CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022571Orig1s000

MEDICAL REVIEW(S)

Memo to File
Deputy Director for Safety

NDA number: 22-571
Date of submission: September 28, 2009
Applicant: Shionogi Pharma, Inc.
Drug: Glycopyrrolate oral solution
Drug class: Nonselective antagonist of muscarinic cholinergic receptors
Indication: Treatment of drooling secondary to cerebral palsy and other neurodevelopmental deficits
Date: July 25, 2010

Introduction

This Memo is an addition to Clinical review by Dr. Fred Hyman and PharmTox review by Dr. Norman See regarding divisional post-marketing requirement for certain animal studies.

Background

Glycopyrrolate is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including salivary glands. Glycopyrrolate indirectly reduces the rate of salivation by preventing the stimulation of these receptors.

Current submission is being reviewed for the use of this drug in the treatment of excessive drooling secondary to different neurologic impairments including cerebral palsy. This would involve chronic exposure of the subjects to glycopyrrolate.
It appears that the product has already been used for this condition off label for an extended period of time.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of glycopyrrolate. There was an agreement between the Agency and the company that those studies would be performed post-approval.

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

Glycopyrrolate has not been evaluated for potential to impair fertility.

Non-clinical reviewer concluded that there are no nonclinical approval issues for this drug product.

Regulatory basis for requiring PMRs

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug applications to conduct postmarketing studies (PMR) for certain purposes. The study/trial

must be necessary to assess a known serious risk related to the use of the drug involved; assess signals of serious risk related to the use of the drug; or to identify an unexpected serious risk when available data indicates the potential for a serious risk.

The purpose for conducting non-clinical PMR studies for glycopyrrolate is to identify the unexpected serious risks of carcinogenesis and reproductive toxicity because we have determined that an analysis of spontaneous postmarketing adverse events alone will not be sufficient.

FDA has determined that the Sponsor will be required to conduct the following:

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.

Acceptable toxicokinetic data should be submitted in support of each of these nonclinical issues.

Tatiana Oussova, MD, MPH

Deputy Division Director for Safety,
Division of Dermatology and Dental Products

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

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/s/

TATIANA OUSSOVA
07/29/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-571
Priority or Standard	S
Submit Date(s)	September 26, 2009
Received Date(s)	September 28, 2009
PDUFA Goal Date	July 28, 2010
Division / Office	Division of Dermatology and Dental Products, ODE III
Reviewer Name(s)	Fred Hyman, DDS, MPH
Review Completion Date	May 28, 2010
Established Name	Glycopyrrolate
(Proposed) Trade Name	TBD
Therapeutic Class	Xerostomic Agent (6030503)
Applicant	Shionogi
Formulation(s)	Oral Solution 1 mg/5 mL
Dosing Regimen	Variable: Range of (b) (4) – 0.10 mg/kg t.i.d. up to maximum of 3 mg t.i.d. per titration schedule
Indication(s)	Chronic (b) (4) Severe Drooling In Pediatric Patients Aged 3-16 With Cerebral Palsy, (b) (4) Or Other Neurologic Conditions Associated With Problem Drooling
Intended Population(s)	Pediatric: 3-16

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The conclusions of this review support an approval recommendation for glycopyrrolate oral solution 1mg/5ml, indicated for treatment of chronic (b) (4) severe drooling in children 3-16 years of age with cerebral palsy (CP), (b) (4) or other neurologic conditions associated with problem drooling.

1.2 Risk Benefit Assessment

In this current NDA, the applicant proposes the use of glycopyrrolate in a flavored oral solution to help control (b) (4) severe drooling in children 3-16 years of age with CP and/or related medical conditions. The applicant conducted one pharmacokinetic study, one placebo-controlled pivotal trial and one open label trial to support the efficacy and safety of this drug. The studies were of appropriate design with one primary outcome that the Agency had agreed was acceptable for efficacy demonstration - a statistically significant improvement of three grades on a nine-grade scale that measures drooling. A total of 214 pediatric subjects were exposed to glycopyrrolate solution during this development program; 17 for eight weeks and 197 for six months. The pharmacokinetic trial enrolled 36 healthy adults for one dose of glycopyrrolate liquid. The designs of the trials were also adequate to assess safety. Appropriate laboratory values were monitored and adverse events were recorded both by the investigators at every visit and by the caregivers at home three times per week. Caregivers recorded AE's in a diary in which a checklist of signs and symptoms of adverse events was completed. Due to the property of anticholinergics to increase heart rate, a separate subset of subjects in both clinical trials were used to perform complete ECG testing and evaluation of results.

In addition, several Divisions within CDER's Office of Drug Safety were enlisted to evaluate databases of postmarketing data for currently approved drugs with glycopyrrolate as their active ingredient (Robinul tablets and Robinul for injection). A thorough AERS search was conducted for both approved drugs and drug utilization data was examined to determine past off-label use of the approved glycopyrrolate tablets for treatment of drooling in children. In addition, a mortality rate was calculated for children with cerebral palsy who matched the demographics of the enrolled subjects to help make an assessment of three deaths that occurred in the open label study.

Therapeutic Benefit
The results of the placebo-controlled trial demonstrated that 78% of subjects on drug reached the prespecified definition of clinical improvement in drooling compared to 19% of those on placebo ($p = 0.0016$). The open label trial was not capable of reaching

conclusions without a placebo comparator, but did use the same primary efficacy variable, and was supportive. The open label study demonstrated that the percentage of subjects who achieved the same definition of clinical improvement in drooling was comparable to that result in the controlled trial. The open label study also demonstrated that over a six-month period, the effect was maintained.

Safety Concerns
Anticholinergic adverse events (AEs), including constipation, urinary retention, and flushing were reported with higher incidence in the treatment group compared to the placebo group in the controlled clinical trial. However, none of these anticholinergic adverse events rose to the level of serious in the placebo controlled trial, and in the open label trial, one report of decreased gastrointestinal motility led to hospitalization of that subject for stomach distension from which the subject recovered. The open label study of 6 months duration did not have a comparator group for adequate control; however, the safety monitoring did not uncover any signs of increasing incidence of, or new AE's over time. There was a total of one serious adverse event (SAE) in the placebo controlled trial and 10 SAE's in the open label trial, none of which appeared to be causally related to the drug use. Full narratives of all AE's in both trials are discussed in the Safety section of this review, 7.3.2.

There were three deaths reported during the open-label trial. A review of the narratives provided no evidence of causal relationship between the events and treatment with glycopyrrolate liquid (See Section 7.3.1). Furthermore, United States mortality data were used to compute expected rates in a matched group of children; the results showed that the three deaths in the open label group were within the normal background mortality range for this population.

