changed from: to: "0630117002, 12/97."

These revisions are editorial and are ACCEPTABLE.

3. **According to the Medical Officer, Dr. Lilia Talarico, the word [redacted] should be replaced with the word "thrombocythemia" throughout the package insert. The firm agreed with this change in the November 24, 1998, teleconference.**

4. **Units after platelet count, white blood cell count, etc. should be revised from: [redacted] to: "μL" throughout the package insert to maintain consistency. The firm agreed in the December 11, 1998, teleconference.**

5. **Agrylin is now a registered trademark. Therefore, the superscript after Agrylin should be changed from: "™" to: "®" throughout the package insert. See Attachment 3 for faxes by the firm regarding confirmation of this change.**

Conclusions

1. This supplement should be approved on draft labeling with changes as discussed in A, B1, B2, C, D, E1, E2, G1, G3, G4, and G5 above.

2. On December 16, 1998, the firm was faxed a copy of the draft labeling to be placed behind the action letter (incorporating all labeling changes as discussed above), and concurred with all changes. See Attachment 3 for December 16, 1998, fax from the firm regarding concurrence.

/S/ 12/16/98
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Concur /S/ 12/16/98

Attachments: 1A, 1B, 1C, 2A, 2B, 2C, & 3
cc:
Original NDA 20-333/S-002
HFD-180/Div. Files
HFD-180/DuBeau
HFD-180/Talarico
HF-2/S.Goldman (MEDWATCH)
r/d Init: Talarico 12/15/98
JD/November 24, 1998 (drafted)

APPEARS THIS WAY
ON ORIGINAL

CSO REVIEW

Attachments

13 **Page(s) Redacted**

Draft

Labeling

Appendix

18 **Page(s) Redacted**

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

NDA:	20-333
Drug:	Agrylin (AnagrelideHydrochloride)
Sponsor:	Roberts Pharmaceuticals Corporation
Submission:	Efficacy Supplement (SE1)
Indications:	Treatment of thrombocythemia in Polycythemia Vera (PV)
Date of Submission:	January 2, 1998
Medical Reviewer:	Lilia Talarico, M.D.
Date of Review:	November 2, 1998

DEC 1 1 1998

1.0 INTRODUCTION

Polycythemia Vera (PV) is a chronic, slowly progressing myeloproliferative disorder (MPD) characterized by hyperplasia of all hemopoietic elements and increased circulating RBC mass. During the course of the disease, at least 50% of patients develop thrombocythemia as part of the myeloproliferative condition. Patients with PV are at increased risk for both thrombotic and hemorrhagic life-threatening events and a possibly shortened life expectancy (median survival 13.9 years in patients treated by phlebotomy). The risk of thrombosis is related to the increased blood viscosity due to the elevated RBC mass and to the high platelet counts, the hemorrhagic events are related to the high viscosity and to the functional platelet defect associated with MPDs..

Bleeding usually consists of superficial cutaneous or mucosal hemorrhage, such as epistaxis and GI bleeding. Thrombotic complications include deep vein thrombosis, pulmonary embolism, ischemic neurological events and erythromelalgia, a characteristic ischemic complication of MPD. Hepatic vein thrombosis is seen most frequently in PV patients. The treatment for PV aims at reducing morbidity and preventing life-threatening events by reducing the hematocrit to < 45% for males and < 42% for females and the platelet counts to < 500,000/uL. Phlebotomy is routinely performed for hematocrit > 50%. Phlebotomy reduces the blood viscosity promptly and, eventually causes iron deficiency which reduces erythropoiesis. However, the reduction in RBC mass and the iron deficiency secondary to phlebotomy can further increase platelet production. In fact, in the management of PV, maintenance therapy with a myelosuppressive drug is frequently needed to reduce all blood cell lines, especially to lower the high platelet count. Myelosuppressive therapy reduces the risk of thrombotic and hemorrhagic life-threatening events. Thrombotic events are reduced from 33% to 10%. Currently available myelosuppressive therapies included hydroxyurea, radiophosphorus, interferon alpha, and alkilating agents (busulphan and chlorambucil).

PV can evolve into acute myelogenous leukemia (AML) in about 2% of patients or to myelofibrosis with myeloid metaplasia (MMM) in about 10% of patients when treated with phlebotomy alone. The use of myelosupressive agents has not decreased the PV baseline risk of transformation into AML or MMM, in fact, leukemic transformation has been reported to occur in 11% of patients receiving chlorabucil, 8% radiophosphorus, and 6% hydroxyurea. Thrombocytopenia can occur during induction and early maintenance therapy with hydroxyurea and platelet counts is ultimately maintained at < 400,000/,uL in only 55% of patients on long-term maintenance therapy.

A recent review of long-term therapy with Hydroxyurea in 292 patients with Polycythemia Vera (Najean Y., Rain J-D. Blood 1997; 90:3370-3377), reported a 10% risk of leukemia, 25% risk of thromboembolic events at 13 years and 44% at 16 years. Only 50% of patients who experienced a thromboembolic event had a platelet count in the normal range. Myelofibrosis started at 2 years of therapy, increasing to 17% incidence by 10 years and to 40% incidence by 16 years. Of the patients who developed myelofibrosis, 78% had a permanently high platelet count (> 400,000/juL); only 38% of patients who did not develop myelofibrosis had a permanent platelet count > 400,000/gL.

The availability of a therapy that is effective in lowering the platelet, specific and devoid of leukemic transformation potential would be of significant benefit for patients with MPDs.

Anagrelide hydrochloride (Agrelyn) is a quinazolin derivative developed initially by [redacted] as a platelet aggregation inhibitor. In Phase 1 pharmacology studies, the compound was found to induce thrombocytopenia in humans at the dose required to inhibit platelet aggregation. Anagrelide had specific suppressive effect on platelet production with little or no effect on other hemopoietic cell lines. Anagrelide disrupts the post-mitotic phase of megakaryocyte size and ploidy in humans. Following the observation that the effect of the drug was reversible upon discontinuation, anagrelide was developed as a platelet-reducing agent for the treatment of the thrombocythemia associated with myeloproliferative disorders, including Essential Thrombocythemia (ET), Polycythemia Vera (PV), Chronic Myelogenous Leukemia (CML), Myelofibrosis and Myeloid Metaplasia and Other Myeloproliferative Disorders(OMPD).

On January 1, 1996, the sponsor submitted NDA 20-333 for the approval of Anagrelide as a platelet reducing agent in patients with Essential Thrombocythemia (ET). Three clinical trials (Studies 700-012, 700-014, 700-999) were performed in patients with thrombocythemia of myeloproliferative disorders (ET, PV, CML, OMPD) treated with Anagrelide. The NDA, however, addressed exclusively the data from the ET patient population. The data showed that Anagrelide was safe and effective in reducing the platelet counts and the clinical manifestations of thrombocythemia in patients with ET. Anagrelide was approved for the treatment of ET on March 14, 1997.

On January 2, 1998, the sponsor submitted an efficacy supplement (S-002) to request approval of anagrelide as platelet reducing agent for patients with Polycythemia Vera (PV). Additionally, the sponsor requested that the indication of Anagrelide be expanded to all MPDs requiring reduction of platelets. The NDA 20-333/S-002 addresses in details the efficacy and safety results for the PV patient populations. The results of anagrelide therapy in CML and OMPDs are also provided in this supplement. All the data submitted in NDA 20-333/S-002 were generated from the same three clinical trials that were analyzed in the initial NDA 20-333 only for the patients population with Essential thrombocythemia.

2.0 ANAGRELIDE IN THE TREATMENT OF POLYCYTHEMIA VERA

Two pivotal studies of Anagrelide (Study 700-012 and Study 700-014) and a compassionate-use study (Study 700-999) were conducted in patients with thrombocythemia due to ET, PV, CML, or OMPD. The results of the efficacy and safety of anagrelide in the treatment of Essential Thrombocythemia were reported in NDA 20-333. This review will summarize the efficacy and safety data from subjects with PV and will address the efficacy of anagrelide for all patients with MPDs .

In the clinical studies, the mean platelet count prior to anagrelide therapy was greater than 900,000/uL. In the efficacy analyses, a subject was considered as having achieved a response if the platelet count decreased to < 600,000/uL or was reduced by > 50% from baseline for at least four weeks. The results indicate that anagrelide effectively reduce the platelet count to near or within physiologic range and maintain it without any apparent development of tolerance.

The effect of anagrelide on the hemorrhagic and thromboembolic complications associated with thrombocythemia was also assessed in a subset of patients enrolled in Studies 700-014 and 700-999.

3.0 CLINICAL TRIALS

3.1 Pivotal Studies (Study 700-012 and 700-014)

Studies 700-012 and 700-014 were open-label self-controlled studies to demonstrate the efficacy of anagrelide in reducing the thrombocythemia in patients diagnosed with polycythemia vera (PV), and in maintaining their platelet counts close to or within the normal physiological range.

Study 700-012 was an open-label, self-controlled study of 44 patients with MPDs, including 8 patients with PV, treated with Anagrelide. The objectives of the study were to determine the dose of anagrelide required to decrease the platelet count in thrombocythemic subjects to within or close to the normal range and, secondly, to determine what dose of anagrelide was required to maintain the platelet reduction.
Four PV subjects received anagrelide treatment for four years. Subjects still active in study 700-012 at its termination (N = 4) were transferred to the open study being performed under Protocol 301A.

Study 700-014, similar in design to Study 700-012, enrolled a total of 498 subjects, including 71 patients with the diagnosis of PV. The objective of this study was to determine the number of subjects who had a decrease in their baseline platelet count of 50% or a reduction in their platelet count to < 600,000/uL (defined as responders). Four PV subjects received anagrelide treatment for four years. Subjects still active in study 700-014 at its termination (N = 42) were transferred to the open study being performed under Protocol 301A.

3.2. Non-Pivotal Study (Study 700-999

Study 700-999 was a compassionate-use study that allowed subjects with thrombocythemia to receive treatment with anagrelide under an individual IND. Data were collected in case report forms for all subjects who enrolled in the study, however, in the absence of a detailed protocol for this study, data were not collected in a consistent fashion and strict monitoring and auditing procedures were not followed. Of the 455 subjects enrolled in the study, 38 had a diagnosis of PV. Two PV subjects had 4 years of anagrelide treatment. Subjects still active in the study at its termination (N = 13) were transferred to the study being performed under Protocol 301 A.

The efficacy data from each study were analyzed in the same manner. To be evaluable for efficacy, subjects had to have been treated for a minimum of 4 weeks.

In March 1992, study 301A ("An Open Protocol for the Use of Anagrelide for Subjects with Thrombocythemia") was initiated to include all active subjects from the three studies. The intent of study 301A was to continue to provide anagrelide to subjects with thrombocythemia.

3.3. Efficacy Parameters

The following parameters were used to measure efficacy:

Primary Efficacy Parameters:

-Response rate: the percentage of subjects who were classified as complete responders and partial responders
-Complete Response: a decrease in platelet count to <=600,000/uL or to >= 50% of the baseline value and maintenance of the reduction for at least 4 weeks
-Partial Response: a reduction in platelet count of 20% to 50% from baseline and maintenance of the reduction for at least 4 weeks.

Secondary Efficacy Parameters:

-Time to Complete Response: The time from the first day of 4 weeks of continuous anagrelide treatment to the first day of a complete response
-Reduction in Platelet Count: Platelet counts were recorded at baseline and compared to platelet counts at 4, 12, 24 and 48 weeks, and at 2, 3 and 4 years
-Symptoms Associated with Thrombocythemia:

The effect of anagrelide treatment on the incidence of specific symptoms associated with thrombocythemia was analyzed in a subpopulation of patients who had at least 1 year of treatment.

3.4. Study Population

From a total of 123 study patients with PV, 117 (8 from Study 700-012; 71 from Study 700-014, and 38 from Study 700-999) received at least one dose of anagrelide and comprised the intent-to-treat population (ITT). Ninety-nine (99) PV patients had at least 4 weeks of uninterrupted anagrelide therapy and represented the Efficacy Analysis (EA) population.

The contribution of patients from each study is shown in the following table (Table 3.1, vol.2, .34)

Contribution of Patients from Each Study

	Study Number			All
	700-012	700-014	700-999	Subjects
Subjects				
Total Subjects Enrolled	44	498	455	997
No. of subjects with Dx of PV	8	71	38	117
No. of PV Subjects with at least One Dose of Anagrelide (ITT)	8	71	38	117
No. of PV Subjects Evaluable for Efficacy Analysis (EA)*	7	65	27	99

*Subjects with at least 4 weeks of uninterrupted treatment.

3.5. Patients Demographics

The mean age of the patients with PV was 61 years; 62% were females, and 96% were white.

3.6. Prior Medications

A total of 103 patients had received prior therapy for thrombocythemia, 10 patients had had no prior therapy, and prior therapy was not known for 4 patients. Hydroxyurea and ASA were the most common medications used for the thrombocythemia. A list of the most frequently used prior medications for thrombocythemia (taken by >5% of PV patients) is shown below (Table 3.6.1, vol.2, p.37)

Most frequently (>5%) used prior therapy for Thrombocythemia

Medication	Number (%) of Subjects N=117
Hydroxyurea	84 (72%)
Aspirin	35 (30%)
Radioactive Phosphorus (32P)	23 (21%)
Busulfan	20 (17%)
Dipyridamole	12 (10%)
Interferon alpha	11 (9%)
Melphalan	7 (6%)
Chlorambucil	6 (5%)

3.7 Concomitant Medications

The most frequently used concomitant medications were aspirin, acetominophen and hydroxyurea, taken by 32%, 28%, and 26% of patients respectively. A list of concomitant medications are shown below (Appendix 3.6.2, vol.2, p.70). Patients may h ave taken more than one of these medications concurrently.

4.0 STATISTICAL METHODS

Most analyses were related to time period: baseline (the first day administering of Anagrelide). 4 weeks, 12 weeks, 24 weeks, 48 weeks, 2 years (104 weeks), 3 years (156 weeks), 4 years (208 weeks), and more than 4 years after the first day administering of Anagrelide, respectively.

The primary efficacy endpoint was the last platelet count in each time period.
The secondary efficacy endpoints were
(1) the average platelet count in each time period;
(2) days to beginning of response;
(3) response rate.

