CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022571Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 29, 2010
From	Susan J. Walker, M.D.
Subject	Decisional Memorandum
NDA #	22-571
Applicant	Shionogi Pharma, Inc.
Date of Submission	September 26, 2009
PDUFA Goal Date	July 28, 2010
Proprietary Name / Established (USAN) names	Cuvposa/Glycopyrrolate
Dosage forms / Strength	1mg/5mL
Proposed Indication(s)	Severe drooling in pediatric patients aged 3-16 with Cerebral Palsy, (b) (4) or other neurological problems associated with problem drooling
Action:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Fred Hyman, D.D.S., M.P.H.
Statistical Review	Kathy Fritsch, Ph.D.
Pharmacology Toxicology Review	Norm See, Ph.D.
CMC Review/OBP Review	Yichun Sun, Ph.D.
Clinical Pharmacology Review	Dennis Bashaw, Pharm.D. Jee Eun Lee, Ph.D. (Pharmacometric Reviewer)
DDMAC	Andy Haffer, Pharm.D.
DSI	Not Applicable
OSE/DMEPA	Melina Griffis, R.Ph.
OSE/DEPI	James Williams, Ph.D.; Simone Pinheiro, Ph.D., M.P.H., Msc.
OSE/DRISK	Sharon Mills, B.S.N., R.N., C.C.R.P.
Other	Namita Kothary, Pharm.D., OSE/DPV I Elektra Papadopoulos, M.D., SEALD Suchitra Balakrishnan, Ph.D., DCRP/QT-IRT

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

This application provides for the use of gylcopyrrolate, a synthetic anticholinergic agent, a quarternary ammonium salt, in a liquid formulation for the treatment of excessive drooling in patients with neurologic deficits. Glycopyrrolate has been approved in the U.S. since 1961 as Robinul and Robinul Forte tablets for the treatment of peptic ulcers (NDA 12-827) and has been used off-label for the treatment of pediatric patients with sialorrhea (an unintentional loss of saliva from the mouth). This application provides information to support the safety and efficacy of gylcopyrrolate in this new dosage form-oral solution.

All disciplines recommended approval of this application based upon review of the information submitted by the sponsor. This review incorporates my comments and comments from the Cross Discipline Team Leader, Dr. Jake Kelsey and additional information from the primary review team.

2. Background

Glycopyrrolate has a well established anticholinergic mechanism of action, with reduction in salivary production among the pharmacologic effects. An oral solution formulation was developed by the sponsor for use in pediatric patients with "pathologic" drooling. This condition is normal in infants but usually stops by 15 to 18 months of age. Pathologic drooling is a problem for developmentally disabled individuals, particularly those with cerebral palsy or other neurologic conditions. In the majority of these individuals, drooling is caused by neuromuscular dysfunction, hypersecretion, sensory dysfunction or motor dysfunction. In children with cerebral palsy and other neuromuscular conditions, drooling is primarily due to oral motor dysfunction. Estimates of prevalence of moderate to severe sialorrhea in the developmentally disabled population range from 10% to 37%.

Robinul tablets have been used off-label to control excessive drooling in these patients, with caregivers crushing the tablets and providing the drug substance to patients in food. A limitation of this use, beyond the lack of an approved indication, is that current oral dosage forms are tablets, thus there is limited dosing flexibility. In 2001 an FDA Advisory Committee (Pediatric Subcommittee of the Anti-infective Drugs Advisory Committee) discussed alternatives/ options for development of products to control drooling in patients with neurologic impairment. The committee acknowledged that current tablet formulations were being used off label (crushed and administered) and advised that there was a need for development of formulations for pediatric use to ensure safety and consistency of administration.

The oral solution that is the subject of this application was developed to address dosing flexibility and to provide an approved product for this indication. During the development program the applicant obtained agreements with FDA regarding the preclinical and clinical

information that would be sufficient for their program, which addresses an unmet need for a formulation for this population. The sponsor obtained Orphan Product Designation in 2006.

The sponsor has completed three clinical studies with glycopyrrolate for the proposed indication. Two were efficacy and safety studies, and one was a pharmacokinetic study (FH-00-02). The pivotal efficacy trial (FH-00-01) and an open-label, long-term safety study (SC-GLYCO-06-01) form the basis for the efficacy and safety evaluation of glycopyrrolate oral solution. The mechanism of action of anticholinergics in reducing drooling is well understood and the applicant's application provides adequate evidence of safety and efficacy.

This is the first review cycle for this NDA and there is no foreign marketing experience for this formulation of glycopyrrolate.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

- General product quality considerations

  This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. The labeling and carton/container/closure systems are adequate.

- Facilities review/inspection

  On July 12th, 2010 the Office of Compliance gave an overall "acceptable" recommendation for all facilities involved in the manufacture and testing of the drug substance and drug product.

- Other notable issues (resolved or outstanding)

  There are no other outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

During the development program the applicant obtained agreement from the agency regarding the post-marketing provision of some preclinical information (Guidance Meeting August 2001) and the post-marketing requirements are detailed below.

- General nonclinical pharmacology/toxicology considerations

Glycopyrrolate inhibits parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine at the muscarinic receptors. These peripheral receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia. By this mechanism, glycopyrrolate diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions. The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier. The anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours, following oral administration.

Like other anticholinergics, glycopyrrolate has gastrointestinal, genitourinary, cardiovascular, respiratory, and ophthalmic effects. Glycopyrrolate does not cross the blood-brain barrier, so drowsiness is not a common adverse event. Specifically, glycopyrrolate is known to cause xerostomia, diminished gastrointestinal motility, decreased perspiration, increased body temperature, urinary retention, pupil dilation, loss of focusing accommodation, and increased heart rate. These effects of antimuscarinic drugs make them useful in treating certain conditions such as gastric ulcers, excess perspiration, overactive bladder, and for pupil dilation during ophthalmologic examination. The anticholinergic activity of glycopyrrolate on salivary glands makes it useful for treatment of excessive drooling, the indication for this submission.

Glycopyrrolate is considered to be a nonselective antagonist of muscarinic cholinergic receptors. The binding activity of glycopyrrolate at specific receptor subtypes has apparently not been well characterized. Glycopyrrolate has been demonstrated to inhibit the actions of cholinergic agonists in both in vivo and in vitro models (e.g., inhibition of acetylcholine-induced contractions of isolated guinea pig ileum; inhibition of methacholine-stimulated salivary secretion in anesthetized dogs). The primary pharmacological effect of glycopyrrolate, with respect to NDA 22-571, is inhibition of peripheral muscarinic cholinergic receptors that are associated with salivary glands, resulting in reduced salivation.

Pregnancy Category C:

Carcinogenicity:

- Long-term animal studies have not been performed to evaluate the carcinogenic potential of glycopyrrolate.

- Glycopyrrolate did not elicit any genotoxic effects in the Ames mutagenicity assay, the human lymphocyte chromosome aberration assay, or the rat micronucleus assay.