Because of the known effect of anticholinergics on heart rate, the DCRP/Interdisciplinary Review Team for QT Studies formally reviewed the results of ECG testing in detail and came to the conclusion that there were no significant effects on atrio-ventricular conduction, as measured by the PR interval, or depolarization, as measured by the QRS duration. They further concluded that the QTcF data did not show evidence of any clinically relevant changes in QTcF duration or waveform morphology, nor was there any imbalance in specific or nonspecific outliers. While there are limitations in these studies due to sparse ECG collection and absence of time matched PK sampling, the 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.

Prior Human Experience
Glycopyrrolate, the active ingredient in glycopyrrolate liquid, was first approved in tablet form in 1961 under the name Robinul as NDA 12-827 for the treatment of peptic ulcers, and is still on the market. A second NDA with glycopyrrolate as the active ingredient, 14-764, was approved as Robinul injection in 1975 for intramuscular or intravenous

delivery to decrease secretions during surgery. The sponsor, as well as CDER evaluated all AERS reports and found no significant adverse events that were related to the past drug use. Drug use data has determined that Robinul tablets are frequently used off label to treat drooling in CP children. The most recent data show that approximately (b) (4) prescriptions are filled annually in the United States for Robinul tablets and its generic equivalents for children between the ages of 3 and 16. Although the information regarding the diagnoses of the patients using glycopyrrolate tablets is limited, it appears as though approximately 50% of the current glycopyrrolate usage in children is for drooling in patients with cerebral palsy.

Titration Strategy to Achieve Risk/Benefit Balance
During the trials, caregivers were educated about monitoring for potential adverse events through materials similar to the contents of the proposed patient counseling section of the label, and the patient package inserts. Since the dose needs titration to achieve the optimal balance of drooling reduction and expected anticholinergic adverse events for each subject, this was an important part of the trial. Prior to increasing the dose during the clinical trials, the investigator discussed the AE profile of the subject with the caregiver. During the clinical trials, caregivers demonstrated that they were capable of observing and reporting adverse events to the physician, who used that information to determine an optimal balance of the drooling control and adverse events limitations. Analyses of the final dosing pattern during the trial demonstrated that subjects were successful in being dosed at the optimal dosing through the titration process. The final distribution of doses followed a statistically normal distribution when adjusted for weight, supporting a pattern of subjects who were successfully stabilized at a dose that demonstrated efficacy in its outcome, and tolerability of adverse events.

The successful demonstration of efficacy and safety in the submitted trials, as well as the long history of off-label use of the currently marketed glycopyrrolate in tablet form outweigh the risk of the expected anticholinergic AE's. From a public health standpoint, drug utilization has shown that a significant number of children with CP and related conditions are being prescribed glycopyrrolate for drooling at the present time through off label Robinul use. It can only improve the risk/benefit to approve the liquid dosage form which is more accurate and controllable than the tablets, and contains adequate labeling to make its use safer and more effective. No risk management procedures are recommended by this reviewer.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor has committed to conduct the following nonclinical studies post-approval of NDA 22-571; please refer to the Pharmacology/Toxicology NDA review for a full discussion. These matters are regarded as being post-marketing requirements (PMRs):

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.

2 Introduction and Regulatory Background

2.1 Product Information

Glycopyrrolate is a synthetic anticholinergic agent. It is a quaternary ammonium salt with the following chemical name: 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide. The molecular formula is C19H28BrNO3 and the molecular weight is 398.33. Glycopyrrolate occurs as a white, odorless crystalline powder. It is soluble in water and alcohol and practically insoluble in chloroform and ether. It is completely ionized at physiological pH values.

Glycopyrrolate tablets (Robinul [1 mg tablets]) and Robinul Forte [2 mg tablets]) have been FDA-approved since 1961 for the adjunctive treatment of peptic ulcer disease in adults (NDA 12-827), and Robinul Injection has been FDA-approved since 1975 as preoperative or intraoperative medication in adults and children 2 years of age and older to reduce salivary, tracheo-bronchial, and pharyngeal secretions (NDA 14-764). In this NDA, the applicant has formulated glycopyrrolate as a solution with the concentration of 1 mg/5 mL. The flavored liquid should be easier to administer to this population than the tablets and the liquid should also allow for more accurate titration to an optimal dose.

Antimuscarinic agents competitively inhibit the actions of acetylcholine or other cholinergic stimuli at muscarinic receptors and have little effect on cholinergic stimuli at nicotinic receptors. Antimuscarinics have gastrointestinal, genitourinary, cardiovascular, respiratory, CNS and ophthalmic effects.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved drugs that are indicated for treatment of excessive drooling. The table listed below contains drugs that are approved for other indications but used to treat excessive drooling in children with cerebral palsy, as well as other non-pharmacologic treatments of drooling. Drug treatments that are used include off-label treatment with Robinul, use of scopolamine transdermal patch, and injection of botulinum toxin A into the salivary glands. The literature also shows irreversible procedures to restrict salivary flow in severe cases such as salivary gland surgery and use of radiation to destroy salivary tissue.

Table 1: Available Treatments

Drug Treatment	Approved indication	Comments
Anticholinergic		
Robinul	Peptic ulcers	Widely used off label for drooling
Scopolamine	Motion sickness, ophthalmic purposes	Crosses the blood brain barrier, so less preferable than Robinul.
Atropine sulfate	Antidote to overdose of cholinergic drugs or poisons	Crosses the blood brain barrier, so less preferable than Robinul.
benztropine	Extrapyramidal symptoms of Parkinson's disease	Also used off-label for pre-anesthesia in children
trihexyphenidyl	Extrapyramidal symptoms of Parkinson's disease	Also used off-label for pre-anesthesia in children
Botulinum Toxin A	Cervical dystonia, strabismus, hyperhidrosis, minimize certain facial lines/wrinkles.	Injected into salivary gland for reduced salivation for several months. Risks include inadvertent dysphagia and other adverse events associated with imperfect placement of toxin.
Non- Pharmacologic Treatment		
Surgical Treatment Parotid Duct Resection	Irreversible, potential for too little saliva, risks are associated with surgery	
Biofeedback	Effective treatment in a multitude of medical conditions. Not effective in cognitively-impaired individuals	

2.3 Availability of Proposed Active Ingredient in the United States

Glycopyrrolate tablets (Robinul and Robinul Forte Tablets) have been FDA-approved since 1961 for the adjunctive treatment of peptic ulcer disease in adults, and Robinul Injection has been FDA-approved since 1975 as preoperative or intraoperative medication in adults and children 2 years of age and older to reduce salivary, tracheo-bronchial, and pharyngeal secretions.

This application is for a new dosage form, a flavored liquid to allow for better drug delivery and easier dose adjustment. Drug use data has determined that Robinul tablets are frequently used off label to treat drooling in CP children. The most recent data show that approximately (b) (4) prescriptions are filled annually in the United States for Robinul tablets and its generic equivalents for children between the ages of 3 and 16. The complete data and it sources is discussed fully in Section 8.0 of this review, Postmarketing Experience.