Response status was defined as:
(1) complete response: subject with platelet count >600,000/uL at baseline, platelet count reduced to <=600,000/uL or reduced by >=50% from baseline value after 4 weeks of treatment, and maintenance of the reduction for at least 4 weeks;
(2) partial response: subject with platelet count >600,000/uL at baseline, no complete response after 4 weeks treatment, but 20-50% reduction in platelet count from baseline value was achieves and maintained for at least 4 weeks;
(3) no response: subject with platelet count >=600,000/uL at baseline, less than 20% reduction in platelet count from baseline value;
(4) not counting response: subjects treated for at least 4 weeks, but baseline platelet count was <600,000/uL;
(5) not available for response: days on treatment were less than 4 weeks. These subjects were excluded in efficacy population.

The significant level was set 0.05 for all statistical tests in the analyses.

Prior therapies were tested for difference among studies by Chi-Square test and Fisher's exact test. Occurrence rates of all symptoms were compared between the first month and each other month by Ratio test.

5.0 STUDY RESULTS

5.1 Data Sets

The primary efficacy analysis was performed on two subject populations:

i) Intent-to-Treat (ITT) Analysis Population: all 117 subjects, diagnosed with PV, who received at least one dose of anagrelide

ii) Efficacy Analysis (EA) Population: the 99 subjects, diagnosed with PV, who had at least 4 weeks of anagrelide treatment and met the protocol definition for being evaluable for efficacy.

Secondary efficacy analyses were performed on the data from the ITT population.

5.2 Subjects Disposition

The overall percentage of patients who withdrew from the studies was 35%. The most common reason for withdrawal was for adverse events. No patient discontinued for protocol violation. A summary of patient withdrawals is shown below (Table 3.3, vol.2, p.35)

Table 3.3: Patient Withdrawal

	Study No.			All
	700-012	700-014	700-999	Subjects*
Reason for Withdrawal	N=8	N=71	N=38	N=117
No. withdrawn (%)	4 (50)	19 (27)	18 (47)	41 (35)
Adverse Events	2	9	8	19
Death	-	1	4	5
Complications or Illness	1	2	1	4
Lack of Efficacy	-	1	2	3
Subjects Request	-	3	1	4
Leukemic Transformation	-	-	1	1
Noncompliance	-	-	-	-
Other	1	3	2	6

*Subjects may have withdrawn for more than one reason

5.3 Primary Efficacy Endpoint: Platelet Count Response

A total of 66% of the Evaluable population and 56% of the ITT population had a complete response to treatment with anagrelide. An additional 12% and 10%, respectively, achieved a partial response. The percentage of patients who experienced complete response was lower in the compassionate use study.

The incidence rates of PV patients who achieved complete or partial response are summarized in the following table which include both ITT and EA data. (table 4.1, vol.2, p.39)

Table 4.1: Patients with a Complete or Partial Count Response (ITT and EA populations)

Patients	Study No.			All
	700-012	700-014	700-999	Subjects*
ITT Population	N=8	N=71	N=38	N=117
Complete Responders: N(%)	6(75%)	45(63%)	14(37%)	65(56%)
95% CI	45.0, 100	52.2, 74.6	21.5, 52.2	46.6, 64.6
Partial Responders: N(%)	0(0%)	8(11%)	4(11%)	12(10%)
95% CI		3.9, 18.6	0.8, 20.3	4.8, 15.8
Efficacy Population	N=7	N=65	N=27	N=99
Complete Responders: N(%)	6(86%)	45(69%)	14(52%)	65(66%)
95% CI	59.8, 100	58.0, 80.5	33.0, 70.7	56.3, 75.0
Partial Responders: N(%)	0(0%)	8(12%)	4(15%)	12(12%)
95% CI		4.3, 20.3	1.4, 28.2	5.7, 18.6

Subgroup analyses of age, gender, race, and whether the patient had received prior therapy for thrombocythemia indicated that anagrelide was less effective in patients <=40 years who achieved complete remission at a rate of 29% compared to 74% for patients 41-60 years old and 65% for patients >=61 years. The non-responder rate was particularly high in patients aged <= 40 years with platelet counts >600.000/mm3 (57% non-responder rates compared to 8% and 19% for patients ages 41-60 years and >61 years, respectively). The data from the ITT analysis are summarized in the following table (Appendix 4.1A., vol.2, p.76).

Demographic Characteristics for PV Subjects, by platelet Response Status

VARIABLE		Response Status				Not Evaluable for Response (%) N = 18
		Complete (%) N = 65	Partial (%) N = 12	Nonresponder* (%) N_1* = 17	Nonresponder* (%) N_2* = 5	
Age	≤ 40	2/7 (29)	1/7 (14)	4/7 (57)	0/7 (0)	0/7 (0)
	41-60	28/46 (61)	5/46 (11)	3/46 (7)	2/46 (4)	8/46 (17)
	≥ 61	35/64 (55)	6/64 (9)	10/64 (16)	3/64 (5)	10/64 (16)
	Mean	61	61			
	Range	35 - 85	40 - 78			
Gender	Male	27/45 (60)	5/45 (11)	5/45 (11)	1/45 (2)	7/45 (16)
	Female	38/72 (53)	7/72 (10)	12/72 (17)	4/72 (6)	11/72 (15)
Race	White	62/112 (55)	12/112 (11)	16/112 (14)	5/112 (4)	17/112 (15)
	Black	0/1 (0)	0/1 (0)	1/1 (100)	0/1 (0)	0/1 (0)
	Other	3/3 (100)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)
	Unknown	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	1/1 (100)
Prior Therapy	Yes	60/103 (58)	12/103 (12)	13/103 (13)	4/103 (4)	14/103 (14)
	No	5/10 (50)	0/10 (0)	2/10 (20)	1/10 (10)	2/10 (20)
	Unknown	0/4 (0)	0/4 (0)	2/4 (50)	0/4 (0)	2/4 (50)

† The denominators represent the number of subjects in each subgroup who had at least one dose of anagrelide
*N_1 Patients with baseline platelet count ≥ 600,000/μL.
*N_2 Patients with baseline platelet count < 600,000/μL.

5.4 Secondary Efficacy Endpoints: Time to Platelet Count Response

Time to complete response was defined as the number of days from the start of 4 weeks of continuos therapy with anagrelide, to the first day of a 4-week period in which a platelet count of =< 600.000/mm3, or a decrease of >50% from baseline platelet count was maintained.

Time to partial response was defined as the number of days from the start of 4 weeks of continuous therapy with anagrelide, to the first day of a 4-week period in which a 20% to 50% reduction in platelet count from the baseline value was maintained.

The number of days to a platelet count response for PV patients treated with anagrelide is summarized below. Complete responses occurred a mean of 36 days after the start of a 4 week period of uninterrupted therapy; partial responses occurred a mean of 22 days after.

Time (Days) to Complete or Partial Platelet Response

PV Subjects	Study No			All Studies
	700-012	700-014	700-999	
Complete Responders	N=6 35.3 ± 2.9 (34.5, 36.2)*	N=45 31.9 ± 3.4 (31.5, 32.3)	N=14 54.6 ± 2.5 (54.2, 55.1)	N=65 36.2 ± 3.2 (35.9, 36.4)
Partial Responders	N=0	N=8 25.7 ± 3.0 (24.9, 26.4)	N=4 15.7 ± 7.8 (13.7, 17.7)	N=12 21.9 ± 4.1 (21.0, 22.6)

*( ) 95% Confidence Intervals

Time to platelet count response was longer for patients aged 40 years or less (mean 88.7 days) and for patients who had received prior therapy (mean 89.3 days). Females took longer to achieve partial response than male patients (meann35.8 days compared to 10.9 days).

5.5 Secondary Efficacy Endpoints – Decrease in Platelet Count

After 4 weeks of treatment , the mean platelet count decreased from a baseline of 1051.000/mm3 to 755.000/mm3 (p=0.001) in the efficacy population. Subsequent mean platelet counts were 616.000/mm3 at 12 weeks, 438.000, 438.000/mm3 at 2 years, and 418.000/mm3 at 3 years (p=0.001). The mean platelet counts by time on treatment for the efficacy population are shown in the following table (Appendix 4.2.1, vol. 2, 0.82) and figure (Fig.4.2.1, vol.2, 0.43).

Mean Platelet Count (x1000/mm3) by Time on Treatment for the Efficacy Population

Statistics	Baseline	Time on Treatment					
		Weeks				Years	
		4	12	24	48	2	3
Mean	1051	755	616	505	482	438	418
N	99	97	96	77	65	54	32

5.6 Platelet Count Rebound During Treatment Interruption

Treatment interruption was defined as any discontinuation of anagrelide therapy of => 3 days duration. Rebound was defined as any increase in platelet count that occurred during treatment interruption. Rebound was calculated as the change in platelet count from the time of treatment resumption to the time of treatment interruption.

A total of 47 (40%) patients from the 117 patients with PV in the ITT population interrupted anagrelide therapy over a range of 3 to 460 days. Reasons for interruption included adverse events and platelet counts within physiologic range. Of the 47 patients, 14 had platelet counts at the time of from 254.000 ± 54.000/mm3 at the time of anagrelide interruption to 657.000 ± 110.000/mm3 at the time of anagrelide resumption (-=0.002, paired t-test).

5.7 Secondary Endpoints – Symptoms Associated with Thrombocythemia

Symptoms associated with thrombocythemia were collected separately from other adverse events in the CRFs.. They included GI bleeding, easy bruising, epistaxis, hemoptysis, arterial thrombosis, angina, PE, TIA, erythromelalgia, digital ischemia, acral paresthesia. The occurrence of such symptoms is summarized in the following table.

Symptoms Associated with Thrombocythemia by Number of Patients and Reported Symptoms

Time (months)	Number of Events	Number (%) of Subjects Reporting Events
1	27	16/50 (32)
2	7	5/50 (10)**
3	7	6/50 (12)**
4	6	5/50 (10)**
5	0	0/50 (0)**
6	2	2/50 (4)**
7	2	2/50 (4)**
8	4	2/50 (4)**
9	6	6/50 (12)**
10	1	1/50 (2)**
11	4	3/50 (6)**
12	9	6/50 (12)**

* Multiple records of the same symptom and the same patient within a month were counted as one.
** Significant difference ($p=<0.05$) as comparing with month 1.

In the 50 patients who had received at least one year of therapy with anagrelide, symptoms associated with thrombocythemia were highest during the first month of treatment. A total of 16 patients (32%) reported 27 symptoms during this period. Subsequently, 0%-12% of patients reported thrombocythemia-associated symptoms over the next months.

The specific thrombocythemia-associated symptoms reported during the first year of therapy with anagrelide, for those patients who received at least one year of treatment, are summarized in the following table (Appendix 4.2.3B.i, vol. 2, p. 92).

Summary of Thrombocythemia-Associated Symptoms During 4 Years of Anagrelide Therapy

All Symptoms Coded as Nos. 1 - 15 (Symptom No.)		No. of Reports Per Time Period: Months M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	Years Y2	Y3	Y4	Total Reports
Gastrointestinal bleeding	(1)	2		1										2	1		6
Easy cutaneous/subcutaneous bruising/bleeding	(2)	9	2	2	2					1				2	2		20
Epistaxis	(3)	2	3						1	2	1	2	1	6	1		19
Hemoptysis	(4)												1				1
Bleeding at other sites	(5)	2	1						1			1	2	1			8
Recurrent arterial thrombosis	(6)	1	1														2
Preinfarction angina	(7)	2	1														3
Recurrent pulmonary embolism	(8)	1															1
Intestinal ischemia	(9)						1										1
Transient ischemic attack(TIA)	(10)	2	1	2	1					2		1	1	3			13
Erythromelalgia	(11)	3	1		1									1			6
Digital ischemia	(12)	5	2	1	1		1							1			11
Digital ischemic ulcers	(13)	2							1					1			4
Recurrent venous thrombosis	(14)	2						1							1		4
Acral paresthesia	(15)	4	4	2	1		1		1	1			1	1			16

*Multiple records of the same symptom and the same patient within a month were counted as once.

A summary of the symptoms that the investigators attributed to thrombocythemia, and were not listed as such in the CRF but as 'Other Symptoms', are summarized in the following table (Table 4.2.3, vol. 2, p. 46).

Summary of 'Other' Thrombocythemia-Associated Symptoms

Symptom	No. of PV Subjects Reporting (N = 50)	No. of Incidents Reported
Easy Cutaneous Bruising/Bleeding	6 (12%)	8
Epistaxis	6 (12%)	6
Transient Ischemic Attacks	6 (12%)	8
Acral Paresthesia	5 (10%)	9
Dizziness	4 (8%)	4
Headache	4 (8%)	5
Digital Ischemia	4 (8%)	5
Bleeding at Other Sites	3 (6%)	4

* Multiple records of the same symptom and the same patient within a month were counted once.

The data indicate a decreased incidence of thrombocythemia-associated symptoms with continued anagrelide therapy. This is particularly evident when the incidence of these symptoms are compared to those reported during the first month of therapy. Notably, CVA, TIA and epistaxis persisted during treatment with anagrelide.

The highest incidence of life-threatening symptoms occurring in the 50 PV patients who received at least one year of anagrelide was observed in the first month of therapy (8% in the first month compared to 0%-4% over the following 11 months).

The specific thrombocythemia-associated life-threatening symptoms reported for 50 PV patients treated with anagrelide for at least one year are summarized in the following table (App. 4.3.2.1A.i, vol. 2, p. 100).