- Carcinogenicity testing is to be conducted post-marketing under Post Marketing Requirements (PMR).

Reproductive toxicology:

- Glycopyrrolate has not been evaluated for potential to impair fertility.

- Fertility and general reproduction toxicity study of glycopyrrolate in rats is to be studied post-marketing under Post Marketing Requirements (PMR).

The active moiety, glyccopyrolate, has approved in the U.S. since 1961, and has over 40 years of marketing history. During the development of this product, it was agreed that the applicant would provide these studies in the post-approval period:

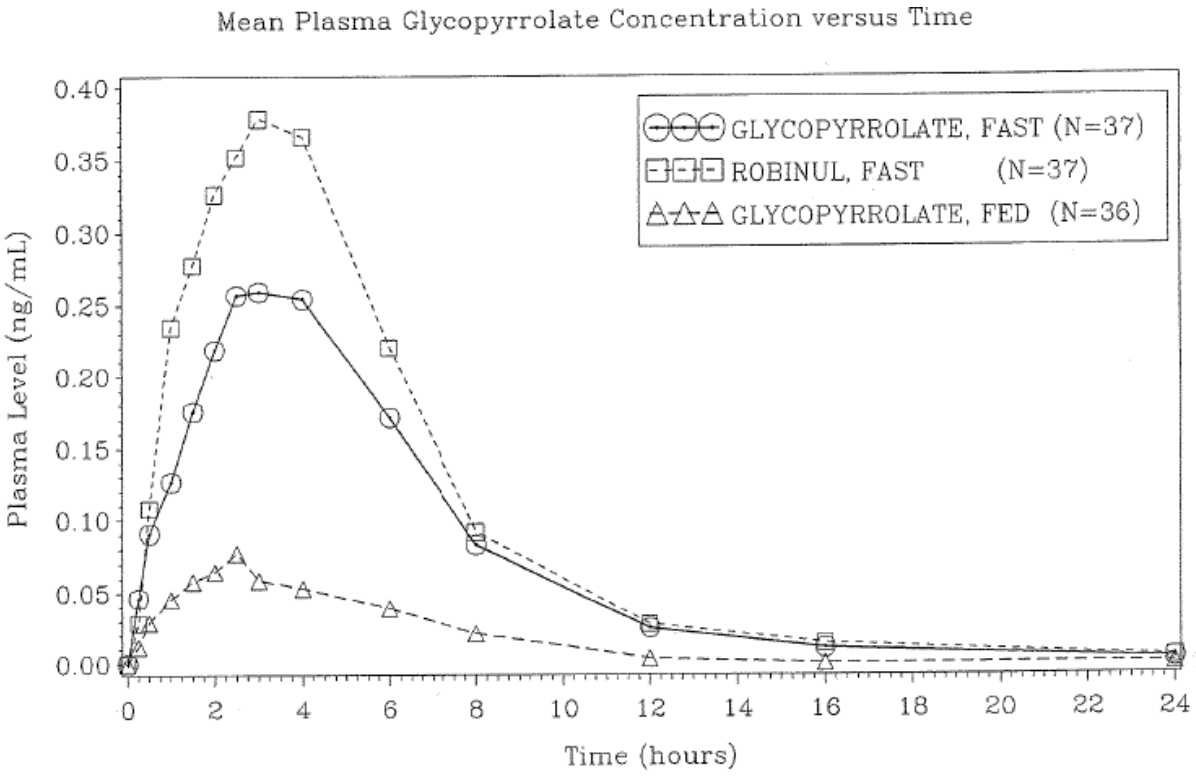
1. Oral (gavage) fertility and general reproduction toxicity study of glycopyrrolate in rats.
2. Oral (gavage) developmental toxicity study of glycopyrrolate in rats.
3. Oral (stomach tube) developmental toxicity study of glycopyrrolate in rabbits.
4. Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of glycopyrrolate in rats, including a postnatal behavioral/function evaluation.
5. A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in mice.
6. A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in rats.

5. Clinical Pharmacology/Biopharmaceutics

Pharmacokinetic evaluations include a bioavailability and food effect study (FH-00-02) and a population PK trial (performed as part of SCGLYCO-06-01). The results the PK trial (FH-00-02) demonstrated that the oral solution is not bioequivalent to the approved tablets. The oral solution was demonstrated to be 26% less bioavailable (AUC) than the marketed tablets. When given with a high fat diet the oral bioavailability of the solution declined in adult subjects by approximately 75%. Only limited population PK data was collected in study SC-GLYCO-06-01, the results of which are in general agreement with the healthy adult data.

Study FH-00-02-Bioavailability and Food Effect

This study was an open-label, randomized, single-dose, three-treatment, three-period crossover study designed to compare the bioavailability of the test formulation (glycopyrrolate oral solution) to the marketed tablet product (Robinul®) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects. The data was remarkable for the lower bioavailability of the oral solution. No explanation or hypothesis was put forward by the sponsor to explain these differences.



Pharmacokinetics:

Arithmetic mean (± SD) pharmacokinetic parameters for glycopyrrolate oral solution (2 mg), fasting and fed

	Cmax ng/mL (n)	Tmax Hours (n)	AUC_{0-T} ng-hr/mL (n)	$AUC_{0-\infty}$ ng-hr/mL (n)	T½ Hours (n)
Glycopyrrolate Oral Solution, Fasting (10 ml; 1 mg/5ml)	0.318 ± 0.190 (n=37)	3.10 ± 1.08 (n=37)	1.74 ± 1.07 (n=37)	1.81 ± 1.09 (n=37)	3.0 ± 1.2 (n=37)
Glycopyrrolate Oral Solution, Fed (10 ml; 1 mg/5ml)	0.084 ± 0.081 (n=36)	2.60 ± 1.12 (n=36)	0.38 ±0.14 (n=36)	0.46 ± 0.13 (n=35)	3.2 ± 1.1 (n=35)
Tablet Glycopyrrolate, Fasting (2 mg; 2 x 1 mg tablet, Robinul®)	0.406 ± 0.197 (n=37)	3.15 ± 0.863 (n=37)	2.34 ± 1.03 (n=36)	2.46 ± 1.15 (n=36)	3.3 ± 1.6 (n=36)

The table demonstrates the apparent decreased bioavailability of the oral solution relative to the oral tablet, with an observed difference of 26% between the mean AUC 0-24hrs. Potential explanations discussed by the review team include unique properties of the tablets formulation and perhaps some unique interaction between the GI tract and the oral solution resulting in a slower absorptive phase. The solution is also more bioavailable in the fasted state. Once an individual dose is determined, the administration relative to meals should be consistent to

avoid loss of effect and the potential to increase the oral dose due to a perception of loss of effect-when in fact it is loss of bioavailability.

Population PK Trial (performed as part of SC-GLYCO-06-01)

The following conclusions were obtained from the analysis:

- The bioavailability in children was found to be between the bioavailability in adults under fed (high-fat meal) and fasted conditions.
- Population pharmacokinetic analysis supports selection of initial doses based on body weight. Then clinical signs can be used to titrate dosing for individual subjects as performed in the study.