2.4 Important Safety Issues with Consideration to Related Drugs

As an anticholinergic drug, glycopyrrolate will produce typical anticholinergic actions such as constipation, urinary retention, lack of sweating, and tachycardia in addition to its desired effect of decreased salivation. The classic anticholinergic drug is atropine, and others in the class include dicyclomine (indicated for irritable bowel syndrome), darifenacin (for treatment of overactive bladder) and scopolamine (to treat nausea from motion sickness). Some of the early antidepressants such as amitriptyline and nortriptyline are anticholinergics as well. Although atropine and scopolamine both cross the blood brain barrier, glycopyrrolate does not, so central nervous system effects such as sedation are significantly limited with glycopyrrolate.

The incidence of expected adverse events is dose-related. Therefore, dose is to be titrated to achieve an optimal balance of effectiveness with minimal anticholinergic-associated adverse events. Even so, there are still risks which require vigilant monitoring. Most commonly, decreased gastric motility can lead to pain from constipation, and in severe cases, pseudo-impaction. Decreased sweating may lead to elevated body temperature, particularly during warm weather. Urinary retention is also a potential anticholinergic adverse event, which requires monitoring and may warrant dose adjustment. The currently marketed anticholinergic drugs contain very similar warnings on their labels that encompass expected adverse events. Due to this knowledge, the clinical trials incorporated adverse events checklists that included the signs and symptoms of known anticholinergic activity. These forms were completed by the caregivers three times per week at home and by the investigators during the visits. In addition, as a part of the protocol of both trials, the sponsor included a separate cardiovascular assessment and analysis (including QT interval) due to the expected tachycardia and potential for related effects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the course of this development program, four FDA meetings were held: September 06, 2000, August 08, 2001, March 20, 2007 and December 15, 2008. During these meetings, the Division provided recommendations for pivotal efficacy study FH-00-01, phase 3, open label, safety and efficacy study SC-GLYCO-06-01, and the overall clinical development plan. Based upon review of the meeting minutes and other communication with the sponsor, it appears as though all FDA recommendations were implemented. The final meeting was a pre-NDA meeting. There was no End-of-Phase 2 meeting.

Highlights of these meetings that affect the review include:

1. During a regulatory guidance meeting that FDA hosted with the sponsor on August 8, 2001, two agreements were made:
   a. "The need for chronic toxicology data will be waived." (verbatim from minutes filed in DARRTS) and
   b. Regarding the primary outcome measure, the Agency stated, "The mTDS is an adequate tool to measure efficacy."
2. A Guidance Meeting was held between FDA and the sponsor on March 20, 2007 to discuss the clinical program, as well as the CMC, toxicology, clinical pharmacology, and regulatory pathways for the NDA. The Agency agreed on the following:
   a. A "well designed study in 100 patients should be adequate to confirm the chronic safety profile in this patient population." (verbatim from minutes in DARRTS) The minutes further stated that "It would be more helpful to have a 12 month study, but 6 months is acceptable if there are 100 evaluable patients."
   b. FDA also recommended evaluating the pharmacokinetics of glycopyrrolate oral solution in the target patient population using a population PK approach and agreed that these data could be obtained from a subset of patients in SC-GLYCO-06-01.
   c. The Agency reiterated that "the Division agreed to waive the need for additional chronic toxicology data" and referenced the August 2001 minutes.

Orphan Status

On June 9, 2006, the Agency granted orphan drug designation of glycopyrrolate for the indication "treatment of pathologic (chronic moderate to sever) drooling in pediatric patients." A follow-up teleconference between the Division and the Office of Orphan Products Development clarified that the indication granted by Orphan Drugs allows flexibility for the Division during the approval process. According to Orphan Drug staff, the orphan indication is a broad one, and a "lesser included indication," as is the recommended indication in this NDA, retains orphan status.

The granting of orphan status did affect one aspect of the placebo-controlled clinical trial; there was an approximately one year break in the trial enrollment during which the sponsor applied for orphan status. For strategic business reasons, the sponsor concluded that they would not continue with the IND unless they received orphan drug status. Therefore, the sponsor temporarily discontinued enrollment after approximately 30 months, at which time 17 subjects had been enrolled. To be eligible for orphan status, the sponsor formally amended the inclusionary criteria as follows: the sponsor's original inclusionary criteria for protocol FH-00-01 was amended from its original population of (b) (4) to limit the age limit to ages 3 – 16. At the same time, they also expanded the indication (b) (4) to drooling in cerebral palsy and other neurological conditions.

Orphan status was granted and the study was restarted; the total hiatus in the trial was approximately one year. Enrollment was then completed 14 months later with a total of 38 subjects. Prior to the change in inclusionary criteria, two of the 17 subjects enrolled were over age 16 (both were 23). The sponsor had proposed to handle these two subjects by analyzing the intent to treat (ITT) and per protocol (PP) data in two ways: with these subjects included and with them excluded. The biostatical review for this NDA addresses the data analysis in full and recommended use of a hybrid analysis method, which resulted in an acceptable outcome.

2.6 Other Relevant Background Information

On April 24, 2001, CDER's Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee met and was supplemented by a number of ethicists, clinicians who care for patients with special needs, and representatives from the CP advocacy community. The subcommittee was convened at the request of the medical officer in DDDP in response to some of the unique concerns that the opening of the glycopyrrolate IND posed. They were charged with providing guidance on the development of antimuscarinic products to control drooling in children with neurologic impairment, especially the development of an optimal dosing strategy that balances benefit and risk. The consensus areas of discussion were as follows:

With regard to study design and implementation:

1. Formulations appropriate for pediatric use should be developed to ensure safety and consistency in administration. These formulations should be palatable and permit easy dose titration. In some cases it would be desirable to have more than one formulation available (e.g., suspensions, chewable tablets, sustained release, and transdermal).
2. In most cases, the child will be unable to identify expected and unexpected adverse events associated with antimuscarinics. Caregivers will need to take responsibility for this and these assessments should be done in conjunction with regular evaluation by medical professionals.

3. Dose titration will be so individualized for each subject, that the optimal dose will be limited primarily by the safety and tolerability of the undesirable anticholinergic adverse events. Therefore, a major component of clinical trials should involve caregiver training for assessment of adverse events. Tools for the assessment of safety and efficacy that will permit the development of an optimal dosing strategy should be developed in clinical trials. If these tools are successful, then they should become part of the instructions for use (i.e., direct patient instructions, parent package information, and “Dosage and Administration" section of labeling).
4. The Teacher Drooling Scale was discussed as being one of the most useful assessment tools for determining improvement in drooling. For assessment of adverse events, the panel discussed the Behavioral and Medical Rating Scale (BMRS). The panel pointed out that it is not a substitute for careful investigation of adverse events, but is a useful adjunctive measurement tool.
5. The trial should reflect the clinical care setting, which is usually a team based, multidisciplinary approach (e.g., subspecialties such as Physical Medicine and Rehabilitation, Otolaryngology and Gastroenterology; Dentistry; and Nursing).