Life-Threatening Symptoms During the First 12 Months of Anagrelide Therapy*

	Symptom Reported (Number of Subjects/Number of Events)*			
Symptom	Months 1-3	Months 4-6	Months 7-9	Months 10-12
Gastrointestinal Bleeding	2/2	0/0	0/0	0/0
Arterial Thrombosis	1/1	0/0	0/0	0/0
Transient Ischemic Attacks	4/4	0/0	2/2	2/2
Recurrent Venous Thrombosis	0/0	0/0	1/1	0/0
Cerebrovascular Accidents	0/0	0/0	0/0	1/1

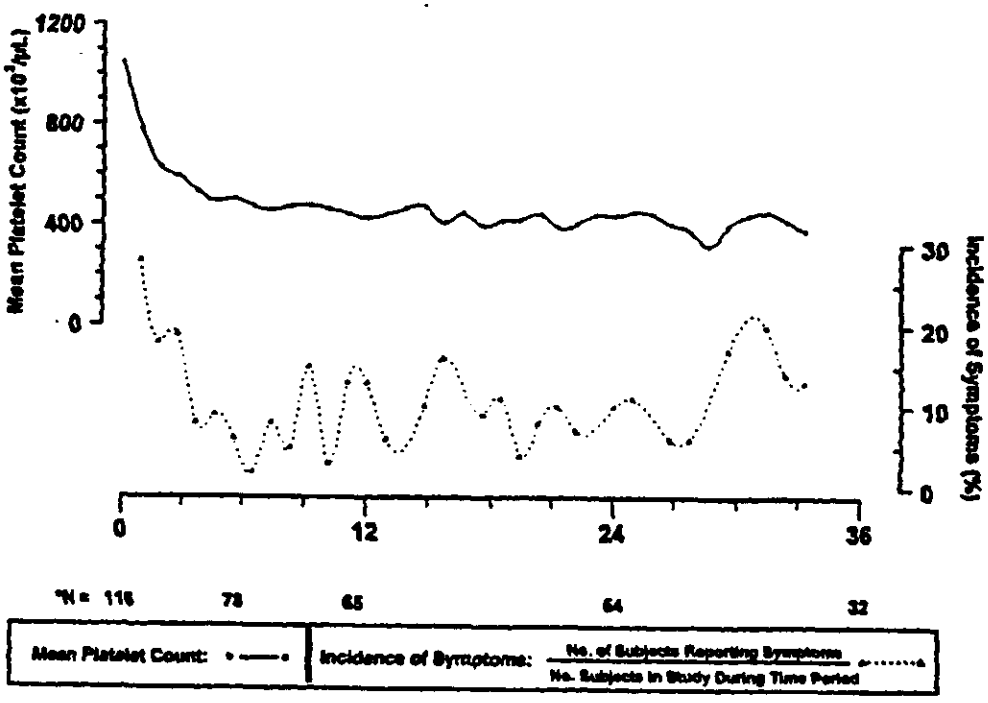
*Multiple records of the same symptom and the same patient within a month were combined.

5.8 Association of the incidence of Thrombocythemia Symptoms and the Mean Platelet Count over Time

A reduction in thrombocythemia-associated symptoms was associated with a reduction in platelet counts. The percentage of patients reporting symptoms increased after two years of treatment, however, the number of patients had decreased to 32 from the initial population of 116 patients by month 36.

The data are summarized in the following figure (vol.2, p.48)

Mean Platelet Count and Incidence of Thrombocythemia-Associated Symptoms over Time (months)



*N = Number of Patients with Assessments

APPEARS THIS WAY
ON ORIGINAL

6.0 EFFECT OF ANAGRELIDE IN CML AND OMPD.

The overall study population enrolled in clinical trials 700-102, 700-014 and 700-999 consisted of 933 patients with MPDs. These included 545 patients with ET, 117 patients with PV, 173 patients with CML, and 86 patients with OMPDs.

The mean platelet counts by time on therapy, for each MPS are summarized in the following table.

Meaan Platelet Count (x1000/mm3) by Time on Treatment for Each Diagnostic Group of MPDs

		Time on Treatment						
		Weeks				Years		
Diagnosis	Baseline	4	12	24	48	2	3	4
ET	1101	696	592	517	503	458	444	479
N	(545)	(509)	(488)	(402)	(337)	(262)	(150)	(42)
PV	1029	746	614	500	487	439	418	425
N	(117)	(114)	(99)	(78)	(66)	(54)	(32)	(7)
CML	1353	788	589	638	503	511	522	697
N	(173)	(162)	(153)	(121)	(83)	(56)	(10)	(2)
OMPD	1069	788	644	512	475	470	398	264
N	(86)	(81)	(72)	(59)	(44)	(35)	(15)	(3)
All Patients	1136	728	599	537	499	481	440	468
	(921)	(866)	(812)	(660)	(530)	(407)	(207)	(54)

ET=Essential Thrombocythemia; PV= Polycythemia Vera; CML= Chronic Myelogenous Leukemia, OMPD= Other Myeloproliferative Disorders.
Platelet count values are expressed as x 10^3/ul; The average platelet value in time period was used in com[utation

As seen from the above table, the degree and time pattern of platelet reduction with anagrelide therapy were similar in each of the diagnostic groups of MPDs.

7. 0 INTEGRATED SUMMARY OF SAFETY

The Integrated Summary of Safety (ISS), submitted in the initial NDA on 4-23-1996, provided a summary of adverse clinical and laboratory events (AE) for subjects enrolled in eight Phase I studies, for all Essential Thrombocythemia (ET) patients enrolled in three clinical studies and in two non-pivotal studies. The AEs reported for all other subjects with thrombocythemia associated with myeloproliferative disorders (MPD) were also summarized in the ISS.

The ISS included all deaths and adverse events leading to study withdrawal for the entire study population of 942 patients treated with anagrelide for thrombocythemia: 551 patients with ET, and 391 patients with PV, CML and other MPD.

7.1 Studies analyzed for Safety

The ISS submitted with the present efficacy supplement will address primarily the data for the patients with PV reported for the clinical studies 700-012, 700-014 and 700-999. The safety data from the Phase I studies and for the ET and other MPDs populations will not be included as they were reviewed with the initial NDA data.

The ISS includes safety data available up to February 29, 1992, for PV subjects enrolled in the three clinical research studies 700-012, 700-014. and 700-999.

7.2 Demographics and Overall Extent of Exposure

A total of 117 PV patients were enrolled in the studies. The mean age of the patients was 61 years; 62 % were females, 96% were Caucasian. Study subjects were treated with anagrelide for a mean of 67 weeks. Twenty percent of the subjects (27/117) received treatment for 2 years.

Concomitant medications were received by more than 7% of subjects, analgesics (aspirin and acetaminophen) were the most frequently administered concomitant medications, received by 31% and 28% of subjects, respectively.

7.3 Deaths

In the clinical trials, one (13%) of the 8 PV subjects enrolled in Study 700-012 and 1 (1.4%) of the 71 PV subjects enrolled in Study 700-014 died either during the study or within 30 days of stopping anagrelide treatment. Five (13%) of 38 subjects enrolled in Study 700-999 died either during the study or up to 30 days after discontinuing anagrelide. None of the deaths were attributed to anagrelide,

Causes of Death Reported in the Clinical Research Studies

Number of Subjects receiving Anagrelide= 117

Cause of Death	N (%) of Patients
CVA	2 (1.7)
MI	1 (0.9)
Pneumonia	1 (0.9)
Disease Progression	1 (0.9)
Pulmonary Hypertension	1 (0.9)
Auto Accident	1 (0.9)
Total Events	7
Total subjects	7 (0.6)

Overall, 70 patients from the total study population of 942 patients (8.8%) with thrombocythemia of MPD died either during the study or within 30 days of discontinuation of therapy. These included 25 patients with ET, 7 patients with PV and 38 patients with CML or OMPDs. A total of 14 patients with CML died of progression of disease. None of the deaths were attributed to anagrelide.

7.4 Discontinuation due to Adverse Events and/or Abnormal Laboratory Tests (Phase I studies, ET and other MPD patients, n=942)

Nineteen of 117 PV subjects (16%) discontinued from the studies because of AEs or abnormal clinical laboratory test results. Overall, a total of 34 adverse events, including 6 cardiovascular events, contributed to discontinuation of anagrelide in 19 patients. The most common AEs included headache in 5 subjects (4.3%) and diarrhea in 5 subjects (4.3%),

In the total study population of 942 patients with MPDs, a total of 161 patients (17%) experienced 255 adverse events that contribute to discontinuation of anagrelide therapy. The most common AEs included headache, diarrhea, edema, palpitation and abdominal pain.

Most of the AEs that led to discontinuation were considered mild or moderate in intensity and related to anagrelide treatment.

7.5 Adverse Events

All AEs were coded using the COSTART dictionary. The digestive system and the body as a whole were the most frequently affected systems during treatment with anagrelide. Overall, headache occurred in 61 (52.1%) of the 117 subjects. Headache was usually treated with acetaminophen or by decreasing the dosage of anagrelide. In some cases, the headache resolved without treatment. Other most frequently occurring AEs were palpitation (35 subjects: 29.9 %), diarrhea (43 subjects: 36.8%), and asthenia (31 subjects: 26.5%).

The most frequently occurring AEs (occurring in 10% or more subjects) among subjects who received anagrelide in the three clinical studies are shown in Table 7.2.1.

Most Frequently Occurring* Adverse Events Reported in Polycythemia Vera Subjects in Clinical Research Studies

	Number of Subjects Receiving Anagrelide = 117	
Adverse Event	N (%)†	Related N (%)
Headache	51 (52.1)	41 (35.0)
Diarrhea	43 (36.8)	22 (18.8)
Palpitation	35 (29.9)	28 (23.9)
Asthenia	31 (26.5)	13 (11.1)
Edema	30 (25.6)	11 (9.4)
Dizziness	25 (21.4)	10 (8.5)
Nausea	23 (19.7)	11 (9.4)
Pain	20 (17.1)	2 (1.7)
Pain abdomen	19 (16.2)	4 (3.4)
Flatulence	18 (15.4)	10 (8.5)
Pain chest	16 (13.7)	1 (0.9)
Rash	16 (13.7)	2 (1.7)
Dyspnea	15 (12.8)	1 (0.9)
Edema peripheral	14 (12.0)	3 (2.6)
Vomiting	14 (12.0)	7 (6.0)
Pruritus	13 (11.1)	0
Anorexia	12 (10.3)	5 (4.3)

* Occurrence in more than 10% of PV subjects
† Number (%) of PV subjects experiencing AE

7.6 Clinical Adverse Event Occurrence Rate by Dosage:

Table 7.2.2 shows the occurrence rates of AEs by anagrelide dosage. The highest rate (27) was seen with dosages => 6.0 mg/day.

Table 7.2.2: AE Occurrence Rates For PV Subjects, by Anagrelide Daily Dosage

Dosage (mg/day)	No.Rx Days	No.Unique AEs*	No.AE* / 1000 RxDays	No.Tx Days	No. All AEs	No.All AEs/ 1000 RxDays
< 2.0	26,693	199	7.5	38,634	277	7.2
2.0-2.9	33,149	296	8.9	43,750	373	8.5
3.0-3.9	20,358	134	6.6	26,006	171	6.6
4.0-4.9	68,600	228	3.3	122,204	352	2.9
5.0-5.9	2,326	36	15.2	4,413	53	12.0
≥ 6.0	1,484	40	27.0	3,610	75	20.8
Indeterm.	N/A	51	N/A	N/A	55	N/A
All	152,653	933	6.1	238,617	1,301	5.5

* Multiple occurrences of the same AE for each subject are only counted once
+ Includes AEs in off-treatment period or occurring when the dosage was unknown

7.8 Clinical Adverse Events By Body System:

Table 7.2.3 lists the number (%) of subjects with AEs by body system. A total of 96 subjects (82.1%) experienced AEs. Most AEs occurred in the body as a whole (77 subjects: 65.8%). Other frequent AEs were in the GI (68 subjects, 58.1%) and the CV system (59 subjects, 50.4%).

Table 7.2.3: Number (%) of PV Subjects with At Least One AE*

Body System	Number (%) of Subjects
Body As A Whole	77 (65.8)
Digestive System	68 (58.1)
Cardiovascular System	59 (50.1)
Nervous System	46 (39.3)
Metabolic and Nutritional Disorders	40 (34.2)
Respiratory System	34 (29.1)
Skin and Appendages	35 (29.9)
Special Senses	16 (13.7)
Urogenital System	23 (19.7)
Hemic and Lymphatic System	14 (12.0)
Musculoskeletal System	16 (13.7)
Total Subjects	96 (82.1)

* A subject may be included in more than one body system.

The distribution and the incidence rates of adverse events in the PV patients population was similar to that reported for the entire study population as described in the initial NDA. Only the events reported in Body As A Whole and in the Cardiovascular System will be desribed here in detail.

Headache was the most frequently reported AE in the Body As A Whole, occurring in 61 (52%) of the 117 subjects. The headache was considered by the investigator to be related or probably related to anagrelide treatment in 53 (45%) of subjects.. Headache was considered severe in 15 (2.8%) of the subjects. Headache was usually treated with acetaminophen or by decreasing the dosage of anagrelide. In some cases, headache resolved without treatment.

Other AEs that occurred frequently in the body as a whole were asthenia (31 subjects: 27%), abdominal pain (19 subjects: 16%), and pain (20 subjects: 17%). The majority of the episodes of abdominal pain were considered mild or moderate in intensity.

One subject experienced a life-threatening episodes of chest pain. The event was considered to be not related to anagrelide treatment. One subject experienced coronary ischemic pain and underwent PTCA. Three subjects experienced life-threatening or serious abdominal pain

One subject esperienced peritonitis secondary to gangrenous appendicytis. One patient experienced paralytic ileus.

Nine subjects (7.6%) experienced body as a whole AEs that led to discontinuation of anagrelide treatment. The most common AEs in this system that contributed to discontinuation were headache (5 subjects:4.3%), asthenia (2 subjects: 1.7%). .abdominal pain (1 subjects: 0.9%).

Cardiovascular System: Palpitation was the most common AE in the CV system, occurring in 35 (29.9%) PV subjects. A total of 33 (28%) subjects had episodes that were considered related or probably related to anagrelide, two of these subjects experienced severe palpitation.

Episodes of tachycardia were reported in 9 (7.7%) subjects; three subjects had episodes of tachycardia that were considered severe in intensity. Eight (6.8%) subjects had episodes that were considered related or probably related to anagrelide.

Hypotension occurred in three (2.6%) subjects. One subject experienced life-threatening hypotension that required pressor therapy. The episode was not considere related to anagrelide.
One subject with aortic stenosis was hospitalized with syncope.

Congestive heart failure was reported in 5 (4.3%) subjects, and it was considered severe in four subjects.

One patient experienced an episode of thrombophlebitis.

Six cardiovascular system AEs led to discontinuation of anagrelide treatment. The most common AEs in this system that contributed to discontinuation were:

heart failure	(2 subjects: 1.7%)
hypotension	(2 subjects: 1.7%)
tachycardia	(1 subject: 0.9%)
hypertension	(1 subject: 0.9%)

Cardiovascular events (MI, preinfarction angina, recurrent arterial thrombosis, recurrent PE, TIA, recurrent DVT, CVA, TE) were examined in a retrospective review of 492 subjects with thrombocythemia treated with anagrelide (mean dose: 2.3 mg/day po) for up to 4 years. Ninety-two percent (175/191) of the subjects with a prior history of CV disease and 96% (288/301) of the subjects with no prior history of CV disease had no CV events on treatment. Fifty-seven subjects who experienced pretreatment CV events had no on-treatment CV events. Twenty-nine subjects who had no pretreatment CV events experienced on-treatment cardiovascular events (P = 0.002). These results indicate that the known CV effects of anagrelide do not increase CV disease morbidity in subjects with thrombocythemia.