I concur with the biopharmaceutics conclusion that population pharmacokinetic analysis supports selection of initial doses based on body weight. Clinical signs can be used to titrate dosing for individual subjects as was performed in the study.

Drug-drug interactions:

The clinical and biopharmaceutics reviewers have addressed drug-drug interactions and these will be included in labeling. Drug interactions for this drug and other anticholinergics have been well characterized in the published literature. Interactions cited specifically for glycopyrrolate include 1) wax matrix solid oral potassium dosage forms and 2) acetaminophen. Glycopyrrolate may facilitate gastric mucosal damage after ingestion of wax-matrix potassium chloride tablets, and glycopyrrolate may decrease gastric emptying and delay the absorption of acetaminophen. (Hansten and Horne's Drug Interactions, 2009; Tatro DS, Drug Interaction Facts, 2010)

Other drug interactions with anticholinergics in general include; acetaminophen, amatandine, atenolol, cefoprozil, cimetadine, digoxin, haloperidol, levodopa, metformin, nitrofurantoin, solid oral dosage forms of potassium chloride, and thiazide diuretics. (Tatro DS, Drug Interaction Facts, 2010)

Thorough QT study or other QT assessment:

The Interdisciplinary Review Team for QT Studies Consultation, (Division of Cardio-Renal Products (DCRP)), reviewed the sponsor's QT assessment for glycopyrrolate and evaluated effects of glycopyrrolate related to tachycardia/tacharrhythmias.

The DCRP reviewer evaluated the sponsor's data as well as conducted an MGPS data mining analysis of the AERS data base for AE's related to QT prolongation and other cardiac arrhythmias with glycopyrrolate. The consultation concluded that there were no significant effects on atrio-ventricular conduction, as measured by the PR interval, or depolarization, as measured by the QRS duration. The QTcF data did not demonstrate evidence of any clinically relevant changes in QTcF duration or waveform morphology. There was no imbalance in specific or nonspecific outliers. The reviewer acknowledged that there are limitations in both studies, including sparse ECG collection and absence of time matched PK sampling.

However, the reviewer's conclusion is that "data suggest that large effects on the QT or other ECG intervals by glycopyrrolate are unlikely." The reviewer further commented that with regards to cardiovascular issues, the sponsor's proposed labeling is reasonable.

The population pharmacokinetics data revealed that plasma levels for glycopyrrolate solution are 25% lower than that of the currently marketed tablet; therefore, a TQT study for this application is not required.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Glycopyrrolate oral solution has demonstrated efficacy versus placebo in the treatment of pathologic drooling in patients with cerebral palsy or other neurologic conditions. Glycopyrrolate was awarded orphan drug designation for the "treatment of pathologic (chronic moderate to severe) drooling in pediatric patients" in 2006. The applicant conducted a placebo-controlled study in 38 subjects and a single-arm, open-label study in 137 subjects

The studies conducted under the IND are detailed below.

Summary of Clinical Trials Conducted under the IND

Study Title	An Open, Randomized, Three-Way Crossover Trial to Compare the Relative Bioavailability of Glycopyrrolate Liquid 2 mg (1 mg / 5 mL) and Robinul Tablets 2 mg (1 mg x 2), and to Determine the Effect of Food on the Bioavailability of Glycopyrrolate Liquid 2 mg (1 mg /5 mL)	A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Oral Glycopyrrolate Liquid (1 mg per 5 mL) for the Management of Problem Drooling Associated with Cerebral Palsy or other Neurologic Conditions in Children	A Six-Month, Multi-Center, Open-Label Study to Assess the Safety and Efficacy of Oral Glycopyrrolate Liquid for the Treatment of Pathologic (Chronic Moderate to Severe) Drooling in Pediatric Patients 3 to 18 Years of Age with Cerebral Palsy or other Neurologic Conditions
Protocol Number	Study FH-00-02	Study FH-00-01	Study Sc-GLYCO-06-01
Phase	1	3	3
Indication	Pharmacokinetic Effect of Food Study	Problem drooling/sialorrhea	Problem drooling/sialorrhea
Type of study	Open label 3-arm cross-over single dose	Randomized, double-blind, placebo-controlled	Open-label

	pharmacokinetics		
Number of patients	36	38	137
Population	Healthy adults 18 -43 years of age	Patients 3 to 16 years old with chronic, moderate to severe drooling associated with cerebral palsy or other neurologic conditions	Patients 3 to 18 years old with chronic, moderate to severe drooling associated with cerebral palsy or other neurologic conditions
Treatment period	36 hours	8 weeks	24 weeks
Scheduled visits during treatment	Day 1, Day 8 and Day 15. Each subject using the three dosing regimens as given below, one at each visit.	Day 1, Week 2, Week 4, Week 6, Week 8	Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24
Treatment groups	1. Glycopyrrolate liquid fasting 2. Glycopyrrolate liquid fed 3. Glycopyrrolate tablets fasting	Glycopyrrolate oral solution (1 mg/5 mL) TID or placebo TID	Glycopyrrolate oral solution (1 mg/5 mL) TID
Dose levels	Single dose of 2 mg glycopyrrolate	0.02mg/kg, 0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.1 mg/kg	0.02mg/kg, 0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.1 mg/kg
Study Period	October 2001 – February 2002	November 2002 – April 2007	April 2007-May 2008
Sites/Countries	1 site, Baltimore, MD	10 sites in US	29 sites in US

No efficacy data was collected in the pharmacokinetic study, and this is described previously.

The applicant conducted a randomized, placebo-controlled 8-week study (FH-00-01) in 38 subjects and an open-label, single-arm 24-week study (Sc-GLYCO-06-01) in 137 subjects. Twelve subjects participated in both studies. Subjects were 3 to 23 years of age and had chronic moderate to severe pathologic drooling due to cerebral palsy or other neurological conditions. The majority of subjects were age 3 to 16 (36/38 or 95% in Study FH-00-01 and 120/137 or 88% in Study Sc-GLYCO-06-01). Study FH-00-01 originally had no upper age limit for enrollment, but was amended during the study to have a maximum age limit of 16 years. Study Sc-GLYCO-06-01 had an upper age limit of 18 years. Both studies were conducted in the United States.

Studies were similar in inclusion/exclusion criteria, study procedures, safety, and efficacy evaluations. Subjects initiated treatment at a dose of 0.02 mg/kg three times per day and were titrated over a 4-week period to a maximum dose of 0.1 mg/kg (but no more than 3 mg) three times per day. Parents and caregivers recorded assessments on the Modified Teacher's Drooling Scale (mTDS) every two weeks (in FH-00-01) or every 4 weeks (in Sc-GLYCO-06-01). On each mTDS assessment day, parents and caregivers recorded the mTDS assessments in the early morning (pre-dose) and 2 hours after each dose (mid-morning, afternoon, and evening). The primary efficacy endpoint was based on the change from baseline in the subject's mean mTDS. A responder was defined as having at least a 3-point improvement on the mean mTDS.