Comments regarding the ethical conduct of clinical trials in vulnerable populations:

1. Children with disabilities in the care of their parents or legal guardians and who are incapable of effective communication should not be excluded from clinical trials based solely on their disability.
2. As described in 45 CFR 46.406, patients from vulnerable populations with the condition of interest should have access to clinical trials directed at their disease or condition.

Reviewer’s Comment: Point #3 above was interpreted by the sponsor as testing the caregiver before and after reading a manual for comprehension of its contents. Although the results of this testing showed that the caregivers improved by an average of 1.6 points out of 25, it should be noted that the caregivers did well even before reading the manual. It is not practical nor has it been shown to be beneficial to require that a caregiver’s manual be included with each Rx for glycopyrrolate. However, the highlights from this manual have been incorporated into the Patient Package Insert (PPI).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is all electronic, and is well organized. The applicant responded in a timely fashion to requests that were sent in the 74-day letter, as well as other information requests during the course of the review.

3.2 Compliance with Good Clinical Practices

The studies were conducted in compliance with good clinical practices. After discussion with the team and the reviewer from the Division of Scientific Integrity (DSI), it was decided that a DSI inspection was not warranted. There were no issues identified during the review process that raised integrity concerns, the active drug has been marketed for 40 years, and the one pivotal trial that was placebo-controlled enrolled too few subjects in each center to justify an on-site investigation.

3.3 Financial Disclosures

Financial disclosure was complete. None of the clinical investigators entered into any financial arrangement with the applicant in which compensation was associated in any way with the outcome of the studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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.

However, at the time of this review, the review of the container and carton labels is still pending and the Office of Compliance has not yet issued an overall “Acceptable” recommendation for all the facilities involved in the manufacture and test of the drug product.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

Based upon the conclusions of the pharmacology reviewer of this NDA, glycopyrrolate did not elicit any genotoxic effects in the Ames mutagenicity assay, the human lymphocyte chromosome aberration assay, or the rat micronucleus assay. In addition, glycopyrrolate was reasonably well tolerated in mice at levels that equate to a human equivalent dose of approximately 8 times and 20 times the maximum clinical dose proposed in this NDA. At these levels, pupil dilation was noted in all test animals, but

there were no remarkable effects on hematology, clinical chemistry, mean organ weights, or gross pathology.

The Pharmacology /Toxicology reviewer concluded that there were insufficient data submitted to address the effects of glycopyrrolate on fertility of rodents, developmental toxicity (teratology) of rodents and nonrodents, prenatal and postnatal development of rodents, and carcinogenesis of mice and rats. As such they are requiring additional studies as PMR's (Refer to Section 1.4 of this review for the list).

In terms of chronic toxicity testing in animals, an agreement was made with the Division in 2007 that chronic toxicology studies could be waived due to the long history of off-label use of glycopyrrolate (refer to Section 2.5 of this review, Regulatory History). Nonetheless, the sponsor conducted and submitted results of 90-day toxicology studies which was reviewed by Pharmacology/Toxicology staff and did not uncover any signals. It is prudent to review the long-term clinical evidence presented in this NDA for this chronic-use drug in order to add support to the decision to waive animal testing for chronic toxicology.

Towards that end, there is a long history of the safe use of glycopyrrolate in humans. During review of this NDA, it was revealed that Robinul tablets have been approved for use as a treatment of peptic ulcers since 1961, and there has been widespread use of it in children with similar medical backgrounds to the target population for the glycopyrrolate liquid. Drug utilization data has shown that approximately (b) (4) tablets of Robinul are sold every year, (b) (4) of which are prescribed annually to children under 18. An examination of all AERS reports and other related databases did not uncover any serious adverse events related to this extensive glycopyrrolate use. In addition, the three deaths that occurred during the open label study submitted to this NDA were not related to the drug use, and were within the normal background mortality rate for this population. In summary, there has been no signal to support a need for nonclinical chronic toxicology studies to be conducted as a part of the review process.

4.4 Clinical Pharmacology

Two studies were conducted under the IND to evaluate the clinical pharmacology of glycopyrrolate. Study FH-00-02 was a crossover study conducted in healthy adults to examine the food effect and bioavailability of glycopyrrolate oral solution in healthy adults. This study also included a relative bioavailability evaluation of glycopyrrolate oral solution fasting versus Robinul 1 mg tablets fasting. The open label pivotal trial, Sc-GLYCO-06-01 included Clin Pharm testing specifically focused on determining how to calibrate the pharmacokinetic characteristics for body size, to determine whether exposure in children best resembled the fasted or fed states in adults, and to determine whether other covariates contributed to the pharmacokinetic characteristics in children.

4.4.1 Mechanism of Action

Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, inhibits parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine. Because glycopyrrolate operates on the muscarinic acetylcholine receptors, it competitively inhibits the actions of acetylcholine or other cholinergic stimuli at muscarinic receptors and has little effect on cholinergic stimuli at nicotinic receptors, on structures innervated by postganglionic cholinergic nerves, and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic 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, in contrast to atropine sulfate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily. Following oral administration, the anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours.

4.4.2 Pharmacodynamics

Like other cholinergics, glycopyrrolate has gastrointestinal, genitourinary, cardiovascular, respiratory, and ophthalmic effects. Some antimuscarinic agents such as atropine cross the blood brain barrier to cause CNS effects such as drowsiness. However, glycopyrrolate does not, so drowsiness is not a common adverse event. Specific known effects of glycopyrrolate include: xerostomia, diminished gastrointestinal motility, decreased perspiration, increased body temperature, urinary retention, pupil dilation, loss of focusing accommodation, and increased heart rate. These expected effects of antimuscarinic drugs make them useful in treating certain conditions such as gastric ulcers, excess perspiration, overactive bladder, and pupil dilation during ophthalmologic examination. Treatment of drooling, the indication for this submission, is also a positive therapeutic use for the xerostomic effect of glycopyrrolate.