Digestive System: Diarrhea and nausea were the most frequent AEs reported in 43 (37%) and 23 (20%) subjects, respectively. The majority of these events were considered mild or moderate in intensity. Serious episodes of diarrhea or nausea occurred in 5 subjects One subject was hospitalized for pancreatitis. Thirteen subjects (11 %) experienced digestive system AEs that led to discontinuation of anagrelide treatment.

Hemic and Lymphatic System: Three (2.6 %) subjects experienced anemia which was severe in one subject. Thrombocytopenia occurred in 2 (1.7%) subjects. The events were considered to be related to treatment.

Metabolic and Nutritional System: The most frequently reported metabolic and nutritional system AE was edema, which occurred in 30 (27%) of the PV subjects who received treatment with anagrelide. Two subjects were hospitalized for edema; one patient also had dyspnea and abdominal pain. One patient was hospitalized for ventricular tachycardia and weight loss.

Musculoskeletal System: Arthralgia occurred in 7 (6%) subjects; none of these events were considered related or probably related to anagrelide. One subjects had severe arthralgia. One subject experienced arthrosis requiring incision and drainage. .

Nervous System: Dizziness was reported in 25 (21%) subjects and it was mild or moderate in 19 (16%) subjects. In 18 subjects, dizziness was considered related or probably related to anagrelide treatment. Other common nervous system AEs were paresthesia and depression, occurring in 8 (7%) and 6 (5%) subjects, respectively. The majority of these AEs were mild or moderate in intensity.
Two subjects were hospitalized with nervous system AEs. One patient had a mild cerebral infarct and one patient had confusion. Neither event was considered drug-related.

Respiratory System: Dyspnea occurred in 15 (13%) subjects. Eight (7%) subjects experienced episodes of dyspnea considered to be related to anagrelide treatment. Dyspnea was severe in 1 (0.9%) subjects.
Four subjects were hospitalized for dyspnea, one of these patients had interstitial pneumonia and one for life-threatening ARDS requiring intubation.
Of note, 4 patients developed pulmonary infiltrates during therapy. Open lung biopsy in one patient showed fibrosis consisitent with drug reaction.

7.9 Clinical Laboratory Data Safety Evaluation

Clinical Studies: The following analyses were performed to assess the clinical laboratory data:
-mean values over time (using unbalanced repeated measures),
-three consecutive values that changed from baseline using predetermined criteria ("shift analysis"),
-three or more markedly abnormal values anytime during the study.

The number and percentage of patients who experienced marked abnormalities (MA) on three or more occasions during the clinical trials are summarized in the following table.

Number (%) of PV subjects with marked abnormal tests occurring on three or more occasions

Laboratory Tests	Number (%) of PV patients
Hematology	
Hemoglobin	N=113
Low	11 (9.7)
High	--
Hematocrit	N=110
Low	7 (6.4)
High	--
White Blood Cells	N=113
Low	1 (0.9)
High	70 (61.9)
Serum Chemistry	
SGOT	N=73
Low	--
High	--
Creatinine	N=73
Low	--
High	2 (2.7)

No unexpecetd adverse events were reported in the literature aside for four cases of pulmonary infiltrates occurring during anagrelide therapy. One patient has lung biopsy consistent with drug-induced lung fibrosis. The patient's conditions improved upon discontinuation of anagrelide.

8.0 CONCLUSIONS

The results of this study indicate that the administration of Anagrelide can reduce platelet count in patients with PV significantly and maintain platelet count within normal range for at least 4 years. The estimated mean of days to beginning of complete response was 36.2 days; the estimated mean of days to beginning of partial response was 21.8 days.
A total of 55.6% achieved complete response based on the intent-to treat population (65 out of 117 subjects) and 65.7% (65 out of 99) for the efficacy population. Partial response was achieved by 10.3% of patients based on the intent-to-treat population (12 out of 117 subjects) and by12.1% (12 out of 99) for the efficacy population.

The time to beginning of complete response for the subjects with prior therapy were reduced significantly compared to the subjects without prior therapy.

Concomitant to the reduction in platelet counts, a reduction of symptoms associated to thrombocythemia was observed. The occurrence rates of subjects with symptoms were compared between the first month and each other month. Ratio tests showed the occurrence rate in each of second month to 12th month was significantly less than the rate in the first month.

Similar efficacy of anagrelide for reduction of platelet counts was observed in parients with CML or OMPD. The patterns of response in terms of degree, time of occurrence (initial and complete) and dose rerquirements were similar for all MPD.

The most frequently occurring adverse events were headache (52.1%), diarrhea (36.8%), palpitation (29.9%), asthenia (26. 5%), edema (25.6%), dizziness (21.4%). Leukocytosis occurred after long-term treatment (24 weeks or more).

9.0. COMMENTS AND RECOMMENDATIONS

Subjects with myeloproliferative disorders and thrombocythemia, particularly if elderly and with platelet counts greater than 1 million/uL of long duration, can experience hemorrhagic or thrombotic events. In symptomatic patients, reduction in platelet number can improve the clinical manifestations and reduce the risks or recurrence of thrombo-hemorrhagic events.

The management of thrombocythemia associated with PV and other myeloproliferative disorders has required the use of myelosuppressive agents including alkylating agents, hydroxyurea, radioactive phosphorus, alpha-interferon. Most of these agents, however, can suppress all hemopoietic precursor cells and are potentially leukemogenic. Frequently, antiplatelet drugs, such as aspirin or dipyridamole, are also administered to thrombocythemic patients to prevent thrombotic complications. However, the drugs often produces bleeding complications and are contraindicated for those patients who experience concomitant thrombotic and hemorrhagic events.

Selective suppression of megakaryocytes is particularly desirable in Polycythemia Vera where phlebotomy can control the red cell mass. In this condition, however, platelet production can actually increase after phlebotomy and with the development of iron deficiency.

Anagrelide is a quinazoline derivative which decreases platelet production in humans by disrupting the post-mitotic phase of megakaryocyte development reducing megakaryocyte size and ploidy. The effect of

anagrelide on megakaryocyte is specific, dose-related and reversible. No suppression of production or maturation defects have been demonstrated in the erythroid or myeloid series with the administration of anagrelide at therapeutic doses and for prolonged periods. At higher dose, anagrelide inhibits platelet function in all species, by interfering with the action of the cyclic nucleotide diphospho-esterase and with the release of arachidonic acid by phospholipase.

The clinical evaluation of anagrelide as a platelet reducing agent has been carried out in two open-label, self-controlled pivotal trials (700-012 and 700-014) and one compassionate-use study (700-999). A total of 933 patients with thrombocythemia of myeloproliferative disorders were enrolled in the studies: 550 patients with Essential Thrombocythemia (ET), 117 patients with Polycythemia Vera (PV), 179 patients with Chronic Myelogenous Leukemia (CML), and 87 patients with other Myeloprolifetative disorders (OMPD).

The availability of anagrelide that: 1) can decrease platelet production by specific and reversible suppression of megakaryocytes, 2) has no effect on the myeloid and erythroid stem cells, 3) is free of leukemogenic potentials, and 4) has a safety profile that makes them suitable for prolonged use, represents a significant advance in the treatment of thrombocythemia of MPDs.
The combination of anagrelide and phlebotomy would eliminate or delay the need for chemotherapy in PV. Other myeloproliferative disorder where selective suppression of platelet production is desirable, include Myelofibrosis and Myeloid Metaplasia as patients may be already anemic or leukopenic and, thus, poor candidates for myelosuppressive chemotherapeutic regimens.

Anagrelide was approved on March 14, 1997 for reduction of platelet counts in patients with ET.
On January 2, 1998, the sponsor submitted an efficacy supplement to NDA (20-333/S-002) for the approval of Anagrelide as platelet reducing agent for patients with Polycythemia Vera, CML, and other myeloproliferative disorders (OMPD).

The data provided by the sponsor in support of the efficacy and safety of anagrelide for patients with PV were generated from the three clinical trial of anagrelide for thrombocythemia of MPD. The results of these studies showed that anagrelide effectively reduced the platelet count in the patient population with ET, PV, CML and OMPD. Anagrelide also improved the clinical symptoms associated with thrombocythemia.

Efficacy was shown by:
- comparing the pretreatment mean platelet count and the mean count during anagrelide therapy,
- reporting on the time to initial response (first reduction of platelet count to the target range of $\leq$600,000/uL or $\geq$50% reduction from baseline value).
- reporting on the time to complete response (reduction of platelet count to the target range of $\leq$ 600,000/uL or $\geq$ 50% less than baseline value for > 4 weeks),
- comparing the frequency and severity of symptoms of Thrombocythemia at the start and during therapy.
- reporting on safety variables.

Based on the ITT population (N = 117), 56 % of PV subjects were complete responders, 10% were partial responders, giving 66% of PV subjects with an overall satisfactory response.
Sixty-six percent (66%) of the evaluable PV patients (EA) were classified as complete responders, and 12% of the EA subjects were classified as partial responders. Thus, 78% of the EA subjects had a satisfactory response to anagrelide treatment. On average, complete response was seen approximately 36 days after the first dose of a continuous 4 week period of treatment. Interruption of treatment was followed by an increase in platelet count.

The subset of patients with symptoms related to thrombocythemia who received anagrelide therapy for at least one year, experienced a significant improvement of thrombocythemia-related symptoms during therapy. The clinical improvement paralleled the reduction in platelet number.

Anagrelide therapy effectively reduced platelet counts in patients with other myeloproliferative disorders. The analysis of the sequential platelet counts from patients with CML or OMPD treated with anagrelide showed similar pattern of reduction both in terms of degree and time on treatment.

Anagrelide was less effective in young adults with MPDs that in elderly patients.

Myeloproliferative disorders are rare in the pediatric population. Only 12 pediatric patients among 4060 adult and elderly patients with myeloproliferative disorders were enrolled in the open-label compassionate use study 301D. The age ranged from 6.8 to 17.4 years. The pediatric population included 8 patients with ET, 2 patients with CML, 1 patient each with PV or OMPD.
The patients were started on anagrelide therapy with 0.5 mg qid to a maximum daily dose of 10 mg. Median duration of treatment was 18 months. The efficacy and safety of anagrelide in the pediatric patients were similar to that observed in adults.

As for young adults, the benefits of therapy with anagrelide in children is still controversial, particularly if they are asymptomatic as it may occur when the thrombocythemia is diagnosed by routine platelet counts.

Anagrelide suppresses platelet production selectively and with a wide therapeutic range. Prolonged therapy with anagrelide (up to 4 years) in ET patients did not affect WBC or RBC production and survival. Few patients developed reductions in platelet counts below the desired level.
The changes in WBC and the anemia that occurred in study patients were mostly due to progression of the underlying myeloproliferative disease. No cases of rapid onset thrombocytopenia or neutropenia suggestive of immune mechanisms were reported.

In conclusion, anagrelide is an efficacious treatment, decreasing the platelet count and the incidence of symptoms associated with a high platelet count for thrombocythemic subjects with ET, PV, CML and OMPD. It is effective in subjects who have failed or been intolerant of other anti-thrombocythemia therapy. Furthermore, unlike other agents used to treat thrombocythemia, the action of anagrelide is specific to platelets; overall, it has no clinical effect on the plasma level of other formed elements in the blood, and it does not interfere with specific procedures or therapies indicated for each myeloprolifertive disorder, i.e., plhebotomy in PV or chemotherapy in CML.

Most AEs were mild in intensity and decreased over time on anagrelide therapy. The frequency and severity of the adverse events were dose-related. The most frequently occurring adverse events were headache, GI complaints, and cardiovascular events.
Headache occurred in 44% of subjects and led to discontinuation of anagrelide in 22 subjects (4%). Headache was probably due to the vasodilator effect of anagrelide.

The adverse events of greatest clinical significance were the cardiovascular events. These events were attributed to the pharmacologic effects of anagrelide (phosphodiesterase inhibition and vasodilatatioh direct positive inotropic effect). Palpitations, tachycardia and arrhythmia were the most common cardiovascular AEs.

Overall, 16% of subjects discontinued from the clinical studies due to an AE or abnormal laboratory test result related to treatment with anagrelide. The AE resolved after anagrelide was discontinued.

Mean hemoglobin and hematocrit values decreased gradually over time for all subjects. White blood cell values rose through 48 weeks of treatment and then gradually decreased toward baseline at 4 + years. For most patients, the changes were consistent with progression of the underlying disease.

A review of published literature on anagrelide revealed that the AEs reported were comparable to those seen in the clinical studies. One published study reported the occurrence of pulmonary infiltrates in 4 patients. An open-lung biopsy was performed on one patients showing pulmonary fibrosis consistent with a drug reaction. Four cases of pancreatitis were reported, with negative rechallenge in one patient.

A total of 70 patients (7.4%) died either during the study or within 30 days of stopping anagrelide treatment: 25 patients had ET, 7 patients had PV. Mortality was higher for patients with CML due to the underlying disease. None of the deaths were attributed to treatment with anagrelide. The most common causes of death were cerebrovascular accident (8 deaths [2%]), myocardial infarction (5 deaths [1 %]), and cardiac arrest (3 deaths [1 %]).

Since the time of approval of anagrelide for Essential Thrombocythemia, clinical and post-marketing data indicate that the drug can safely be administered for prolonged periods. Many patients have received anagrelide for over 8-9 years.

In conclusion, the available data indicate that anagrelide is effective for the reduction of platelet number in patients with thrombocythemia associated to all myeloproliferative disorders and that the regimen has an acceptable safety profile. The currently available drug product and formulation appear as effective as that used in the clinical trials.

Approval of anagrelide for the treatment of thrombocythemia of myeloproliferative disorders (ET, PV, CML or OMPD) is recommended. Dosage and regimen of anagrelide are similar for all thrombocythemic states of myeloproliferative disorders..

Because of the incidence and severity of adverse events observed at higher doses, treatment should be started at the initial dose of 2 mg/day in two or four divided doses. Daily dosage should only be increased by 0.5 mg per week in order to achieve and maintain platelet reduction to <600.000/uL. Dose escalation should not exceed the daily dosage of 10 mg. The maintenance dosage is titrated according to platelet count and depends of individual patients' tolerance. Due to the dose-related frequency and severity of adverse events, patients failing to maintain an acceptable platelet reduction with a daily dosage of anagrelide greater than 6.0 mg, are not likely to tolerate higher dose regimens for prolonged periods.