Primary endpoint:

The primary outcome measure was the proportion of patients who had a change of three levels on the modified Teacher's Drooling Scale (mTDS) (Responders) from baseline to week 8 (Responders). Participants in the advisory committee meeting in 2001 recommended use of this scale to demonstrate efficacy, based primarily upon its history of use in research on drooling in CP patients. At a regulatory guidance meeting with the sponsor on August 8, 2001, the division confirmed that this endpoint would be acceptable.

Study FH-00-01

Study FH-00-01 treated 38 subjects age 3 to 23 with either glycopyrrolate or placebo for 8 weeks. Doses of glycopyrrolate were titrated over a 4-week period from a starting dose of 0.02 mg/kg three times per day to a maximum dose of the lesser of 0.1 mg/kg or 3 mg three times per day. Parents or caregivers assessed drooling levels using the 9-point Modified Teacher's Drooling Scale (mTDS) where scores ranged from 1 = 'Dry: never drools' to 9 = 'Profuse: clothing, hands, tray and objects become wet; frequently'. On designated assessment days, the parents and caregivers recorded mTDS scores 4 times per day (before the morning dose and then 2 hours after each dose. Daily mTDS scores were summarized with the mean of the three post-dose assessments (mid-morning, afternoon, evening). Treatment response was defined as at least a 3-point improvement from baseline to Week 8 in daily mean mTDS scores. The reviewer's analyses for the number of responders as well as the mean change from baseline are presented in Table 1. While there were some adjustments between the applicant and reviewer analyses, these did not result in discordant outcomes and all analyses led to statistically significant results and the conclusion that glycopyrrolate is superior to placebo in the treatment of pathologic drooling.

Reviewer's Efficacy Analysis (FH-00-01)

	Glycopyrrolate N=20	Placebo N=18	p-value
Responders	15 (75%)	2 (11%)	<0.0001
Mean Change			
Baseline	6.79	5.59	
Week 8	3.08	5.06	
Change (sd)	3.71 (2.18)	0.54 (1.93)	0.0002

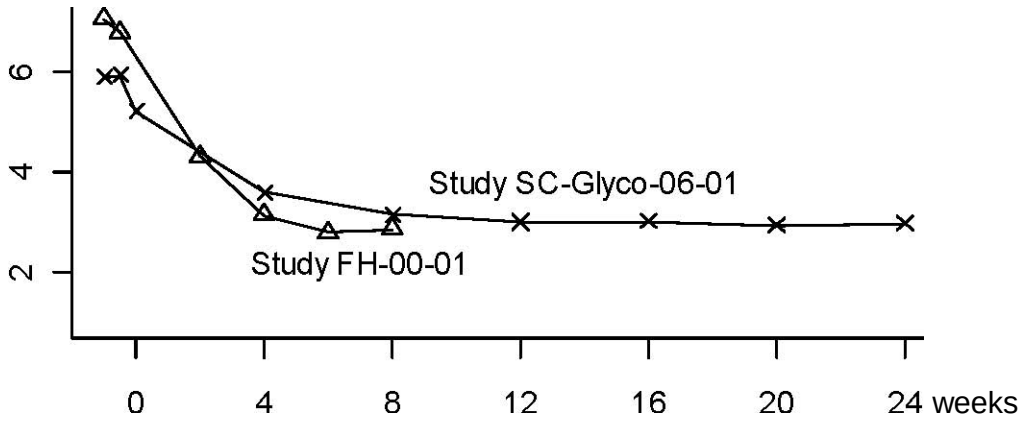
Study Sc-GLYCO-06-01

Study Sc-GLYCO-06-01 is a single-arm, open-label study to assess the safety and efficacy of glycopyrrolate solution for the treatment of pathologic drooling. The study population included subjects age 3 to 18 with cerebral palsy or other neurologic conditions who weighed at least 13 kg. All subjects received glycopyrrolate in this study. Subjects were treated with study medication three times a day (TID) for 24 weeks. The dosage levels of study treatment were titrated. The dosing regimen and titration schedule were the same as in Study FH-00-01. Subjects began at the dose of 0.02 mg/kg TID. Every 5-7 days subjects could increase or decrease a dose level based on a discussion between the investigator and parent/caregiver based on response or adverse events. The possible dose levels were 0.02, 0.04, 0.06, 0.08, and

0.1 mg/kg TID. The maximum allowed dose was 3 mg TID. The optimal dose for a subject was to be identified by Week 4 and maintained through Week 24. To be enrolled in the study, subjects were to have chronic drooling in the absence of treatment to the extent that the chin or clothing becomes wet most days by confirming mTDS score ≥5. Subjects were classified as either naïve or non-naïve to glycopyrrolate at baseline.

Efficacy was assessed using the Modified Teacher's Drooling Scale (mTDS) by the parent/caregiver. The mTDS is defined in Section 3.1.1.2. The baseline observations were to be taken on the two days prior to the first day of treatment (Days -2 and -1). Drooling severity was assessed four times per day (7-8 am, 9-10 am, 3-4 pm, and at bedtime, approximately 9-10 pm), approximately two hours after each of the three daily doses. The parent/caregiver also used the mTDS to assess drooling on this schedule on Days 1, 28, 56, 84, 112, 140, and 168.

Daily Mean mTDS Scores for Studies Sc-GLYCO-06-01 and FH-00-01



I concur with the conclusion of the biostatistics and clinical reviewers that although Protocol FH-00-01 experienced changes during the course of the study and many computational details were inadequately defined in the protocol and SAP, because all of the reasonable interpretations of the results lead to the conclusion of a statistically significant treatment effect for glycopyrrolate, Study FH-00-01 demonstrates the efficacy of glycopyrrolate for the treatment of pathologic drooling.

I also concur that Study Sc-GLYCO-06-01 is a supportive open-label 24-week study. In this study, subjects tended to have lower baseline mean mTDS scores than in Study FH-00-01, but the mean mTDS scores at Week 8 were similar, and the improvement achieved by Week 8 was generally maintained throughout the course of the study.

8. Safety

Primary safety data were gathered from studies FH-00-01 – (a double blind controlled study) and open label study Sc-GLYCO06-01. Safety data was also collected from the PK study in which subjects received only two doses of glycopyrrolate liquid – once under fasting conditions and once under fed conditions. However, multiple safety parameters were collected during the trial, including blood chemistries, vital signs, and adverse events. Secondary source data includes an evaluation of the postmarketing database of Robinul, a glycopyrrolate tablet approved under NDA 12-827 in 1961 to treat gastric ulcers, and widely used off-label to treat drooling in children with CP. A summary of this information is presented below. Safety data was also gathered from adverse events databases and drug utilization databases for Robinul.