4.4.3 Pharmacokinetics

Table 2: Summary of Pharmacokinetic Parameters for Glycopyrrolate after Oral Administration of 2 mg as Glycopyrrolate Liquid under Fasted and Fed Conditions and as Robinul Tablet under Fasted Conditions

Parameter*	Glycopyrrolate Liquid 2 mg (1 mg/5 mL) Fasted	Robinul® Tablet 2 mg (2 × 1 mg) Fasted	Glycopyrrolate Liquid 2 mg (1 mg/5 mL) Fed
Cmax (ng/mL)	0.318 ± 0.189 (37)	0.406 ± 0.197 (37)	0.084 ± 0.081 (36)
Tmax (h)	2.53 (37) [0.50 – 6.00]	3.00 (37) [1.50 – 6.00]	2.50 (36) [1.00 – 6.08]
AUC(0-t) (h×ng/mL)	1.74 ± 1.07 (37)	2.34 ± 1.03 (37)	0.38 ± 0.14 (36)
AUC(inf) (h×ng/mL)	1.81 ± 1.09 (37)	2.45 ± 1.15 (36)	0.46 ± 0.13 (35)
λz (h^{-1})	0.2626 ± 0.0965 (37)	0.2528 ± 0.1025 (36)	0.2325 ± 0.0551 (35)
t½ (h)	3.02 ± 1.20 (37)	3.31 ± 1.57 (36)	3.21 ± 1.05 (35)

*Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Oral glycopyrrolate has low oral bioavailability, a median of 3.3% is found in plasma. Oral glycopyrrolate produced low plasma concentrations (Cmax 190-440 pg/mL) lasting up to 12 hours. After IV injection of 0.006 mg/kg, the mean distribution phase half-life was 2.22 ± 1.26 minutes and with a mean elimination phase half-life of 0.83 ± 0.27 hours. Plasma levels 6 hours post dose were nearly 10-fold greater in uremic patients than in controls. Elimination of glycopyrrolate is impaired in patients with severe renal impairment. Glycopyrrolate is excreted largely unchanged in the urine.

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. Of note is that the adult data revealed a somewhat less variable dosage form than the oral solution form.

The food effect data indicate the mean Cmax under fed high fat meal conditions is about 74% lower than the Cmax observed under fasting conditions. Similarly, the mean AUC for the liquid (fed) treatment was 3 to 4 times lower than those observed for the liquid (fasted) treatment. These data indicate that a high fat meal reduces the oral bioavailability of glycopyrrolate liquid if taken shortly after a meal. Glycopyrrolate liquid should be dosed at least one hour before meals as reasonably feasible.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: 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 pharmacokinetics	Randomized, double-blind, placebo-controlled	Open-label
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

5.2 Review Strategy

The sponsor conducted three clinical trials under this IND; one phase 1 pharmacokinetics study and two phase 3 trials (see table in Section 5.1, above). The Phase 1 trial was a single dose trial that was conducted to examine the biopharmaceutics profile of the tablet and the liquid, and to determine the effect of food on the bioavailability of the liquid. This study had no efficacy parameters, but did collect safety data, so it will be briefly reviewed in the safety section of this review only. The phase 3 studies can be pooled to a limited extent, as they both have the same primary efficacy outcome and both evaluate the drug's safety. However, there are significant differences as are noted in the table above. The most important difference is that FH-00-01 is a randomized, blinded 8-week trial with a placebo and Sc-GLYCO-06-01 is an open label 24-week trial.

The two trials are nearly identical in inclusion/exclusion criteria, study procedures, and both safety and efficacy evaluations. Both trials measured the number of subjects who achieved an improvement in their drooling scores of 3 or greater as their primary endpoint for measuring clinically significant efficacy. Because the open label study has no comparator group, it is not accepted by CDER as a conclusive demonstration of efficacy. However, study Sc-GLYCO-06-01 is supportive in that the efficacy outcome should be similar to that observed in the placebo controlled trial, and this study provides additional information about efficacy over a longer duration than trial FH-00-01.

To evaluate safety, the placebo trial is much more useful than the open label trial by controlling for background adverse events. This can help in uncovering the relationship between observed AE's and study drug; on the other hand, the open label trial, which is longer in duration by four months, gives us more subject-days on drug, which helps to uncover less frequently occurring AE's as well as valuable information about the patterns of AE's over time.

Therefore, in the remainder of Section 5 of this review, the individual studies will be summarized with an emphasis on the differences in protocols between the two. However, the detailed review of efficacy and safety based upon the outcomes of the studies will be reviewed side by side in Sections 6 and 7 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Table 4: Study Plan Synopsis for FH-00-01

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
	Screen (Day -21 to -9)	**Baseline (Day -8 to 0)**	**Day +1**	**Week 2 (Day 14)**	**Week 4 (Day 28)**	**Week 6 (Day 42)**	**Week 8 (Day 56)**	**Dropout**
Informed Consent	X							
Inclusion/ Exclusion	X							
Demographics	X							
Medical History	X							
Physical Exam	X						X	X
Randomization			X					
Study Medication			X	X	X	X	X	X
Caregiver Training	X		X				X	X
Blood Chemistry	X						X	X
CBC	X						X	X
Urinalysis	X						X	X
12-Lead ECG	X						X	X
Pregnancy Test	X						X	X
mTDS Caregiver	Dispense Diary			X	X	X	X	X
Global Assessments							X	X
mBMRS	Instruct Caregiver, Dispense Diary		X	X	X	X	X	X
Caregiver Diary (c)	Instruct & Dispense		X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X
Concomitant Meds	X		X	X	X	X	X	X

Table 5: Study Plan Synopsis for Study Sc-GLYCO-06-01

	Visit 1	Baseline	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 Exit Visit [a]
	Screen Day -14 to -3	Day -2	Day -1	Day 1	Week 4 Day 28 [b]	Week 8 Day 56 [b]	Week 12 Day 84 [b]	Week 16 Day 112 [b]	Week 20 Day 140 [b]	Week 24 Day 168 [b]
Informed consent	X									
Inclusion/exclusion	X									
Demographics	X									
Medical/surgical history	X									
Physical examination	X									X
Washout prohibited medications	X									
Study medication				X	X	X	X	X	X	X [c]
Training manual	X			X	X	X	X	X	X	
Blood chemistry	X									X

Hematology [g]	X				PK	PK	PK	PK	PK	X
TSH and free T_4 [d]	X									
Urinalysis	X									X
Vital signs	X			X	X	X	X	X	X	X
12-lead ECG	X				X		X			X
Pregnancy test [e]	X			X						X
mBMRS assessment	X [f]	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
mTDS assessment	X [f]	X	X	X	X	X	X	X	X	X
VAS	X [f]	X	X	X	X	X	X	X	X	X
Parent/caregiver's global assessment										X

Trial procedures and timelines

Below is a table of procedures for both pivotal trials. Highlights include: Prior to being randomized to either the test product or placebo, eligible subjects received measurements of safety and efficacy. Study doses are titrated over the first four weeks to optimal response, beginning at 0.02 mg/kg t.i.d. up to 0.1 mg/kg t.i.d. (not to exceed a maximum dose of 3 mg t.i.d., regardless of weight). Safety assessments included standard AE monitoring, laboratory measures, and ECG evaluation.