Due to the the infrequent occurrence of myeloproliferative disorders in children, information on the use of anagrelide in the pediatric population remains limited.

Appropriate revisions of the proposed labeling for anagrelide have been discussed with the sponsor.

/S/

Lilia Talarico, M.D. 12-11-98

cc:
NDA 20-333
HFD-180
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/10/98 jgw
N\20333811.0LT

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

STATISTICAL REVIEW(S)

/S/

STATISTICAL REVIEW AND EVALUATION

Date:

NDA: 20-333/ SE1-002
Drug Class: Class 1S
Drug name: Agrylin (anagrelide hydrochloride) Caps
Applicant: Robert Pharmaceutical Corporation
Indication: Treatment of patients with Polycythemia Vera (PV)
Documents Reviewed: Two volumes, dated January 2, 1998; Volumes 6.29, 6.31 and 6.31 (original submission, January 1996)
Medical Officer: Talarico, Lilia, MD.
Statistical Reviewer: Mohamed Al-Osh, Ph.D., HFD-720
User Fee Due Date: January 2, 1999

SEP - 1 1998

Key Words/ Phrases:

Polycythemia Vera diagnosis, Essential Thrombocythemia (ET), Reduction in platelet counts

Major Issues:

(i) There are no statistical analysis plans in the protocols.

(ii) Treatment efficacy was defined in terms of reduction in the platelet count, however enrollment of some patients was not based on platelet counts.

(iii) Two different criteria were given for defining treatment efficacy without specifying where each criteria should be used.

(iv) No treatment period was specified for measuring efficacy and the sponsor's data, being presented at selective time points, makes it difficult to verify the efficacy response criteria.

I. Background:

Agrylin has been recently approved, March 14, 1997, for the treatment of patients with Essential Thrombocythemia (ET) to reduce their elevated platelet count and the risk of thrombosis. The sponsor, in this supplemental submission, is requesting approval to expand the indication to include patients with Polycythemia Vera (PV). Anagrelide was designated, on June 11, 1985, as an orphan drug for the treatment of PV, which is a chronic, slowly progressing disease, characterized by high red cell mass and usually by hyperplasia of all bone marrow elements. Patients with the disease may later develop thrombocytosis.

In support of the efficacy and safety claim of agrylin in PV patients, the sponsor submitted efficacy data which comprised part of the original NDA submission (NDA#: 20-333, August 20, 1993) for the treatment of patients with ET. The data were the result of two pivotal studies (Study #'s: 700-012 and 700-14); and subjects with thrombocythemia due to ET, PV, chronic myelogenous leukemia (CML), or other mylopro- liferative disorder (OMP), were enrolled in these 2 studies. The efficacy data from these clinical trials relevant to the ET indication were reviewed by A.J. Sankoh, Ph.D. (Statistical Review, dated July 17, 1996). The current review deals with the efficacy data from these studies relevant to the requested PV indication. In addition, this review considers the efficacy data from a supportive study (# 700-999) included in this submission. It is not clear to this reviewer, from the sponsor description, whether the data from this study were included in the original submission for the ET indication.

No study protocols were included in this submission. Consequently, when needed, this reviewer referred to the IND protocols of the two pivotal studies (as given in the original submission, Volumes: 6.29, 6.31 and 6.34 of the clinical submission of the original NDA). Below, we give a brief description of the two pivotal studies and the supportive study, as related to the PV indication.

II. Description of Studies and Efficacy Endpoint:

After a brief description of the sponsor's studies we discuss the study endpoints, methods of analysis and the study population analyzed.

II.A. I. Pivotal studies

The two pivotal studies (#'s: 700-12 and 700-14) were multi-center, open-label baseline-controlled studies in which all subjects were treated with anagrelide. The objectives of Study 700-012 were to determine the dose of anagrelide required to decrease the platelet count in subjects with thrombocythemia to within or close to the normal range; and, secondly, to determine the required dose of anagrelide needed to maintain this decrease. The study enrolled 44 subjects, eight of whom had a diagnosis of PV. Four PV subjects had 4 years of anagrelide treatment. Subjects still active in the study at its termination (N = 4) were transferred to the study being performed under protocol 301A.

Study 700-014 was of similar design to Study 700-012 and enrolled a total of 498 subjects, of whom 71 were diagnosed with PV. The objective of this study, as given in the current submission (page 3 0015, Vol 1), was to determine the number of subjects who were classified as responders. That is, the percent of subjects who had a decrease in their baseline platelet counts of ≥ 50% or a reduction in their platelet count to ≤ 600,000/μL. Four PV subjects had 4 years of anagrelide treatment. Subjects still active in the study at its termination (N = 42) were transferred to the study being conducted under protocol 301A.

II.A. II. Supportive Study

Study 700-999 was a compassionate-use study, in which subjects with thrombocythemia were allowed to receive anagrelide treatment under an IND. The sponsor indicated that although the conduct of this study was similar to that of Study 700-14, this study was not subject to the strict monitoring procedure of the pivotal studies. Of the 455 subjects enrolled in Study 700-999, 38 had a diagnosis of PV. Two PV subjects had 4 years of anagrelide treatment. Subjects still active in the study at its termination (N=13) were transferred to the study being conducted under protocol 301A.

II.B. Patients Enrollment, Efficacy Parameters and Analysis Plan:

II.B.I. PV Diagnosis and Treatment Plan:

The diagnosis of PV, according to the study description (Vol. 1, *page. 3.0004)*, was based on the following two sets of criteria (classified under A and B):

- A1 Increased red cell mass
- A2 Normal arterial oxygen saturation
- A3 Splenomegaly
- B1 Platelet count ≥ 400,000 /μL, in the absence of iron deficiency or bleeding
- B2 Leucocytosis (≥ 12,000/μL, in the absence of infection)
- B3 Elevated leucocyte alkaline phosphatase
- B4 Elevated serum B_{12} .

The diagnosis was considered positive if A1, A2 and A3 were present; or, if A1 and A2 were present with any two of B1, B2, or B3. It is not clear to this reviewer the purpose of including B4 in this case.

The anagrelide treatment started at doses of 0.5 - 2.0 mg every 6 hours. The dose was increased if the platelet count remained high, but not to more than 12 mg each day. No treatment window was specified for treatment, and consequently for efficacy assessment. The sponsor, however, indicated that the mean duration of anagrelide therapy was 67 weeks and that 23% of patients received treatment for 2 years or more.

In addition, the study description did not specify the intervals at which platelet count measurements were to be taken, and consequently to judge efficacy. However, the proposed outsert (Agrylin capsules are marketed without a carton) label for thrombocytosis indicates (page 2 0019, Vol. 1) that platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until the maintenance dosage is reached

II.B.II. Efficacy Parameters and Analysis Plan:

The statistical report (page 10 0014, Vol. 2) stated that the primary efficacy parameter was defined as the percentage of subjects who were classified as complete responders and partial responders.

Complete responders were defined as those patients whose platelet counts were reduced to $\leq$ 600,000/μL or by $\geq$ 50% from baseline value, after 4 weeks treatment and who maintained the reduction for at least 4 weeks. Partial responders were defined as those patients who experienced a 20% to 50% reduction from baseline in platelet counts for at least 4 weeks. The baseline count is the value obtained immediately prior to treatment initiation; in most cases, this was obtained the day of or the day prior to starting anagrelide.

The secondary efficacy endpoints were:

(i) Time to complete response; that is the time from the first day of 4 weeks of continuous anagrelide treatment to the day of complete response.
(ii) Reduction in platelet count; platelet counts were presented at baseline and compared to platelet counts at 4, 12, 24 and 48 weeks and at 2, 3, and 4 years.
(iii) Symptoms associated with thrombocythemia; here the effect of anagrelide treatment on the incidence of specific symptoms associated with the presence of thrombocythemia was analyzed for subjects who had at least one year of treatment.

There was no statistical analysis plan in the protocol. However, the statistical summary report indicated, on page 10 0029, Vol 3, that the statistical analyses of the efficacy data consisted of:

(i) Construction of 95% confidence interval for the response rate using the normality assumption;

(ii) Use of repeated measures model to compare the baseline platelet count with that of each other time period; and

(iii) Conduct pairwise comparisons between platelet counts of each two time periods.

II.C. Populations Analyzed:

The sponsor (in their efficacy analysis) considered the following two data sets:

(i) An intent-to-treat (ITT) population, consisted of those subjects who received at least one dose of anagrelide data set; and

(ii) An efficacy data population, consisted of those subjects treated with anagrelide for at least 4 weeks and who did not have a treatment interruption of 3 or more consecutive days during the 4 weeks treatment period.

A total of 123 PV subjects were enrolled in the three clinical trials (700-0012 ,-0014 and -999). Out of these, 117 subjects received at least one dose of anagrelide and were included in the ITT population. Six patients were excluded since, according to the sponsor, their dose information or platelet counts were not available. Eighteen subjects were not treated for at least 4 weeks, consequently 99 subjects were included in the efficacy population. Table 1 presents the disposition of the PV patients in the three clinical trials, classified by study, center and the population analyzed.

Table 1/ Reviewer's Table
Polycythemia Vera (PV) subjects, received anagrelide treatment, classified by study, center and population analyzed

Center		1	2	3	4	5	7	9	Total
Population/ Study									
ITT Pop.	700-012	7	0	0	0	1	0	0	8
	700-014	21	5	8	26	9	1	1	71
	700- 999	38	0	0	0	0	0	0	38
	Total								117
Efficacy Pop.	700-012	6	0	0	0	1	0	0	7
	700-014	16	4	8	26	9	1	1	65
	700-999	27	0	0	0	0	0	0	27
	Total								99

Source: Compiled from the Sponsor's Table 3.2, Vol 3, p. 10 0037

The mean age of all 117 patients enrolled in these studies was 61.2 years; 39% were male; and 96% were white. Of the 117 patients, 103 had prior therapy for thrombocythemia, 10 had no prior therapy and the therapy status of the remaining four subjects was unknown.

Attachment A.1 provides a SAS data listing for the patients included in the analysis, their platelet counts at selected (by the sponsor) time points, as well as some other measurements considered later in this review. Table A.2.1 (Attachment A.2) shows the sponsor's listing of the patients excluded from the ITT analysis and the reasons for their exclusion.

III. Sponsor's Analysis Method and Results:

III.I Efficacy Results for the Primary Endpoint (Complete and Partial Responses):

Table 2 summarizes the sponsor's efficacy results for the primary endpoint, percentage of subjects who had a complete or a partial response, classified by study and population analyzed.

Table 2/ Reviewer's Table
Number (%) of Subjects With Complete and Partial Responses to Anagrelide Treatment
(Classified By Study and Population Analyzed)

	Study #			
Population/ Response	700-012	700-014	700- 999	Total
ITT Pop./ n	8	71	38	117
Complete Responders	6 (75%)	45 (63%)	14 (37%)	65 (56%)
95% C.I.	(45.0, 100.0)	(52.2, 74.6)	(21.5, 52.2)	(46.6, 64.6)
Partial Responders	0 (0%)	8 (11%)	4 (11%)	12 (10%)
95% C.I.	-	(3.9, 18.6)	(0.8, 20.3)	(4.8, 15.8)
Efficacy Pop. / n	7	65	27	99
Complete Responders	6 (86%)	45 (69%)	14 (52%)	65 (66%)
95% C.I.	(59.8, 100.0)	(58.0, 80.5)	(33.0, 70.7)	(56.3, 75.0)
Partial Responders	0 (0%)	8 (12%)	4 (15%)	12 (12%)
95% C.I.	-	(4.3, 20.3)	(1.4, 28.2)	(5.7, 18.6)

Source: Compiled from the Sponsor's Tables 4.0.1 and 4.0.2, Vol 3, p. 10 0038 -39

The results of Table 2 show consistency in the treatment response across the three studies, whether one considers the ITT or the efficacy population. Overall, the complete response rate was 55.6% based on the ITT papulation and 65.7% for the efficacy population. The confidence intervals of complete response rate were 46.6% to 64.6% for the ITT population and 56.3% to 75.0 % for the efficacy population. The confidence intervals for the complete response for the ITT and the efficacy population overlap indicating that there no significant difference in the response rate between the two populations analyzed. Results for the partial response across the three studies are also similar upon exclusion of Study 700-12 from this comparison due to its small number of patients,

III.II. Efficacy Results for the Secondary Endpoints:

This section presents the efficacy results for the following secondary endpoints: (a)Time to response, (b) Platelet counts, and (c) Symptoms associated with thrombocythemia.

III.II. A. Time to Response:

Table 3 presents the sponsor's efficacy results for the secondary endpoint, average number of days to complete and partial responses. These efficacy results are the same for the ITT and the efficacy population since they are calculated for responders only.

Table 3/ Sponsor's Table

Geometric Mean of The Number of Days to Complete and Partial Responses

Population/ Response	Study # 700-012	700-014	700- 999	Total	Total [a]
Complete Resp./ n=	6	45	14	65	65
	35.3 ±2.9	31.9 ±3.4	54.6 ± 2.5	36.2 ± 3.2	36.2 ± 3.2
95% C.I.	(34.5, 36.2)	(31.5, 32.3)	(54.2, 55.1)	(35.9, 36.4)	(27.3, 47.9)
Partial Responders n=	0	8	4	12	12
	-	25.7 ±3.0	15.7 ±7.8	21.8 ± 4.1	21.8 ± 4.1
95% C.I.	(-)	(24.9, 26.4)	(13.7, 17.7)	(21.0, 22.6)	(9.9, 48.2)

[a] Results in this table. except the last column. are compiled from the sponsor's efficacy results (no table number was given) page 10 0018 volume, and those of the last column ([a]) are taken from the sponsor's Table 5.4.1, page 10 0057, Vol. 3.

This reviewer has two comments concerning the results of Table 3. First, one might question the appropriateness of the geometric mean, and its interpretation, for this type of data. If the reason for its use was the large outliers in the time to response (see SAS data listing in Attachment A.1) and that the mean time to response are likely to be affected by these outlier, one could use more stable measures of central tendency such as the median or quartiles. This point will be addressed later in this reviewer's re-analysis (Section IV). The second point is that the 95% confidence intervals for the mean time to response are very narrow, and show discrepancy in the last two columns, which were taken from different tables as presented by the sponsor. The cause of this discrepancy in these results which were calculated from the same data is not clear to this reviewer. This casts doubt on the accuracy of the findings of Table 3.