Adequacy of Safety Assessments: Overall, the assessments conducted by the sponsor and submitted to this NDA are adequate to support safety. Dr Fred Hyman has provided an extensive review within the primary clinical review documents and portions of his assessment will be summarized. I concur that the safety plan is challenging, as the target population is cognitively impaired, necessitating adverse event monitoring in conjunction with the subject's parent or caregiver. In addition, most of the subjects were affected prior to study entry by multiple and often serious concomitant medical conditions. The adverse events associated with anticholinergic drugs are well understood and predictable, and I concur that these can be managed by the health care provide/physician on a case by case basis. While the number and size of the trials submitted is relatively small, there is substantial use of this moiety off-label for this indication, and the conduct of these trials is extremely challenging.

Patients expected to receive this medication will be under the care of a physician who can appropriately monitor for adverse events and adjust dosage as necessary. The dose for glycopyrrolate liquid is titrated to achieve a maximal therapeutic dose with tolerable adverse events for each subject. Children have used glycopyrrolate off label for many years and the therapeutic range was well known before the clinical trials had begun. In order to allow for a fairly wide range of dosing exploration, both trials mandated a starting dose of 0.02 mg/kg body weight. After one week on the first dose, that starting dose was doubled for one week, then tripled at three weeks for one week of use; and quadrupled at week 4 for one week. The maximum dose is reached at the end of the 4 weeks, when subjects received the final titration, which was 0.10 mg/kg body weight. At each weekly evaluation, if the investigator determined that adverse events were becoming troublesome, the dose is reduced to the prior one.

The table below summarizes exposure to study drug. Of note is the mean total dose of study drug for patients in the pooled glycopyrrolate oral solution-treated population was 643.2 mg. and the highest total dose was 1500 mg. This table supports the success of the dose titration scheme as the distribution of dosing is as expected in individualized responses to the drooling control and the adverse events. The mean daily dose of glycopyrrolate for subjects in Study FH-00-01 was 0.1548 mg/kg. At 3 doses per day, the average individual dose was therefore 0.0516 mg/kg, which is the mid-range of the allowable titration ranges of 0.01 mg/kg to 0.1

Exposure to Study Drug – Safety Population

	FH-00-02: One – dose pharmacokinetics study with glycopyrrolate liquid and tablets	**FH-00-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 20**	**Sc-GLYCO-06-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 137**	**Pooled Studies FH-00-01 and Sc-GLYCO-06-01: Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 157**	**Placebo N = 18**
Length of Study*	36 hours	8 Weeks	24 Weeks	8 and 24 weeks	8 Weeks
Total dose (mg)					
N	36	20	137	157	17
Mean (SD)	2	256.5 (115.56)	699.6 (452.13)	643.2 (449.23)	0.0 (0.00)
Min, Max	2,2	28, 465	4, 1581	4, 1581	0, 0
Missing		0	0	0	1
Total dose range (mg); n (%)					
≤ 600	NA	20 (100.0%)	67 (48.9%)	87 (55.4%)	17 (94.4%)
> 600 to ≤ 900		0	23 (16.8%)	23 (14.6%)	0
> 900 to ≤ 1200		0	22 (16.1%)	22 (14.0%)	0
> 1200 to ≤ 1500		0	23 (16.8%)	23 (14.6%)	0
> 1500		0	2 (1.5%)	2 (1.3%)	0
Missing	0	0	0	0	1
Mean daily dose (mg/kg)					
Mean (SD)	.030	0.1513 (0.05377)	0.1548 (0.06507)	0.1544 (0.06360)	0.000 (0.00000)
Min, Max	.039, .021	0.022, 0.266	0.019, 0.308	0.019, 0.0308	0.000
Missing	0	0	0	0	1

mg/kg. Similarly, the mean daily dose of glycopyrrolate for subjects in Study Sc-GLYCO-06-01 was 0.1513 mg/kg. At 3 doses per day, the average individual dose was therefore 0.0504 mg/kg, which is also the mid-range of the allowable titration ranges of 0.01 mg/kg to 0.1 mg/kg.

Routine clinical testing included physical examinations, 12 lead ECG screening, clinical laboratory evaluations, and measurement of vitals signs. Adverse events were observed by

both care givers and investigators. Although not a formal content valid scale, the modified Behavioral and Medical Rating Scale (mBMRS) was used to assist caregivers in observing adverse events and is a useful adjunct.

Major Safety Results

Subjects enrolled in these studies generally had extensive co-morbidities and were frequently residing in institutions due to the severity of their physical disabilities. (X percent with feeding tubes etc).

There were no deaths reported during the placebo controlled trial, FH-00-01. Three subjects who participated in the 6-month open label study (Sc-GLYCO-06-01) died within 30 days of the last study dose. These cases have been extensively analyzed by the review team with the conclusion that there is no evidence to conclude that glycopyrrolate was causally related to any of the deaths. Summary narratives from the clinical review are presented below:

Patient Narratives:

Patient 1403: Multiorgan failure secondary to septicemia

This 5-year old (b) (4) male resided in an institutional setting.

Medical History:

- Cerebral palsy (spastic and quadriplegic)
- Extreme prematurity (25 weeks gestation age)
- Hypoxic ischemic encephalopathy/ intermittent hypoxemia.
- Tracheostomy and gastrostomy.
- Essential hypertension
- Chronic respiratory failure, chronic respiratory disease, bronchitis, pneumonia
- Constipation, gastritis, bilateral inguinal hernias, cortical blindness, seizures, , chronic pain, and insomnia, dandruff, eczema, candidiasis, hip/pelvic dislocation, femur fracture,

Concomitant medications: Baclofen (via pump), clonazepam, clonidine, hydrochlorothiazide, spironolactone, melatonin, ranitidine, multivitamin tablets (Poly-Vi-Sol) with iron, budesonide, ipatropium bromide, salbutamol, macrogol, fentanyl transdermal system, Calmoseptine ointment, chloroxylenol/aluminium dihydroxyallantoinate powder, selenium sulfide, acetaminophen, ibuprofen, simethicone, diphenhydramine, fleet enema, morphine, lorazepam, neomycin and polymyxin, lisinopril, sulfmethoxazole/trimethoprim, potassium chloride and sodium chloride.

Prior to entering the trial, the child was under treatment for persistent hypertension with diuretics and clonidine, and lisinopril The subject was enrolled in the clinical trial and was titrated over four weeks to his optimal dose of 0.04 mg/kg. At that time, the subject developed

a urinary tract infection and was started on sulfmethoxazole/trimethoprim. Within two days, the subject developed hypotension, decreased urinary output, and foul smelling urine. his urinalysis was positive for blood, nitrates and leukocytes. The conditioned worsened within the following two days, with escalating symptoms, including decreased heart rate and saturations. Within that same day, the subject died of multi-organ failure. Given the subject's pre-existing conditions, the review team has concluded that there is no evidence to support that the multi-organ failure was related to treatment with glycopyrrolate liquid.