Table 6: Comparison of Procedures and Assessment of both Pivotal Trials

Study Title	**Study FH-00-01**: *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*	**Study Sc-GLYCO-06-01:** *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*
Design	Phase 3, multicenter, randomized, double blinded, placebo controlled	Phase 3, open label
Duration	8 weeks	24 weeks
Number of Sites	10, all in U.S.	29, all in U.S.
Objectives:	To assess: • The efficacy of glycopyrrolate in this population • The safety of glycopyrrolate in this population • The caregiver's ability to identify adverse events between visits so that the	To assess • Continued efficacy of maintenance doses of the drug • The safety of the drug given chronically • Population pharmacokinetics.

	investigator can optimally titrate the dose.	
Inclusion Criteria	Male or female ages 3 through 16.	Male or females ages 3 – 18.
	The remainder of the criteria are identical in both trials as follows: • Weigh at least 13 kg (27 lbs) • Have profuse, severe drooling in the absence of treatment so that clothing became damp on most days (approximately five to seven days per week); and a diagnosis of cerebral palsy and/or mental retardation or any other neurologic impairment or condition. • A reliable caregiver as determined by the investigator is living with the subject. • Also of note is that the protocol specifically allows enrollment of subjects with tracheostomies or gastrostomy feeding tube.	
Exclusion Criteria	Identical for both trials: • Pregnancy • Use of glycopyrrolate liquid within approximately 24 hours prior to Baseline • Use of any of the prohibited anticholinergic or cholinergic medications specified in the protocol within three plasma half-lives of the medication prior to Baseline • Medical conditions contraindicating anticholinergic therapy including: o "Glaucoma, obstructive uropathy, uretovesicular reflux, reactive airway disease, myasthenia gravis, hyperthyroidism, cardiac arrhythmias and/or tachycardia, and/or clinically significant ECG abnormalities as determined by the investigator."	
Treatments	The primary treatment being studied in this trial is glycopyrrolate liquid at a concentration of 1mg per 5 mL. There is a 1:1 randomization of subjects to a matched placebo. Both trials have the same daily dosing schedule. Study medication will be administered TID at 7–8 AM, 1–2 PM, and 7–8 PM by the parent/caregiver (or school nurse if the patient is in school during these hours of the day). Prior to being randomized to either the test product or placebo, subjects had baseline measurements of safety and efficacy.	
Dose Titration	In both studies, study doses are titrated over the first four weeks to optimal response, beginning at 0.02 mg/kg t.i.d up to 0.1 mg/kg TID (not to exceed a maximum dose of 3 mg t.i.d, regardless of weight). After starting at Dose Level 1, doses will be increased every five to seven days in increments of 0.02 mg/kg TID, according to the dose titration schedule. If anticholinergic adverse events become intolerable, the parent/caregiver will be instructed to contact the investigator, who will	

	reduce the dosage to the previous dose-level in the schedule and have subjects continue to use that dose-level for the remainder of the study (or until side effects require another reduction to the next-lowest dose-level.) If no significant drug-related AEs are reported by the caregiver, the investigator will increase the subject to the next dosing level. This will continue during the 4-week time period, until optimal individual response or a maximum of 0.1 mg/kg TID or 3 mg TID is attained, whichever is lesser as indicated in the dose titration schedule. During the titration period, investigators will assess patients every five to seven days by telephone and adjust the dose until an optimal dose has been achieved. After dose titration is completed, the Investigator is not to change the dose so that safety and efficacy data may be recorded for the maintenance dose until the end of the study. However, if the Investigator determines that for a given patient an intermediate dose between two dose levels in the dose titration schedule is more adequate, use of the intermediate dose is acceptable.	
	The titration to optimal dosing is reached at Week 4 in this trial and remains constant for the remainder of the 8 week trial duration.	The titration to optimal dosing is reached at Week 4 in this trial and remains constant for the remainder of the 24 week trial duration.
Caregivers Training	A consideration of both studies involved measurement of the caregiver's ability to interpret the signs of efficacy and associated anticholinergic adverse events. During the trials, each caregiver reviewed instructional materials about titrating the dose and observing for adverse events in subjects. Caregivers never increased the dose on their own; they reviewed their record of adverse events with the investigator and the investigator made the decision about increasing the dose. Caregivers were allowed to decrease dose levels due to concerns about adverse events; however, they were then required to immediately inform the Investigator.	
Efficacy Evaluations		
Primary Efficacy Outcome Measurements	The Teachers Drooling Scale (TDS; described in section 6.1.4 in detail) is the primary outcome measurement. This scale is completed four times by the caregiver during the pre-specified evaluation days - 7 AM, 9 AM, 3 PM, 9 PM	
	TDS evaluation in this trial is at baseline and on Days 14, 28, 42 and 56.	TDS evaluation at baseline and on days 28, 56, 84, 112, 140 and 168 (corresponding to 4, 8, 12, 16, 18 and 24 weeks).
Other endpoint measurem	Global Assessment of Treatment(1-5 scale for statement, "This is a worthwhile treatment") at Week 8 or	Global Assessment of Treatment and Training Manual identical to other study, with exception that the

ents	last visit for withdrawals - Separate Caregiver-Reported and Investigator-Reported Global Assessment of Training Manual at Week 8 or last visit for withdrawals "The training manual was helpful." Yes or no. Separate Caregiver-Reported and Investigator-Reported	assessment is at Week 24 or the last visit for withdrawals. This open label study added a VAS Caregivers Assessment of drooling performed on the same day as the TDS.
Safety Evaluations		
AE	Adverse events and concomitant medications will be recorded on the appropriate CRF pages. The mBMRS will continue to be used by the parent/caregiver every two to three days throughout the study as well as by the investigator (as a scripted verbal questionnaire) during visits. The investigator will review the diary with the parent/caregiver to be sure mTDS, VAS, and mBMRS assessments are completed correctly. The investigator will indicate on the CRF whether AEs (or SAEs) were identified by the parent/caregiver's use of the mBMRS–this will permit data analysis to distinguish between AEs identified by mBMRS and AEs not identified by mBMRS. AE's are determined by the investigator, from the diary and mBMRS form and from interviewing the parents/caregiver.	
Laboratory testing	Testing included hematology, Serum biochemistry, Urinalysis, TSH and free T4 (in nonverbal, non-mobile patients), urine or blood pregnancy test: (if applicable) (Details of testing is discussed in Section 7.2.4 of this review entitled Routine Clinical Testing.	
	Laboratory testing was conducted at screening and Week 8.	Laboratory testing was conducted at screening and Week 24.
ECG	Glycopyrrolate, as an anticholinergic, is expected to increase the heart rate. In anticipation of the need to address cardiac effects, the sponsor incorporated ECG analysis into both the placebo-controlled trial and the open label trial on all randomized subjects with at least one available baseline and one treatment. Full discussion of these results appears in Section 7.4.4 of this review.	

Amendments to Protocol:

Study protocol FH-00-01 was amended three times.