III.II.B. Comparison of Platelet Count:

Table 4 summarizes the sponsor's efficacy results for comparing the average and last platelet counts by time of treatment.

Table 4/ Reviewer's Table

Mean of Last [1] and Average [1] Platelet Count (x1000) by Time of Treatment (ITT Population)

Measurement Type	Statistics	Baseline	Week 4	Week 12	Week 24	Week 48	Year 2	Year 3	Year 4
	N	116 [2]	113	98	78	65	54	32	7
Last	Mean	1037	698*	578*	489*	470*	454*	446*	468*
Last	Std	446	387	266	219	189	166	231	161
Average	Mean	1037	750*	613*	506*	482*	438*	418*	423*
Average	Std	446	320	242	205	164	146	155	130
	Mean Base	1037	1040	1054	1040	985	1008	1047	920

Source: Sponsor's Tables: 5.3.1, 5.3.2, 5.3.3: Vol. 2, page 10 0051-0053

[1] 'Last' refers to the last observation of the time period and 'Average' refers to the average of the observations of the time period.

[2] There is no platelet count for one patients(# 999001567) at any time point; this might be the reason for sponsor's use 116 instead of 117 patients in the ITT analysis.

* Results of comparing the mean platelet count with that of the baseline is significant (p=0.0001).

The results of Table 4 show that there was a significant decrease in the mean platelet count over the course of anagrelide treatment. Starting with baseline platelet count of 1037,000/μL the mean of the last platelet count decreased to 698,000/μL by Week 4. Similarly, the average platelet count during the 4 weeks of treatment decreased to 750,000/μL from the baseline value of

1037,000/μL. These results show also that there was a significant decrease within 24 weeks of treatment, and that platelet count remained relatively stable after the 24 th week. Figure A.2.1 (Attachments A.2) shows the sponsor's graphical display of the platelet count over the course of anagrelide treatment.

In addition to comparing the platelet count at each of time points: 4 weeks, 12 weeks, 24 weeks, 48 weeks, 2 years and 3 years to the baseline platelet count the sponsor conducted, for the ITT population, pairwise comparisons between platelet counts for each two periods. The results of the analysis show that there is a significant reduction in platelet count until week 12, and the reduction becomes not significant after 12 weeks. Results for comparing the average platelet count for various time points show no significant reduction in platelet count after 24th week of treatment (see Attachment A.3).

III.II.C. Efficacy Results Based on Symptoms Associated with Thrombocythemia:

The sponsor's efficacy results are based on symptoms data from PV subjects who had at least 1 year of anagrelide treatment. There were 50 such subjects whose adverse event rates during the year were compared with that of the first month of therapy which was defined as the baseline rate. The sponsor findings (page 30022, Vol. 1) were:

(i) The overall incidence of adverse events associated with thrombocythemia (cutaneous bleeding, epistaxis, transient ischemic attacks, acral paresthesia, dizziness, digital ischemia) decreased from incidence of 32% during the first month of therapy to between 2% and 10% during the last three months of treatment and

(ii) The incidence of life-threatening events (transient ischemic attacks, gastrointestinal bleeding, arterial thrombosis, cerebrovascular accidents, recurrent thrombosis) decreased from an incidence of 8% during the first month of therapy to between 2% and 4% during the last three months of treatment.

IV. Reviewer's Comments and Analysis:

There are several issues of concern to this reviewer, some of these issues are related to the conduct (enrollment) of the trials, efficacy assessment and the sponsor's data as given at

selected time points. This reviewer, along with J. DuBeau (CSO), held a telecommunication with the sponsor on 6/15/98, to request explanation of the efficacy evaluation and interpretation of some of the results. Below we list this reviewer's concerns and the sponsor's response to some of these concerns. Then, toward the end of this section we examin the impact of theses issues on the sponsor's efficacy results.

(i) The discussion in Section II (page 3) implies that a patient meeting criteria A1- A3 is eligible for enrollment in the trial, regardless of his/her platelet count at baseline. In fact, the IND protocol of these studies, as given in the original submission (1996), specifies the set of criteria listed under A1-A3 as primary (or major) criteria, and those listed under B1-B4 (in which B2 involves platelet counts) as minor (secondary) criteria. For Study 700-012, the cut-off point for the platelet count in B2 was set to be 650,000/ μL instead of 400,000 μL (page 8 1381 Vol 6.29). For enrollment eligibility, the protocol indicates that in the absence of splenomegaly, the presence of any two minor (B) criteria can be substituted for A3 (page 8 1381 Vol 6.29 and page 8 2179 Vol 6.31). This is different from the enrollment criteria given in this submission (page 3) which requires, in the absence of A3, the presence of two of the three criteria B1, B2, B3.

Because enrollment into the trials was not based on platelet count whereas treatment efficacy is defined in terms of reduction in the platelet counts, efficacy evaluation becomes subjective and difficult to verify.

(ii) The criteria for treatment efficacy is not well defined. In fact, Study 700-012 protocol did not specify this criteria explicitly. Study 700-014 protocol (page 8 2182, Vol 6.31) defined complete response as reduction of platelet count to ≤ 600,000/ μL or a reduction by at least 50% from the counts before initiation of anagrelide therapy (see Section II, page 4). It is not clear when the 600,000/ μL or the 50% cut-off points should be used for judging efficacy. The choice of an efficacy criterion becomes important if one recognizes that there are 11 (out of 116) patients whose platelet count was below the 600,000/ μL threshold at the baseline; in addition to one baseline measurement being missing for one patients (see Attachment A.1).

This reviewer requested the sponsor, during the telecommunication, to explain how the above two criteria are used to evaluate efficacy. The sponsor's response was that the 50% criterion was applied to patients with platelet count at baseline ≥ 1000,000/ μL, and that 600,000 threshold criterion was applied to patients with platelet counts < 1000,000/ μL. Then the reviewer's raised

the point that some patients meet the definition of success before treatment since their platelet counts were below 600,000/ μL . The sponsor's replied that there were only a few such patients and they were not considered in the efficacy analysis but they were considered in the safety analysis. The sponsor's data listing, however, shows that this is not the case. The data in Attachment A.1, sorted by baseline platelet count, show that among the 11 patients with platelet count below 600,000 at baseline, there were 2 complete responders and 2 partial responders.

(iii) Another issue related to the efficacy evaluation is that no treatment period was specified. Complete response was defined in terms of reduction in platelet count, as discussed in (ii) above, for at least 4 weeks. This criteria does not address the case in which platelet counts fluctuate up and down. The patient's data listing in Attachment A.1 shows that there are about 13 patients whose platelet count increased after it decreased. Now, the issue in evaluating efficacy for these patients, and probably for others as well, is whether the decline in platelet count lasted for at least 4 weeks (which is the efficacy criterion). The sponsor's data, as presented in Attachment A.1, show platelet counts during the following times: Baseline, Week 4, Week 12, Week 24, Week 48, Year 2, Year 3, Year 4, even though efficacy assessment requires weekly readings of platelet count. This reviewer requested weekly data during the telecommunication, however, the sponsor replied that they might have such data and they will send them if they do. However, this reviewer did not receive this data from the sponsor by the time of completion of this review.

(iv)The efficacy population was defined as those subjects treated with anagrelide for at least 4 weeks and did not have a treatment interruption of 3 or more consecutive days during the 4 weeks treatment period. The sponsor's data listing (Attachment A.1) shows that these patients (designated by the letter U in the RESP column) have measurement at 4 weeks, and not thereafter. However, the data does not indicate if these patients were treated for 4 weeks and stopped (since there are no measurements after 4 weeks). The data does not indicate also the length of treatment interruption, if any.

The above issue should not have much effect on the efficacy analysis, however, since as discussed before on page 7 (following Table 2), the efficacy results for the ITT population are not significantly different from those of the efficacy population.

(v) The issue about the appropriateness of the geometric mean, and its interpretation, for the time to response outcome was raised before (page 8). However, one notes that the sponsor is not

making an efficacy claim concerning this time (no hypothesis was tested). Consequently, one might view the average number of days to response as merely an indication of the length of time to treatment response. Table 5 shows the median time to response for the anagrelide complete and partial responders

Table 5/ Reviewer's Table
Median Number of Days to Complete and Partial Responses

Population/ Response	Study # 700-012	700-014	700- 999	Total
Complete Resp./ n=	6	45	14	65
Median [50th percentile]	43	29	52	35
[25,75 percentiles]	[25, 138]	[11, 64]	[29, 133]	[19, 67]
Partial Responders/ n=	0	8	4	12
Median [50th percentile]	-	33.5	8	16
[25,75 percentiles]	(-)	[8, 66]	[5.5, 163]	[8, 66]

The results of Table 5 show that, overall, the time to response for 50% of the complete responders was 35 days and for partial responders was 16 days. There is some variability among the results from the three studies. For complete responders, the minimum median time to response occurred for Study 700-014 (29 days). For the partial responders, the minimum median time to response occurred for Study 700-999 (8 days).

In the remainder of this section we address the implication of the reviewer's comments raised above on the efficacy results. These are mainly relevant to the enrollment criteria and the assessment criteria as listed under (i) and (ii) above.

Concerning the enrollment of patients with baseline platelet count below the 600,000 threshold, one can argue that the inclusion of these patients have little, if any, effect on the sponsor's efficacy results. As discussed above among the 11 patients enrolled in the studies with platelet count below 600,000, there were 2 complete and 2 partial responder (according to sponsors efficacy evaluation). Thus, the complete and partial response for this subgroup of patients is below that of the overall population (56% and 10% respectively for complete and partial

responders in the ITT population, Table 2, page 6). Consequently, even if one excludes these patients from the analysis, the sponsor's reported efficacy results would be affected very little.

This reviewer's concern about the criteria used to evaluate efficacy (see VI (ii), page 10) seems also to have little, if any, effect on the efficacy results. This is clear from checking the platelet count data over the course of anagrelide treatment, as given in Attachment A.1 (see also Figure A.2.1 in Attachment A.2). In addition, the results of Table 4 (page 8) show that the reduction in platelet count from baseline was highly significant at each of the time points given (4 weeks, 12 weeks, 24 weeks, 48 weeks, 2 years, 3 years) whether one considers the average or the last measurements in each of these interval.

The results of Table 4 can be viewed as addressing the comment raised concerning the unavailability of the weekly data. The average platelet count during each of the time intervals reported is not too different from the last measurement for the same time interval. Thus, ruling out that unexpected cases in which platelet count might vary greatly from week to week, one might argue that the reduction in the platelet count was relatively stable following its reduction (see Figure A.2.1, Attachment A.2). Consequently, the significant results in comparing the average platelet count during each time period reported in Table 4 with those of the baseline is evidence that the decline in platelet counts lasted at least 4 weeks, as required by the efficacy criteria.

V. Safety and Pediatric Use:

The sponsor indicated that the most common adverse events associated with anagrelide treatment of PV patients were: headache (52%), diarrhea (36.8%), palpitation (30%) and asthenia (27%). In addition, the sponsor stated that the intensity of these adverse events tended to be mild to moderate and their incidence tended to decrease over time during anagrelide therapy.

Concerning pediatric use, the safety and efficacy assessment of anagrelide in patients under age 16 years has not been established.

VI. Summary:

In this submission the sponsor is requesting approval to expand the indication of using anagrelide capsules in the treatment of patients with Essential Thrombocythemia (ET) to include patients with Polycythemia Vera (PV). Anagrelide was designated as orphan drug for the treatment of PV.

For support of the safety and efficacy claim of anagrelide, the sponsor submitted efficacy data which comprised part of the original NDA submission for treatment of patients with ET (NDA#: 20-333, August 20, 1993). The data were from two pivotal studies (Study #'s: 700-012 and 700-14) and a supportive study (# 700-999). Each of the studies enrolled subjects with thrombocythemia due to ET, PV, CML , or OMP.

One hundred seventeen patients diagnosed with PV were enrolled in the studies and treated with anagrelide. These patients constituted the ITT population. Of these 117 patients, 99 patients met the efficacy population definition, that is, treatment with anagrelide for at least 4 weeks and without treatment interruption for more than 3 days.

The efficacy criterion was defined in terms of reduction in elevated platelet count, and responders were classified as complete or partial responders. Complete responders were defined as those patients whose platelet counts were reduced to less than or equal to 600,000/μL or by greater than or equal to 50% from baseline value after 4 weeks treatment and maintaining the reduction for at least 4 weeks. Partial responders were defined as those patients who experienced a 20% to 50% reduction from baseline in platelet counts for at least 4 weeks. The secondary endpoints were: (i) time to complete response; (ii) reduction in platelet count and (iii) symptoms associated with thrombocythemia.

Efficacy results were consistent across the three studies. Below is a summary of the overall efficacy results for the three studies combined. The complete responders rate was 56% for the ITT population and 66% for the efficacy population (Table 2, page 6). The 95% confidence intervals for these two population response rates overlap, thus indicating that there was no significant difference in the response rate for the two population analyzed. Similarly, the partial responders rates for the ITT and the efficacy population were similar (10% and 12% respectively; Table 2, page 6). For the secondary endpoints, comparison of the last and average platelet counts for the time points: 4 weeks, 12 weeks, 24 weeks, 48 weeks, 2 years and 3 years

show highly significant reductions from baseline platelet count (Table 4, page 8). The median time to response was 35 days for complete responders and 16 days for partial responders (Table 5, page 12).

In Section IV (pages 9-13) this reviewer raised several issues dealing with the enrollment of patients in the trials, the efficacy assessment, the periods for which the sponsor presented efficacy data and questioned the appropriateness of using the geometric mean as measure for the time to response. However, this reviewer concluded that these issues have little, if any, affect on the reported highly significant results for anagrelide treatment. Thus, from statistical point of view, the efficacy results support the sponsor's claim for efficacy of anagrelide in reducing elevated platelet counts in PV patients.

VII. Conclusion:

The efficacy results presented in this submission support the sponsor's claim that anagrelide is effective in reducing elevated platelet count in PV patients and in maintaining such reduction for at least 4 weeks. In this reviewer's assessment, the efficacy results in this submission thus support the sponsor's request for expansion of the current indication of using anagrelide in the treatment of patients with Essential Thrombocythemia (ET) to include patients with Polycythemia Vera (PV).