There are many confounding factors in this case, including an apparent primary event (urinary tract infection) that could possibly be related to drug treatment. Urinary retention is a documented adverse event resulting from anticholinergic treatment, and urinary retention can lead to urinary tract infection. The patient was diagnosed and treated medically, and subsequently developed rapid worsening and died within approximately 48hrs. It is possible that multiple co-morbidities and other factors involved in treatment may have contributed to this outcome. In my opinion, a causal relationship with study drug has not been established.

Patient 1709: aspiration pneumonia (fatal outcome). This 12-year-old, white male, resided in an institutional setting.

Medical History:

- Cerebral Palsy (spastic and quadriplegic)
- Recurrent pneumonia
- Intractable seizure
- Profound mental and motor retardation
- MIC-KEY gastrostomy feeding tube
- Gastroesophageal reflux
- Controlled reactive attachments disorder
- Bilateral hip dislocations

Concomitant medications: baclofen, valproic acid, levetiracetam, acetaminophen, bisacodyl, diazepam rectal gel, ibuprofen, phospha neutral, phenobarbital, macrogol, senna, lansoprazole, salbutamol 0.083% u.d., adapalene 0.19, ciprofloxacin, lorazepam, morphine and furosemide.

The subject was enrolled in the clinical trial and titrated over four weeks to the maximum allowable dose of 15 mL (0.086 mg/kg). After treatment with study drug for approximately 3 months, the subject developed aspiration pneumonia with emesis and respiratory distress and required 3 liters of oxygen to maintain a saturation of more than 93%. Two days later, the subject developed edema, respiratory distress a distended bladder, which required catheterization. The patient had been voiding well while taking glycopyrrolate liquid during the study, making it unlikely that glycopyrrolate liquid was contributing to his voiding dysfunction. However, due to the severity of the illness, glycopyrrolate liquid was temporarily discontinued at that time. One day later, the subject's status elevated to respiratory failure, and he was given only palliative care until his death two days later. No autopsy was performed and the cause of death was listed as respiratory failure secondary to the aspiration pneumonia.

The Clinical Pharmacology review included an examination of Subject 1709's values for

albumin clearance, bilirubin clearance, AST clearance and ALT clearance which all indicated normal hepatic function and clearance. Similarly, examination of Subject 1709's renal functions based upon CRCK and CL, and BUN and CL indicated normal kidney function and clearance.

The primary event appears to be aspiration pneumonia. There is no evidence to support a causal relationship between the event of aspiration pneumonia and treatment with glycopyrrolate liquid.

Patient 2906: anoxic encephalopathy (fatal outcome) this 17-year-old, white female living at home with parents

Medical History:

- Cerebral palsy (spastic and quadriplegic)
- Hydrocephalus
- Grade 1 seizures
- Osteoporosis
- Gastroesophageal reflux disease
- Recurrent strep
- Spinal fusion
- Bilateral hip replacement
- Bilateral ureter replacement

Concomitant Medications:
dantrolene, ranitidine hydrochloride, clonidine, baclofen, metoclopramide, hydrochloride,carnitine,alendronate sodium, macrogol, budesonide, valproate, semisodium, carbamazepine, naproxen sodium, guaifenesin, diazepam, Fleets enema, and bisac

The subject was enrolled in the clinical trial and was titrated to a stable dose of 0.10 mg/kg over four weeks. The subject was on drug for 4.5 months upon presenting to the emergency room with a fever (100.4ºF), abdominal pain, nausea, and vomiting. A diagnosis of urinary tract infection was made after a positive urine culture revealed Enterococcus 13,000 colony forming units/mL and gamma hemolytic Streptococcus 13,000 colony forming units/mL. The patient was treated with intravenous levofloxacin, hydromorphone hydrochloride, ondansetron hydrochloride, lorazepam, intravenous fluids, ibuprofen, and paracetamol. Oxygen (2 L/min) was administered via a nasal cannula. A nasogastric tube and a Foley catheter were also inserted. Study drug was discontinued at that time. Two days later, she developed gastroparesis. An abdominal ultrasound revealed the presence of liver hemangiomas. The patient was initially started on antibiotics, but treatment was discontinued when blood cultures were found to be negative. The patient's fever subsequently resolved after the antibiotics were withdrawn. The patient was aggressively treated with laxatives and enemas for the constipation and was given metoclopramide hydrochloride and macrogol. On (b) (6) the patient was discharged to home in stable condition with instructions regarding follow-up.

One week after discharge, while she was being fed at home, she began gurgling and turned blue. Emergency medical service was called. Her father started cardiopulmonary resuscitation, and the patient vomited. When the paramedics arrived, the patient had no pulse and was not breathing. A chest X-ray showed diffuse bilateral alveolar and interstitial infiltrates. The impression was that the patient experienced probable respiratory arrest and subsequent cardiac arrest secondary to acute lung aspiration, which resulted in severe anoxic brain injury and profound acidosis. The family decided to withdraw artificial medical support and pursue only comfort measures until the subject's death one day later.

No autopsy was performed, and the cause of death was listed as aspiration leading to respiratory distress syndrome, severe anoxic brain injury, shock and death. There is no evidence supporting a causal relationship between glycopyrrolate use and the subject's death.

The Clinical Pharmacology review included an examination of Subject 2906's values for albumin clearance, bilirubin clearance, AST clearance and ALT clearance which all indicated normal hepatic function and clearance. Similarly, examination of Subject 2906's renal functions based upon CRCK and CL, and BUN and CL indicated normal kidney function and clearance.

The primary event appears to be choking while feeding, leading to hypoxia and death. There is no evidence to support a causal relationship between the event of choking/immediate hypoxia and treatment with glycopyrrolate liquid.

Epidemiology discussion

The Division of Epidemiology (DEPI) was requested to examine mortality data from databases for individuals with cerebral palsy, to elucidate the expected mortality rates for individuals with similar ages and severity of condition. Comparisons to published cerebral palsy mortality rates cannot be used to directly inform this question. However, qualitative comparisons between the mortality rate observed in Sc-GLYCO-06-01 and publications from unselected cohorts of pediatric cerebral palsy patients older than one year of age did not provide sufficient evidence to unequivocally conclude that the Sc-GLYCO-06-01 mortality rate was different than the expected background rate. The Sc-GLYCO-06-01 trial had a greater proportion of severely disabled patients than published pediatric cohorts, with 51.1% of Sc-GLYCO-06-01 trial patients requiring a feeding tube compared with only 6-7% in cohorts studies.

Serious Adverse Events (SAE's):

Twelve glycopyrrolate oral solution-treated subjects had a total of 15 SAEs. Most SAEs were considered not related or unlikely related to study drug. Of the 15 SAEs, only four (nystagmus, esophageal candidiasis, dehydration, and gastrointestinal motility disorder) were considered related definitely, probably, or possibly related to treatment with glycopyrrolate. See table below.