1. Amendment # 1 specifically allowed enrollment of subjects with tracheostomies or gastrostomy feeding tube. It was implemented before the first subject was enrolled, so there was no impact on the trial.
2. Amendment #2 modified the inclusionary criteria (b) (4) to "subjects up to a

maximum of 16 years of age with cerebral palsy, (b) (4) or any other neurologic impairment or condition associated with problem drooling." This was done to meet the requirements for orphan status (as was discussed in further detail in Section 2.5 of this review)

3. Amendment #3 modified the data analysis for the subjects who had been enrolled under the old criteria as follows: (1) age excluded patients were replaced with new patients who meet the 3-16 year old age criterion and the other inclusion/exclusion criteria; (2) added replacement patients were each assigned a new patient number according to the usual sequence of enrollment consistent with enrollment procedures in place since the initiation of the study, (3) age-excluded patients were excluded from PP primary efficacy analyses, and (4) confirmatory PP analyses were performed, which included age-excluded patients."

   Before Amendment #3 was implemented, two patients with cerebral palsy had been enrolled who were over age 16 (Patient 5002 in the glycopyrrolate group was 23 and Patient 1002 in the placebo group was 20). Although these patients were replaced with new patients and were excluded from efficacy analyses, data for these patients were included in the analysis of safety. The statistical reviewer discussed this analysis in detail, and found it acceptable.

Protocol Violations/Deviations
Two patients in the glycopyrrolate group had deviations from inclusion/exclusion criteria.

1. Patient 2004 had undergone surgery previously to control sialorrhea, but the surgery failed so the sponsor approved an exemption for the patient to be enrolled.
2. Patient 6005 did not undergo a pregnancy test at Screening because no sample was collected. However, subsequently a sample was collected, and the result was negative. No violations/deviations were reported for the placebo group.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

In this section, the methods, analyses and discussion of the efficacy for the proposed indication is reviewed. There is one indication proposed for this NDA, which is as follows: "The treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients aged 3-16 with cerebral palsy, (b) (4) or other neurologic conditions associated with problem drooling."

6.1.1 Methods

Refer to Section 5.3 of this review, *Discussion of Individual Studies/Clinical Trials,* for a table that includes the methodology for the analysis of the clinical efficacy data. As discussed, the two pivotal trials will not be pooled for efficacy due to the considerable differences in design. The design and endpoints for both safety and efficacy were appropriate, although the open-label clinical trial is only supportive for efficacy, due to not having a placebo group. Given the knowledge of anticholinergics, appropriate exclusionary criteria were used, which will also be reflected in the labeling. Although all subjects had to have severe drooling to be enrolled, the sponsor enrolled subjects with a variety of degrees of co-morbidity factors. The majority of subjects had CP, but some subjects had conditions other than CP that caused severe drooling, including Angelman syndrome and Rett syndrome. Although the vast majority of subjects were spastic and quadriplegic, some had lesser degrees of spasticity and paralysis. All of these important baseline characteristics are noted along with basic demographic information in the next section of this review.

The sponsor intentionally chose a pediatric population for the indication, so the effects on older patients are not known. With the exception of geriatric subjects, there is generally more safety concern in children than adults, and the label should reflect that the labeled population is children only. More details are provided in the remainder of this review about the demographic and other baseline characteristics, and what impact these parameters have on efficacy and safety.

6.1.2 Demographics

Table 7: Demographic Profile for Both Trials

Demographic Characteristic	FH-00-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 19	Sc-GLYCO-06-01 Glycopyrrolate Oral Solution (1 mg per 5 mL) N = 137	Placebo N = 17
Age (years)			
N	19	137	17
Mean (SD)	10.2 (3.8)	11.0 (4.4)	8.7 (4.0)
Min, Max	4, 16	3, 18	3, 16
Age group (years)			
≥ 3 to ≤ 11	12 (63.2%)	69 (50.4%)	12 (70.6%)
≥ 12 to ≤ 18	7 (36.8%)	68 (49.6%)	5 (29.4%)
Sex			
Male	13 (68.4%)	77 (56.2%)	9 (52.9%)
Female	6 (31.6%)	60 (43.8%)	8 (47.1%)
Childbearing potential			
No	4 (66.7%)	41 (68.3%)	4 (50.0%)
Yes	2 (33.3%)	19 (31.7%)	4 (50.0%)
Race			
White	16 (84.2%)	98 (71.5%)	10 (58.8%)
Black or African-American	2 (10.5%)	29 (21.2%)	7 (41.2%)
Other	1 (5.3%)	10 (7.3%)	0
Ethnicity			
Hispanic or Latino	3 (15.8 %)	15 (11.0%)	6 (35.3%)
Not Hispanic or Latino	16 (84.2%)	121 (89.0%)	11 (64.7%)
Missing	0	1	0

The table above summarizes basic demographic information from both pivotal trials. The majority of patients were male (68.4% of the patients in the FH-00-01 glycopyrrolate group, 52.9% in the placebo group, and 56.2% in the Sc-GLYCO-06-01 study), and white (84.2% of the patients in the FH-00-01 glycopyrrolate group, 58.8% in the placebo group, and 71.5% in the Sc-GLYCO-06-01 study) with a higher percentage of patients between 3 and 11 years of age (63.2% of the patients in the FH-00-01 glycopyrrolate group, 70.6% in the placebo group, and 50.4% in the Sc-GLYCO-06-01 study) than between 12 and 18 years of age. Regarding body weight, 57.9% of the patients in the FH-00-01 glycopyrrolate group, 58.8% in the placebo group, and 46.6% in the Sc-GLYCO-06-01 study were above the 5th weight percentile for age while the remaining patients were below this percentile.