APPEARS THIS WAY
ON ORIGINAL

Mohamed Al-Osh, Ph.D.
/S/
Mathematical Statistician 9/1/98

Concur:

A.J. Sankoh, Ph.D.
(Acting Team Leader) /S/ 9/1/98

Michael Welch, Ph.D.
(Acting Division Director) /S/

DIAGNOSIS (OTHER MYELPROLIFERATIVE DISORDER)

50	Non specified cases of myeloproliferative disorders with thrombocythemia
15	Myelofibrosis
14	Agnogenic Metaplasia
3	Chronic leukemia, Unclassified
2	Sideroblastic Anemia
2	Information No Listed
1	Unknown

Redacted 2

pages of trade

secret and/or

confidential

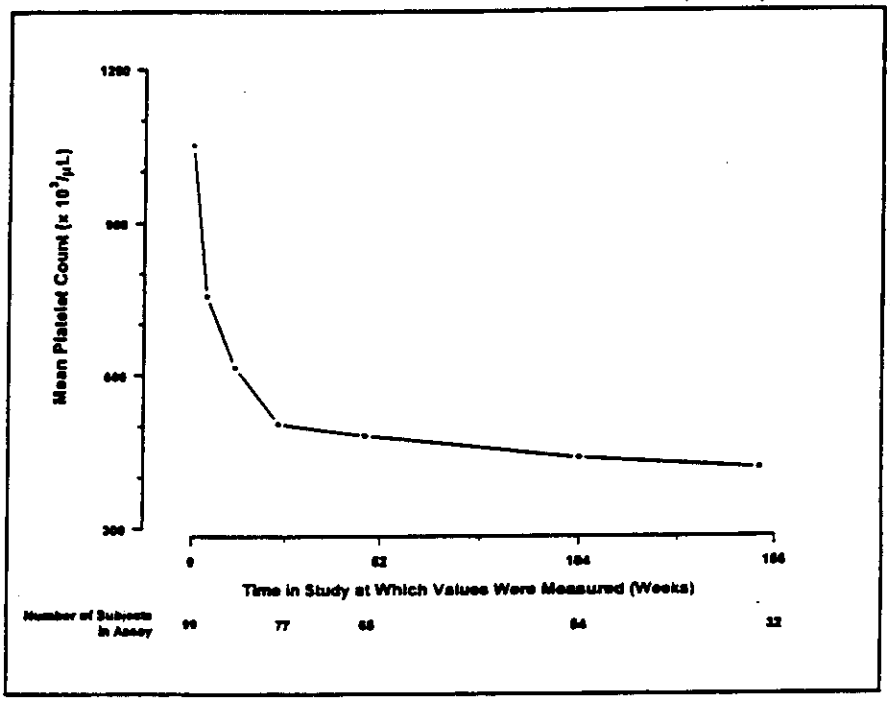
commercial

information

Attachment A.2

Figure A.2.1:

Decrease in platelet count with Time of Anagrelide therapy along with the number of patients in the efficacy evaluable population, (Studies #: 700-012, -014, and -999)



Source: Sponsor's submission page 10 0019, Vol. 3

Table A.2.1:

List of patients excluded from all analysis (Studies #: 700-012, -014, and -999)

OBS	PAT_ID	INITIAL	DIAGNOSIS	SEX	RACE	REASON	COMMENTS
1	014001100		PV	FEMALE	WHITE	NO DOSE INFORMATION	ENTERED STUDY 301
2	014001121		PV	MALE	WHITE	NEVER TAKE ANAGRELIDE	
3	999001414		PV	MALE	WHITE	NO DOSE INFORMATION	
4	999001472		PV	MALE	WHITE	NO PLATELET INFORMATION	ENTERED STUDY 301
5	999001520		PV	MALE	WHITE	NO POST-TREATMENT DOSE, PLATELET INFORMATION	
6	999001527		PV	FEMALE	WHITE	NO POST-TREATMENT DOSE, PLATELET INFORMATION	ENTERED STUDY 301

Source: Sponsor's submission page 10 0036, Vol. 3.

Attachment A.3

Sponsor's results of pairwise comparison of platelet counts between each two periods using last observation in each time period, ITT population, Studies #: 700-012, -014, and -999

Dependent Variable: PLAT1

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	25623564.88191040	4270594.14698508	42.18	0.0001
Error	549	55586223.81008590	101249.95229524		
Corrected Total	555	81209788.69199640			

R-Square	C.V.	Root MSE	PLAT1 Mean
0.315523	48.70362	318.19797657	653.33543165

Source	DF	Type I SS	Mean Square	F Value	Pr > F
WKS	6	25623564.88191040	4270594.14698508	42.18	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
WKS	6	25623564.88191040	4270594.14698508	42.18	0.0001

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
WEEK 4 VS BASELINE	1	6567674.66519330	6567674.66519330	64.87	0.0001
WEEK 12 VS BASELINE	1	11181156.68507760	11181156.68507760	110.43	0.0001
WEEK 24 VS BASELINE	1	13972144.77107200	13972144.77107200	138.00	0.0001
WEEK 48 VS BASELINE	1	13369418.78604270	13369418.78604270	132.04	0.0001
WEEK 104 VS BASELINE	1	12510799.33889260	12510799.33889260	123.56	0.0001
WEEK 156 VS BASELINE	1	8737997.18965516	8737997.18965516	86.30	0.0001
WEEK 12 VS WEEK 4	1	756424.41086504	756424.41086504	7.47	0.0065
WEEK 24 VS WEEK 4	1	2008162.27766214	2008162.27766214	19.83	0.0001
WEEK 48 VS WEEK 4	1	2140964.23630862	2140964.23630862	21.15	0.0001
WEEK 104 VS WEEK 4	1	2174729.67754265	2174729.67754265	21.48	0.0001
WEEK 156 VS WEEK 4	1	1577560.63963991	1577560.63963991	15.58	0.0001
WEEK 24 VS WEEK 12	1	340589.36282765	340589.36282765	3.36	0.0672
WEEK 48 VS WEEK 12	1	453541.91210332	453541.91210332	4.48	0.0348
WEEK 104 VS WEEK 12	1	534557.75064646	534557.75064646	5.28	0.0220
WEEK 156 VS WEEK 12	1	416899.54301413	416899.54301413	4.12	0 0429
WEEK 48 VS WEEK 24	1	13035.07785548	13035.07785548	0.13	0.7199
WEEK 104 VS WEEK 24	1	39888.13778814	39888.13778814	0.39	0.5305
WEEK 156 VS WEEK 24	1	41774.30512820	41774.30512820	0.41	0.5209
WEEK 104 VS WEEK 48	1	7723.46190716	7723.46190716	0.08	0.7825
WEEK 156 VS WEEK 48	1	12077.73838224	12077.73838224	0.12	0.7299
WEEK 156 VS WEEK 104	1	1145.63350560	1145.63350560	0.01	0.9153

Source: Sponsor's submission pages 10 0054, Vol. 3.

Attachment A.3 cont.

Sponsor's results of pairwise comparison of platelet counts between each two periods using average of observations in each time period, ITT population, Studies #: 700-012, -014, and -999)

Dependent Variable: PLAT1

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	25956390.41442210	4326065.06907036	50.75	0.0001
Error	549	46799817.28742380	85245.56882955		
Corrected Total	555	72756207.70184590			

R-Square	C.V.	Root MSE	PLAT1 Mean
0.356758	43.53509	291.96843807	670.65076240

Source	DF	Type I SS	Mean Square	F Value	Pr > F
WKS	6	25956390.41442200	4326065.06907035	50.75	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
WKS	6	25956390.41442200	4326065.06907035	50.75	0.0001

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
WEEK 4 VS BASELINE	1	4711206.04207978	4711206.04207978	55.27	0.0001
WEEK 12 VS BASELINE	1	9534835.81264717	9534835.81264717	111.85	0.0001
WEEK 24 VS BASELINE	1	13118027.17765700	13118027.17765700	153.89	0.0001
WEEK 48 VS BASELINE	1	12816988.72457930	12816988.72457930	150.35	0.0001
WEEK 104 VS BASELINE	1	13204743.36461710	13204743.36461710	154.90	0.0001
WEEK 156 VS BASELINE	1	9596270.97944105	9596270.97944105	112.57	0.0001
WEEK 12 VS WEEK 4	1	981810.93326687	981810.93326687	11.52	0.0007
WEEK 24 VS WEEK 4	1	2735131.61935723	2735131.61935723	32.09	0.0001
WEEK 48 VS WEEK 4	1	2959219.49292715	2959219.49292715	34.71	0.0001
WEEK 104 VS WEEK 4	1	3551076.64936942	3551076.64936942	41.66	0.0001
WEEK 156 VS WEEK 4	1	2743207.70339176	2743207.70339176	32.18	0.0001
WEEK 24 VS WEEK 12	1	494295.27969558	494295.27969558	5.80	0.0164
WEEK 48 VS WEEK 12	1	670866.22387556	670866.22387556	7.87	0.0052
WEEK 104 VS WEEK 12	1	1065905.95663375	1065905.95663375	12.50	0.0004
WEEK 156 VS WEEK 12	1	916253.08904909	916253.08904909	10.75	0.0011
WEEK 48 VS WEEK 24	1	21004.21756099	21004.21756099	0.25	0.6198
WEEK 104 VS WEEK 24	1	148815.72741708	148815.72741708	1.75	0.1870
WEEK 156 VS WEEK 24	1	176555.20953776	176555.20953776	2.07	0.1507
WEEK 104 VS WEEK 48	1	56978.74708789	56978.74708789	0.67	0.4140
WEEK 156 VS WEEK 48	1	87473.85396029	87473.85396029	1.03	0.3115
WEEK 156 VS WEEK 104	1	7971.20122602	7971.20122602	0.09	0.7599

Source: Sponsor's submission page 10 0055, Vol. 3.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20333	**Trade Name:**	AGRYLIN(ANAGRELIDE HYDROCHLORIDE)CAPSULE
Supplement Number:	2	**Generic Name:**	ANAGRELIDE HYDROCHLORIDE
Supplement Type:	SE1	**Dosage Form:**	Capsule; Oral
Regulatory Action:	AP	**Proposed Indication:**	Treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
____Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Status	ADEQUATE Labeling for ALL PEDIATRIC ages
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
12/11/98-The original NDA was approved 3/14/97 with the following Phase IV commitment: The firm submitted pediatric information on March 2, 1998.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

Signature

Date 12/16/98

APPEARS THIS WAY
ON ORIGINAL

Redacted 15

pages of trade

secret and/or

confidential

commercial

information

EXCLUSIVITY SUMMARY FOR NDA #: 20-333 SUPPL #: 002

Trade Name: Agrylin® Generic Name: anagrelide hydrochloride

Applicant Name: Roberts Laboratories Inc. HFD #: 180

Approval Date: December 16, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#: 20-333 Agrylin® (anagrelide hydrochloride) Capsules

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study # 700-012 "Anagrelide for Platelet Reduction in Subjects with ET."

Study # 700-014 "A Phase II Study of Anagrelide for the Treatment of Subjects with Thrombocythemia."

Study # 700-999 "Anagrelide for the Control of Thrombocythemia When Medically Indicated (Compassionate Use Program)."

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /X/	NO /___/
Investigation #2	YES /X/	NO /___/
Investigation #3	YES /X/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 20-333	Study # 700-012
NDA # 20-333	Study # 700-014
NDA # 20-333	Study # 700-999

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /X/	NO /___/
Investigation #2	YES /X/	NO /___/
Investigation #3	YES /X/	NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NDA # 20-333	Study # 700-012
NDA # 20-333	Study # 700-014
NDA # 20-333	Study # 700-999

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

/S/ 12/11/98
Signature Date
Title: Regulatory Health Project Manager

/S/ 12-11-98
Signature of Office/ Date
Division Director

cc: Original NDA 20-333/S-002
HFD-180/Div. File
HFD-180/DuBeau
HFD-93 Mary Ann Holovac
r/d Init: Talarico 12/1/98
JD/December 1, 1998 (drafted)

APPEARS THIS WAY
ON ORIGINAL

ROBERTS
PHARMACEUTICAL
CORPORATION

CERTIFICATION OF LEGALITY

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, I hereby certify that Roberts Laboratories Inc. did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 in connection with this clinical submission.

Drew Karlan

Drew Karlan, Vice President, Worldwide Regulatory Affairs 12/30/97 **Date**

APPEARS THIS WAY
ON ORIGINAL

MERIDIAN CENTER II, FOUR INDUSTRIAL WAY WEST, EATONTOWN, NEW JERSEY 07724-2274 • TEL. (732) 389-1182 / FAX (732) 389-1014

PATENT INFORMATION

Agrelin® (anagrelide hydrochloride) Capsules
New Drug Application For Human Use

1. Active Ingredient:	Anagrelide Hydrochloride
2. Strengths:	0.5 mg/capsule 1.0 mg/capsule
3. Trade Name:	Agrelin®
4. Dosage Form, Route of Administration	Capsules, Oral
5. Applicant and Firm Name:	Roberts Laboratories Inc., a subsidiary of Roberts Pharmaceutical Corporation
6. NDA Number Assigned:	20-333
7. Approval Date:	Submitted for review on December 30, 1995
8. Exclusivity - Date first ANDA could be approved and length of exclusivity period:	To be determined pending FDA review and approval.
9. Orphan Drug Product Application Number Assigned:	87-208

10. Applicable patent numbers and expiration date of each:

Patent Number	Type of Patent	Patent* Owner	Expiration Date
3,932,407	Composition of Matter	BMS	Expired 01/13/93
4,146,718	Composition of Matter	BMS	03/27/96
4,208,521	Process	BMS	06/17/97
4,357,330	Composition of Matter	BMS	11/02/99
Re.31,617	Composition of Matter	BMS	6/26/2001

*Bristol-Myers Squibb

United States Patent [19]

Beverung, Jr. et al.

[11] **3,932,407**

[45] **Jan. 13, 1976**

[54] **OPTIONALLY SUBSTITUTED 1,2,3,5-TETRAHYDROIMIDEZO(2,1-B)-QUINAZOLIN-2-ONES AND 6(H)-1,2,3,4-TETRAHYDROPYIMIDO(2,1-B)QUINAZOLIN-2-ONES**

[75] Inventors: **Warren Neil Beverung, Jr., Minoa; Anthony Partyka, Liverpool, both of N.Y.**

[73] Assignee: **Bristol-Myers Company, New York, N.Y.**

[22] Filed: **Nov. 6, 1974**

[21] Appl. No.: **521,306**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 416,891, Nov. 19, 1973, abandoned, which is a continuation-in-part of Ser. No. 396,638, Sept. 12, 1973, abandoned, which is a continuation-in-part of Ser. No. 291,450, Sept. 22, 1972, abandoned, which is a continuation-in-part of Ser. No. 223,723, Feb. 4, 1972, abandoned.