Subjects in Safety Population with Serious Adverse Events (From Clinical review)

Patient ID	Preferred Term	Severity	Outcome	Relationship	Maximal Dose (mg/kg)
FH-00-01 glycopyrrolate oral solution					
08002	Convulsion	Severe	Recovered	Not related	.05
Sc-GLYCO-06-01 glycopyrrolate oral solution					
0502	Pneumonia	Moderate	Recovered	Unlikely	.06
0807	Esophageal candidiasis	Severe	Recovered w/ sequelae	Possible	.047
	Tonsilar hypertrophy	Moderate	Recovered	Not related	
1304	Dehydration	Moderate	Recovered	Not related	.06
1503	Otitis media	Moderate	Recovered	Unlikely	.02
	Dehydration	Mild	Recovered	Possible	
1601	Therapeutic agent toxicity	Severe	Recovered	Not related	.03
1901	Nystagmus	Severe	Recovered	Probable	.01
2806	Convulsion	Moderate	Recovered	Not related	.02
	Hydrocephalus	Severe	Recovered	Not related	
2810	Pneumonia	Severe	Recovered	Not related	.04
2910	Cellulitis	Moderate	Recovered	Not related	.04
3006	Pneumonia	Moderate	Recovered	Not related	.08
3505	Gastrointestinal motility disorder	Moderate	Recovered	Possible	.06

Discontinuations due to AEs:

Sixteen patients discontinued treatment because of an AE (15 in the pooled glycopyrrolate oral solution group and 1 in the placebo group). Three patients had an AE with a fatal outcome, discussed above. Two patients withdrew consent to participate in the study (patient/parent decision) because of an AE for a total of 21 discontinuations. Sixteen of the 21 patients (76%) had AEs that were considered related to treatment with study drug. The most common AEs were gastrointestinal. See table below for details.

AE listing for Dropouts (From Dr. Hyman's review)

Patient Number	Preferred Term	Outcome	Severity	Serious	Relationship
FH-00-01/placebo					
01002	Constipation	Recovered	Moderate	No	Probable
	Dry mouth	Recovered	Moderate	No	Probable
	Flushing	Recovered	Moderate	No	Probable
	Disturbance in attention	Recovered	Mild	No	Possible
	Somnolence	Recovered	Mild	No	Possible
	Aggression	Recovered	Moderate	No	Possible
FH-00-01/glycopyrrolate oral solution					
06009	Abdominal distension	Recovered	Moderate	No	Possible
Sc-GLYCO-06-01/glycopyrrolate oral solution					
0807	Oesophageal candidiasis	Rec. w/ seq.	Severe	Yes	Possible
1403	Hypokalemia Hyponatremia	Recovered	Severe	No	Unlikely Not related
1504	Vomiting	Recovered	Moderate	No	Possible
1602	Diarrhea	Recovered	Moderate	No	Possible
1709	Respiratory distress	Recovered	Severe	No	Unlikely
	Hemoptysis	Recovered	Moderate	No	Not related
1901	Nystagmus	Recovered	Severe	Yes	Probable
2601	Pallor	Recovered	Mild	No	Possible
2602	Constipation	Recovered	Moderate	No	Probable
2603	Convulsion	Recovered	Moderate	No	Probable
2701	Dysgeusia	Recovered	Severe	No	Definite
2703	Abnormal behavior	Ongoing	Severe	No	Possible
2801	Constipation	Recovered	Moderate	No	Definite
2807	Restlessness	Recovered	Moderate	No	Possible
2814	Vomiting	Ongoing	Moderate	No	Possible
2906	Nausea	Recovered	Moderate	No	Not related
	Vomiting	Recovered	Moderate	No	Not related
	Pyrexia	Recovered	Severe	No	Not related
	Abdominal pai	Recovered	Severe	No	Not related
	Urinary tract infection	Recovered	Moderate	Yes	Not related
2911	Asthma	Ongoing	Mild	No	Not related
3005	Abnormal behavior	Recovered	Mild	No	Unlikely
3502	Choking	Recovered	Severe	No	Possible
3505	GI motility disorder	Recovered	Moderate	Yes	Possible

Treatment Emergent Adverse Events:

(b) (4) of the pooled population had constipation. The other most frequently observed gastrointestinal system TEAEs were vomiting (b) (4). Dry mouth was reported for (b) (4) of the pooled population. Other system organ classes were affected as noted in the table below. Labeling will reflect these events.

Most Frequently Observed Treatment-Emergent Adverse Events

System Organ Class Preferred Term	FH-00-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 20	Sc-GLYCO-06-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 137	Pooled Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 157	Placebo N = 18
Gastrointestinal disorders	17 (85.0%)	68 (49.6%)	85 (54.1%)	8 (44.4%)
Constipation	6 (30.0%)	28 (20.4%)	34 (21.7%)	4 (22.2%)
Vomiting	6 (30.0%)	24 (17.5%)	30 (19.1%)	2 (11.1%)
Diarrhoea	3 (15.0%)	24 (17.5%)	27 (17.2%)	4 (22.2%)
Dry mouth	8 (40.0%)	15 (10.9%)	23 (14.6%)	2 (11.1%)
Lip dry	1 (5.0%)	5 (3.6%)	6 (3.8%)	0
Nausea	0	4 (2.9%)	4 (2.5%)	0
Abdominal pain	0	3 (2.2%)	3 (1.9%)	0
Chapped lips	0	3 (2.2%)	3 (1.9%)	0
General disorders and administration site conditions	4 (20.0%)	28 (20.4%)	32 (20.4%)	4 (22.2%)
Pyrexia	3 (15.0%)	20 (14.6%)	23 (14.6%)	4 (22.2%)
Irritability	0	8 (5.8%)	8 (5.1%)	0
Infections and infestations	3 (15.0%)	68 (49.6%)	71 (45.2%)	4 (22.2%)
Upper respiratory tract infection	2 (10.0%)	11 (8.0%)	13 (8.3%)	0
Otitis media	0	12 (8.8%)	12 (7.6%)	1 (5.6%)
Urinary tract infection	0	11 (8.0%)	11 (7.0%)	0
Influenza	0	7 (5.1%)	7 (4.5%)	0
Pharyngitis streptococcal	0	7 (5.1%)	7 (4.5%)	0
Pneumonia	0	7 (5.1%)	7 (4.5%)	1 (5.6%)
Sinusitis	1 (5.0%)	6 (4.4%)	7 (4.5%)	1 (5.6%)
Gastroenteritis viral	0	6 (4.4%)	6 (3.8%)	0
Nasopharyngitis	0	5 (3.6%)	5 (3.2%)	0
Viral upper respiratory tract infection	0	5 (3.6%)	5 (3.2%)	0
Ear infection	0	4 (2.9%)	4 (2.5%)	0
Cellulitis	0	3 (2.2%)	3 (1.9%)	0
Oral herpes	0	3 (2.2%)	3 (1.9%)	0
Injury, poisoning, and procedural complications	1 (5.0%)	19 (13.9%)	20 (12.7%)	0
Feeding tube complication	0	5 (3.6%)	5 (3.2%)	0
Procedural pain	0	5 (3.6%)	5 (3.2%)	0
Fall	0	4 (2.9%)	4 (2.5%)	0
Investigations	3 (15.0%)	14 (10.2%)	17 (10.8%)	3 (16.7%)
Urine output	1 (5.0%)	5 (3.6%)	6 (3.8%)	1 (5.6%)