[52] U.S. Cl. ..... 260/256.4 F; 260/251 Q; 260/251 QB; 260/309.2; 260/309.6; 424/251

[51] Int. Cl.[2] C07D 239/84

[58] Field of Search ..... 260/256.4 F

[56] **References Cited**

UNITED STATES PATENTS

3,048,587	...62	Oroshnik	260/256.4 F
3,257,401	6/1966	Wagner	260/256.4
3,598,823	8/1971	Hardtmann	260/256.4 F
3,600,390	8/1971	Sherlock	260/256.4
3,621,025	11/1971	Yu-Wen Jen	260/256.4 F
3,745,216	7/1973	Jen et al.	260/256.4 F
3,790,576	2/1974	De Wald	260/286 R
3,833,588	9/1974	Hardtmann	260/256.4 F
3,859,289	1/1975	Hardtmann	260/256.4 F

FOREIGN PATENTS OR APPLICATIONS

2,025,248	1970	Germany	260/256.4 F

OTHER PUBLICATIONS

Cox et al.; J. Chem. Soc., pp. 2134–2136, (1970).
Beverung et al.; J. Med. Chem., 18, pp. 224–225, (1975).
Loev et al.; Experientia, 27, p. 875, (1971).
Grout et al.; J. Chem. Soc., p. 3551, (1960).
Lempert et al.; Experientia, 18, p. 401, (1962).
Hardtmann; Chem. Abstr., 74, 42373g (1971).
Jen et al.; J. Med. Chem., 15, pp. 727–731, (1972).
North et al.; J. Het. Chem., pp. 655–662, (1969).
Simonov et al.; Pharm. Chem. Jour., pp. 4–6, (1969).
Doleschall et al.; Acta. Chemica Acadamiae Scientiarium Hungaricae, 45, pp. 357–368, (1965).

Primary Examiner—Nicholas S. Rizzo
Assistant Examiner—Mary Vaughn
Attorney, Agent, or Firm—Robert E. Havranek

[57] **ABSTRACT**

Optionally substituted 1,2,3,5-tetrahydroimidazo[2,1-b]-quinazolin-2-ones and 6-[H]-1,2,3,4-tetrahydropyrimido[2,1-b]-quinazolin-2-ones or the pharmaceutically acceptable salts thereof are compounds useful as blood platelet anti-aggregative and/or antihypertensive and/or bronchodilator agents in mammals, including humans.

19 Claims, No Drawings

PATENT CERTIFICATION [21 CFR 314.50(h)]

Agrelin® (anagrelide hydrochloride) Capsules
New Drug Application For Human Use

In the opinion and to the best knowledge of Roberts Laboratories Inc., the undersigned declares that the five patents listed in Item 10 under PATENT INFORMATION are the only licensed patents that are applicable for this new drug application.

Anthony Rascio, Esq.
Vice President/General Counsel
Roberts Pharmaceutical Corporation

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-333/S002

CORRESPONDENCE

MEMORANDUM OF TELECON

DATE: June 15, 1998

APPLICATION NUMBER: NDA 20-333/S-002; Agrylin™ (anagrelide hydrochloride) Capsules

BETWEEN:

Name: Dr. M. Petrone; Vice President, Medical Affairs
Ms. M. Mahoney; Program Manager
Dr. S. Salem; Statistician
Dr. R. Raffa; Associate Director, Regulatory Affairs

Phone: (732) 389-1182

Representing: Roberts Laboratories, Inc.

AND

Name: Dr. M. Al-Osh; Statistician
Ms. J. DuBeau; Regulatory Health Project Manager

Representing: Division of Biometrics III (HFD-720) and Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

SUBJECT: Clarification of Submitted Statistical Information

BACKGROUND:

Roberts Laboratories, Inc. submitted an efficacy supplement for Agrylin™ (anagrelide hydrochloride) Capsules on December 30, 1997, with the proposed new indication of treatment of patients with [redacted] The drug product is currently approved for the following indication: treatment of patients with Essential Thrombocythemia to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms. Dr. Al-Osh requested that the firm be contacted to clarify statistical information contained in this application.

TODAY'S PHONE CALL:

The firm called Dr. Al-Osh and he began the conversation by stating that there are four issues that need to be discussed.

ISSUE 1:

The firm defines subjects as "responders" if the platelet count decreased to ≤ 600,000/μL or by at least 50% from the baseline value. In response to a question from Dr. Al-Osh, the firm stated that if the platelet count was above 1,000,000/μL at baseline, a "responder" would be a subject whose platelet count decreased by at least 50%. If the platelet count was below 1,000,000/μL at baseline, a "responder" would be a subject whose platelet count decreased to ≤ 600,000/μL. Five subjects had a baseline platelet count of ≤ 600,000/μL, and thus, were not counted in the efficacy analysis. Dr. Al-Osh requested that the firm submit these definitions in writing to the supplement.

ISSUE 2:

The data submitted on diskette listed platelet counts for each patient at intervals of 4 weeks, 12 weeks, 24 weeks, 48 weeks, 2 years, 3 years, and 4 years, when available. Dr. Al-Osh requested that the firm submit weekly platelet counts per patient, if available, as efficacy was defined in terms of reduction of platelet counts for at least 4 weeks. In the data listing, one category at the top of this list ("RESP") had letters such as "N", "E", and "U" under it. In response to Dr. Al-Osh's request to define these letters, the firm referred him to Appendix 1 of the supplement. In addition, the firm stated that 18 patients did not have platelet counts drawn after 4 weeks, and thus, were not counted in the efficacy analysis but were included in the safety analysis.

ISSUE 3:

Dr. Al-Osh informed the firm that the means in the table entitled "Number of Days to Complete Response and Partial Response" (page 10 0018) and in table 5.4.1 (page 10 0057) are the same, however, the confidence intervals are different. The firm stated that they will look at this discrepancy and explain in writing why they are different. Dr. Al-Osh requested that the firm also give the median, as opposed to the geometric mean, of the number of days until response. In addition, he stated that he wanted this information separated by study and for the total population.

ISSUE 4:

Regarding platelet counts, Table 5.3.1 includes the words "last" and "average" (page 10 0051) which are not defined. According to the firm, "last" is defined as the last platelet count at a specific visit, and "average"; as the average platelet count since the preceding visit. Dr. Al-Osh requested that the firm submit these definitions in writing to the supplement.

The call was then concluded.

/S/ 6/24/98
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-333/S-002
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
HFD-720/Al-Osh
r/d Init: Al-Osh 6/22/98
JD/June 19, 1998 (drafted)

TELECON

/S/

MEMORANDUM OF TELECON

DATE: February 19, 1998

APPLICATION NUMBER: NDA 20-333/S-002; Agrylin™ (anagrelide hydrochloride) Capsules

BETWEEN:

Name: Mr. Drew Karlan
Phone: (732) 389-1182
Representing: Roberts Laboratories, Inc.

AND

Name: Ms. Julieann DuBeau, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Outcome of the 45-day filing meeting

BACKGROUND:

Roberts Laboratories, Inc. submitted an efficacy supplement for Agrylin™ (anagrelide hydrochloride) Capsules on December 30, 1997, with the proposed new indication of treatment of patients with [redacted] The drug product is currently approved for the following indication: treatment of patients with Essential Thrombocythemia to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms. The 45-day filing meeting was held today.

TODAY'S PHONE CALL:

Mr. Karlan was called and notified that the application has been filed. He was notified that this application is being reviewed for the proposed new indication of treatment of patients with [redacted] The firm must submit another efficacy supplement if they wish to pursue the following indication: treatment of patients with thrombocytosis, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis to ameliorate associated symptoms. Dr. Karlan stated that he understood.

Mr. Karlan was also requested to provide the following information: a statement about the foreign marketing history of the drug and foreign labeling, if appropriate; written documentation regarding drug use in the pediatric population; and proposed unannotated labeling on diskette in Word Perfect 6.1. Mr. Karlan stated that he will provide the above information except for the diskette. He stated that the labeling diskette that was submitted with the application, in Word Perfect 5.1, easily converts to Word Perfect 6.1. The diskette request was then rescinded and the call concluded.

/S/ 3/2/98

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-333/S-002
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
JD/February 20, 1998 (drafted)

TELECON

APPEARS THIS WAY
ON ORIGINAL

17 **Page(s) Redacted**

Draft

Labeling

NDA 20-333/S-002

Roberts Laboratories, Inc.
Attention: Mr. Drew Karlan
4 Industrial Way West
Eatontown, NJ 07724-2274

JAN 15 1998

Dear Mr. Karlan:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Agrylin™ (anagrelide hydrochloride) Capsules

NDA Number: NDA 20-333

Supplement Number: S-002

Therapeutic Classification: Standard

Date of Supplement: December 30, 1997

Date of Receipt: January 2, 1998

This supplement provides for the addition of the following indication: treatment of patients with

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 3, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-333/S-002
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-180/Talarico
HFD-180/Sizer
DISTRICT OFFICE
JD/January 14, 1998 (drafted)

1/15/98

SUPPLEMENT ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: December 14, 1998

FROM: Lilia Talarico, M.D.; Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) 12-14-98

SUBJECT: Correction to December 11, 1998, Medical Officer Review for Agrylin™ (anagrelide hydrochloride) Capsules (NDA 20-333/S-002)

TO: NDA 20-333

On the first page of the December 11, 1998, Medical Officer review for Agrylin™ (anagrelide hydrochloride) Capsules, the "Indications" section states the following: [redacted] The "Indications" section should read as follows: [redacted]

cc:
NDA 20-333/S-002
HFD-180/Div. file
HFD-180/Talarico
HFD-180/DuBeau
HFD-180/Choudary
HFD-180/Duffy
JD/December 14, 1998 (drafted)

APPEARS THIS WAY
ON ORIGINAL

FAX COVER SHEET

TO: Julieann DuBeau, HFD-180 **DATE:** December 16, 1998

FAX: 301-443-9285

FROM: Richard Raffa

SUBJECT: NDA 20,333/S-002 Agrylin Capsules

 # OF PAGES INCLUDING THIS COVER SHEET: 1

MESSAGE

We (i.e., Roberts Laboratories, Inc.) have reviewed the final draft of the Agrylin package insert for thrombocythemia that was faxed to me on December 16, 1998. This fax is to inform you that we are in total agreement with the changes that are incorporated into this draft with the following exceptions:

Under **CLINICAL STUDIES**, the last sentence in the first paragraph should read:

Patients with OMPD included 87 patients who had Myeloid Metaplasia with Myelofibrosis (MMM), and 9 patients who had unknown myeloproliferative disorders.

We understand that the new Agrylin labeling containing these changes will be attached to your Action Letter or Approval Letter regarding the agency's review of Supplement S-002. We will begin to prepare Final Printed Labeling for submission to FDA in response to either the Action Letter or Approval Letter.

Sincerely,

Richard L Raffa

Richard Raffa
Associate Director
Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

RR/mll

Roberts Pharmaceutical Corporation, 4 Industrial Way West, Eatontown, NJ 07724-2274
Telephone: 732-676-1200, Fax: 732-676-1310

DuBeau

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 19, 1998
Time: 10:00 AM - 11:00 AM
Location: Conference room 6B-45, Parklawn Building

Application: NDA 20-333/SE1-002
Agrylin™ (anagrelide hydrochloride) Capsules

Type of Meeting: 45-Day Filing Meeting

Meeting Chair: Dr. Lilia Talarico

Meeting Recorder: Ms. Julieann DuBeau

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. L. Talarico; Division Director
Dr. K. Sizer; Medical Officer
Ms. J. DuBeau; Regulatory Health Project Manager

Division of Biometrics III (HFD-720)

Dr. A. Sankoh; Statistical Team Leader
Dr. M. Al-Osh; Statistician

Division of Scientific Investigations (HFD-340)

Dr. R. Young; Medical Officer
Dr. K. Malek; Medical Officer

Background:

On August 20, 1993, NDA 20-333 was submitted with the following proposed indications: treatment of [redacted] but was subsequently refused for filing on October 8, 1993. In a March 29, 1995, meeting with firm, the Division Director suggested that after the multidisciplinary filing issues were resolved, the firm resubmit the NDA concentrating on the Essential Thrombocythemia indication with expansion of the indication by supplemental application following NDA approval. On January 12, 1996, the firm resubmitted NDA 20-333, which was subsequently approved on March 14, 1997, for the treatment of patients with Essential Thrombocythemia to reduce the elevated platelet count and the risk of thrombosis and

to ameliorate associated symptoms. Utilizing the Division Director's advice provided on March 29, 1995, the firm has submitted this efficacy supplement to expand the indication to include PV.

Meeting Objective:

To determine the fileability of this application.

Discussion Points:

I. Administrative

A. Filing Issues: None

B. Information Requests:

1. A statement about the foreign marketing history of the drug and foreign labeling, if appropriate.

2. Written documentation regarding drug use in the pediatric population.

3. Proposed unannotated labeling on diskette in Word Perfect 6.1.

4. The following were deemed not necessary by the appropriate reviewers to be requested of the firm to provide:

a. A revised overall index, as well as for each technical section, to include page number ranges.

b. Revised CRTs by individual patient data listing.

c. Table of all controlled clinical studies.

C. Other:

The firm provided two proposed package inserts, each with its own indication. One package insert states the indication as follows:

A second package insert states the indication as follows: treatment of patients with thrombocytosis, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated

symptoms [redacted] The firm should be notified that they may submit an additional efficacy supplement with supporting data to expand the proposed indication to treatment of thrombocythemia secondary to myeloproliferative disorders.

II. Clinical

A. Filing Issues: None

B. Information Requests: None

III. Statistical

A. Filing Issues: None

B. Information Requests: None

IV. Division of Scientific Investigations (DSI)

A. Filing Issues: None

B. Information Requests: None. It was determined that no clinical sites need to be audited for this application because the major investigational sites were already audited at the time of the original NDA submission.

Conclusions:

It was decided to file the application. The administrative requests will be forwarded to the firm via telephone call. The project manager will also convey the information under "other", under the Administrative heading, as discussed above. A team planning meeting will be scheduled in July 1998. The PDUFA User-Fee goal date for this application is January 2, 1999, with division level signature. The individual reviewer due date for this application is October 30, 1998.

/S/ 3/2/98
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-333/S-002
HFD-180/Div. Files

HFD-180/CSO/DuBeau
HFD-180/Talarico
r/d Init: Talarico 2/23/98
JD/February 19, 1998 (drafted)

MEETING MINUTES