decreased				
Heart rate increased	2 (10.0%)	0	2 (1.3%)	1 (5.6%)
Metabolism and nutrition disorders	0	7 (5.1%)	7 (4.5%)	0
Dehydration	0	3 (2.2%)	3 (1.9%)	0
Hypokalaemia	0	3 (2.2%)	3 (1.9%)	0
Nervous system disorders	7 (3.5%)	31 (22.6%)	38 (24.2%)	7 (38.9%)
Convulsion	1 (5.0%)	11 (8.0%)	12 (7.6%)	1 (5.6%)
Somnolence	3 (15.0%)	7 (5.1%)	10 (6.4%)	5 (27.8%)
Headache	2 (10.0%)	6 (4.4%)	8 (5.1%)	1 (5.6%)
Disturbance in attention	1 (5.0%)	1 (0.7%)	2 (1.3%)	2 (11.1%)
Psychiatric disorders	4 (20.0%)	17 (12.4%)	21 (13.4%)	5 (27.8%)
Restlessness	1 (5.0%)	5 (3.6%)	6 (3.8%)	2 (11.1%)
Agitation	2 (10.0%)	2 (1.5%)	4 (2.5%)	1 (5.6%)
Crying	1 (5.0%)	2 (1.5%)	3 (1.9%)	1 (5.6%)
Insomnia	0	3 (2.2%)	3 (1.9%)	1 (5.6%)
Intentional self-injury	0	3 (2.2%)	3 (1.9%)	0
Mood altered	1 (5.0%)	2 (1.5%)	3 (1.9%)	2 (11.1%)
Aggression	1 (5.0%)	1 (0.7%)	2 (1.3%)	1 (5.6%)
Renal and urinary disorders	3 (15.0%)	14 (10.2%)	17 (10.8%)	0
Dysuria	0	9 (6.6%)	9 (5.7%)	0
Urinary retention	3 (15.0%)	3 (2.2%)	6 (3.8%)	0
Respiratory, thoracic, and mediastinal disorders	9 (45.0%)	34 (24.8%)	43 (27.4%)	4 (22.2%)
Nasal congestion	6 (30.0%)	15 (10.9%)	21 (13.4%)	1 (5.6%)
Epistaxis	0	7 (5.1%)	7 (4.5%)	0
Upper respiratory tract congestion	1 (5.0%)	6 (4.4%)	7 (4.5%)	1 (5.6%)
Cough	0	2 (1.5%)	2 (1.3%)	2 (11.1%)
Skin and subcutaneous tissue disorders	2 (10.0%)	22 (16.1%)	24 (15.3%)	3 (16.7%)
Rash	0	11 (8.0%)	11 (7.0%)	2 (11.1%)
Urticaria	1 (5.0%)	2 (1.5%)	3 (1.9%)	0
Vascular disorders	5 (25.0%)	19 (13.9%)	24 (15.3%)	3 (16.7%)
Flushing	5 (25.0%)	15 (10.9%)	20 (12.7%)	3 (16.7%)

Electrocardiograms:

The sponsor incorporated ECG analysis into both the placebo-controlled trial and the open label trial for all randomized subjects with at least one available baseline and one treatment ECG. The sponsor conducted several analyses of the data and concluded that there were no ECG effects of glycopyrrolate except for a clinically relevant increase in heart rate.

Consultation was obtained from the Interdisciplinary Review Team for QT Studies Consultation within the Division of Cardio-Renal Products (DCRP).

The e DCRP reviewer concluded that there were no significant effects on atrio-ventricular conduction, as measured by the PR interval, or depolarization, as measured by the QRS duration. The QTcF data did not show evidence of any clinically relevant changes in QTcF duration or waveform morphology. There was no imbalance in specific or nonspecific outliers. The reviewer acknowledged that there are limitations in both studies, including sparse ECG collection and absence of time matched PK sampling. However, the reviewer's conclusion is that "data suggest that large effects on the QT or other ECG intervals by glycopyrrolate are unlikely." The reviewer further commented that with regards to cardiovascular issues, the sponsor's proposed labeling is reasonable

Dr. Hyman completed a comprehensive and thorough review of the material submitted in support of this new formulation of glycopyrrolate. He has concluded that this product is safe and effective for the proposed indication and this reviewer concurs with his conclusion.

Patients treated with glycopyrrolate are at risk for anticholinergic side effects. These anticipated pharmacologic effects are well known and understood, and can be managed individually for patients under treatment. While some of these side effects may be troubling, there is an unmet medical need for this product. Patients are currently being treated with "crushed" tablets in food, with poor quality control and only anecdotal dosing information. This formulation will provide consistent quality, purity, and strength and allow individual dosing titration based upon effect. Dosing is weight based and clearly delineated in labeling.

In my opinion, additional risk evaluation and management strategies are not necessary at this time. The known pharmacologic risks cannot reasonably be mitigated by elements to assure safe use, and these side effects can be clinically monitored for each patient and treatment adjusted accordingly. Approved labeling includes patient and caregiver information clearly describing side effects and other relevant information.

9. Advisory Committee Meeting

There was no advisory committee meeting held during the review NDA review period to discuss this application, as this is not a new molecular entity and there are no new/novel concerns. The Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee held a general discussion regarding the need for a glycopyrrolate liquid shortly

after the IND for glycopyrrolate liquid was opened in 2001 and encouraged development of products specifically formulated for this population/indication.

10. Pediatrics

This product is a designated Orphan Product, and as such is exempt from the Pediatric requirements of the Act.

11. Other Relevant Regulatory Issues

None

12. Labeling

There are no unresolved labeling issues.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action – The application will be approved.

- Risk Benefit Assessment – This product provides a benefit for patients with severe excessive drooling associated with neurologic impairment. There are substantial risks for anticholinergic side effects, but these are well understood and can be managed individually for each patient. This action will provide an approved therapeutic alternative to the off-label use of crushed glycopyrrolate tablets, with a resultant improvement in consistency, quality, and delivery of the drug product.

- Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies – There are no additional recommended post-marketing risk evaluation and mitigation strategies other than routine approved labeling.

- Recommendation for other Postmarketing Requirements and Commitments

  The following studies will be post-marketing requirements.
  - Oral (gavage) fertility and general reproduction toxicity study of glycopyrrolate in rats.
  - Oral (gavage) developmental toxicity study of glycopyrrolate in rats.
  - Oral (stomach tube) developmental toxicity study of glycopyrrolate in rabbits.
  - Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of glycopyrrolate in rats, including a postnatal behavioral/function evaluation.
  - A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in mice.
  - A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in rats.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN J WALKER
07/28/2010