Table 8: Baseline Characteristics: Intent–to-Treat Population

	Trial FH-00-01 Total N = 37		Trial Sc-GLYCO-06-01		
Baseline Characteristic	**Glycopyrrolate N = 20**	**Placebo N=18**	**Total N=137**	**Naïve N=84**	**Non-Naïve N=53**
Mental retardation	20 (100%)	18 (100%)	124 (90.5%)	75 (89.3%)	49 (92.5%)
Speech impairment	20 (100%)	18 (100%)	134 (97.8%)	81 (96.4%)	53 (100.0%)
Oral feeding problems	10 (50%)	8 (44%)	91 (66.4%)	49 (58.3%)	42 (79.2%)
Uses tube for feeding	7 (35%)	5 (28%)	70 (51.1%)	35 (41.7%)	35 (66.0%)
Nutritional status					
Well-nourished	19 (95%)	16 (88%)	120 (87.6%)	71 (84.5%)	49 (92.5%)
Overweight	0	0	3 (2.2%)	3 (3.6%)	0
Under-nourished	1 (5%)	2 (11%)	14 (10.2%)	10 (11.9%)	4 (7.5%)
Patient has cerebral palsy	17 (85%)	15 (83%)	96 (70.1%)	55 (65.5%)	41 (77.4%)
If not CP, other condition:					
Rett Syndrome	2 (10%)	0	3		
Epilepsy	1 (5%)	0	5		
Angelman syndrome	0	0	3		
Chromosomal Disorder	0	0	5		
Encephalopathy	0	0	7		
Other Conditions in Trial Sc-GLYCO-06-01 with one occurrence each include: Global Developmental Disorders, Stickler Syndrome Nemaline rod myopathy, Pierre Robin anomaly, Moyamoya disease, generalized hypotonia, DiGeorge syndrome, autism, and San Filippo syndrome					
Cerebral palsy category 1					
Spastic	15 (88%)	13 (87%)	78 (81.3%)	45 (81.8%)	33 (80.5%)
Hypotonic	1 (6%)	1 (7%)	8 (8.3%)	4 (7.3%)	4 (9.8%)
Ataxic	0	0	2 (2.1%)	1 (1.8%)	1 (2.4%)
Athetoid	0	1 (7%)	3 (3.1%)	2 (3.6%)	1 (2.4%)
Mixed	1 (6%)	0	5 (5.2%)	3 (5.5%)	2 (4.9%)
Missing	3	3	41	29	12
Cerebral palsy category 2					
Quadriplegic	14 (82%)	13 (87%)	79 (82.3%)	45 (81.8%)	34 (82.9%)
Hemiplegic	3 (18%)	1 (7%)	6 (6.3%)	4 (7.3%)	2 (4.9%)
Diplegic	0	1 (7%)	7 (7.3%)	4 (7.3%)	3 (7.3%)
Triplegic	0	0	3 (3.1%)	1 (1.8%)	2 (4.9%)
Residence of patient					
At home with parent	17 (85%)	17 (94%)	91 (66.4%)	60 (71.4%)	31 (58.5%)
At home with foster parent/guardian	3 (15%)	1 (6%)	12 (8.8%)	8 (9.5%)	4 (7.5%)
Institutional setting	0	0	34 (24.8%)	16 (19.0%)	18 (34.0%)
Tracheostomy	0	0	16 (11.7%)	5 (6.0%)	11 (20.8%)

In the table above, the baseline characteristics of the subjects are summarized. The open label trial subjects generally had more severity in their disease symptoms than in the placebo controlled trial. Although it is useful that the second trial enrolled subjects with more diversity in their symptoms and settings, the results should be examined

separately, as they are somewhat different populations. In particular, the following differences between the placebo-controlled trial and open label trial are noted: Every subject in the placebo controlled trial had mental retardation and speech impairment, whereas 91% and 98% of subjects in the open label trial had the respective conditions. None of the subjects in the placebo controlled trials had tracheostomies, whereas 12% in the open label trial did. Every subject in the placebo trial had a CP diagnosis, except for two with Rett syndrome and one with severe epilepsy, whereas the open label trial had a myriad of neurological conditions that were more serious than CP.

The feeding tube incidence was also higher in the open label trial. This is also consistent with none of the placebo subjects residing at home, whereas 25% of those in the open label trial lived in an institutional setting. Another important difference, especially in their ability to tolerate the expected AE's, is that in the open label study, 39% of the subjects had used glycopyrrolate in its tablet form before joining this study (non-naïve subjects), compared to only 16% in the placebo-controlled trial. Of the subjects who had used the tablets before, it can be predicted that they would have been more likely to succeed, as they were able to tolerate the drug in their past. It would be far less likely to have dropouts from AE's or difficulties with the AE's in this non-naïve group, as compared to those who are naïve to treatment.

6.1.3 Subject Disposition

Table 9: Disposition of Subjects in Both Trials

	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 = 160	Placebo N = 18
Enrolled patients	20	160	18
All randomized population	20	137	18
MITT population	19	137	17
Patients who completed the study	17 (89.5%)	103 (75.2%)	15 (88.2%)
Patients who discontinued from the study early	2 (10.5%)	34 (24.8%)	2 (11.8%)
Reasons for discontinuation from the study			
Failed to meet entry criteria	0	2 (1.5%)	0
Lack of efficacy 95% CI	0 [NA, NA]	2 (1.5%) [0.0%, 3.5%]	1 (5.9%) [0.0%, 17.1%]
Adverse event(s)	1 (5.3%)	14 (10.2%)	0
Investigator decision	0	2 (1.5%)	0
Patient non-compliance	0	2 (1.5%)	0
Patient/parent decision	1 (5.3)	5 (3.6%)	1 (5.9%)
Lost to follow-up	0	3 (2.2%)	0
Death	0	3 (2.2%)	0
Other	0	1 (0.7%)	0

As summarized in the above subjects' disposition table, the overall 11% dropout rate during the 8-week placebo controlled trial, and 25% dropout rate from the open label six–month trial is within normal limits. In both trials, AE was the primary reason for drop out, 10% in the open label trial, and 5% in the placebo-controlled trial. It is well known that the anticholinergic adverse events are uncomfortable and some dropouts as a result are to be expected. The three deaths that were cited as a dropout reason are described in full detail in the safety section of this review, and were not related to the study. None of the remaining dropout subjects require further discussion.

6.1.4 Analysis of Primary Endpoint(s)

In this section, the results of the primary endpoint analyses will be presented side-by-side for both the phase 3 controlled clinical trials (FH-00-01) and the phase 3 open label trial (Sc-GLYCO-06-01). The open label study does not have a placebo arm; therefore, a statistical comparison cannot be made and the trials should not be pooled. However, both studies use the same primary endpoint and it is useful to see how well the results from the active arm in the open label study match the active arm's outcome in the placebo-controlled trial. It is also useful to examine the longer-term efficacy of the open label study, since it consists of measurements that continue for six months, whereas the placebo trial ended at two months.

It is noted, however, that for the purposes of labeling and promotion, current CDER guidance strongly discourages the use of open label trial results in the label (citation: FDA's *Guidance for Industry: Clinical Studies Section of labeling for Human Prescription Drug and Biological Products – Content and Format*, January, 2006). Therefore, the intent of this review is to evaluate the open label efficacy results as supportive only.

The primary efficacy measurement is the modified Teacher's Drooling Scale (mTDS). The mTDS consists of a 9-point scale which quantifies the severity and frequency of drooling:

1 = Dry: never drools
2 = Mild: only the lips are wet; occasionally
3 = Mild: only the lips are wet; frequently
4 = Moderate: wet on the lips and chin; occasionally
5 = Moderate: wet on the lips and chin; frequently
6 = Severe: drools to the extent that clothing becomes damp; occasionally
7 = Severe: drools to the extent that clothing becomes damp; frequently
8 = Profuse: clothing, hands, tray and objects become wet; occasionally
9 = Profuse: clothing, hands, tray and objects become wet; frequently

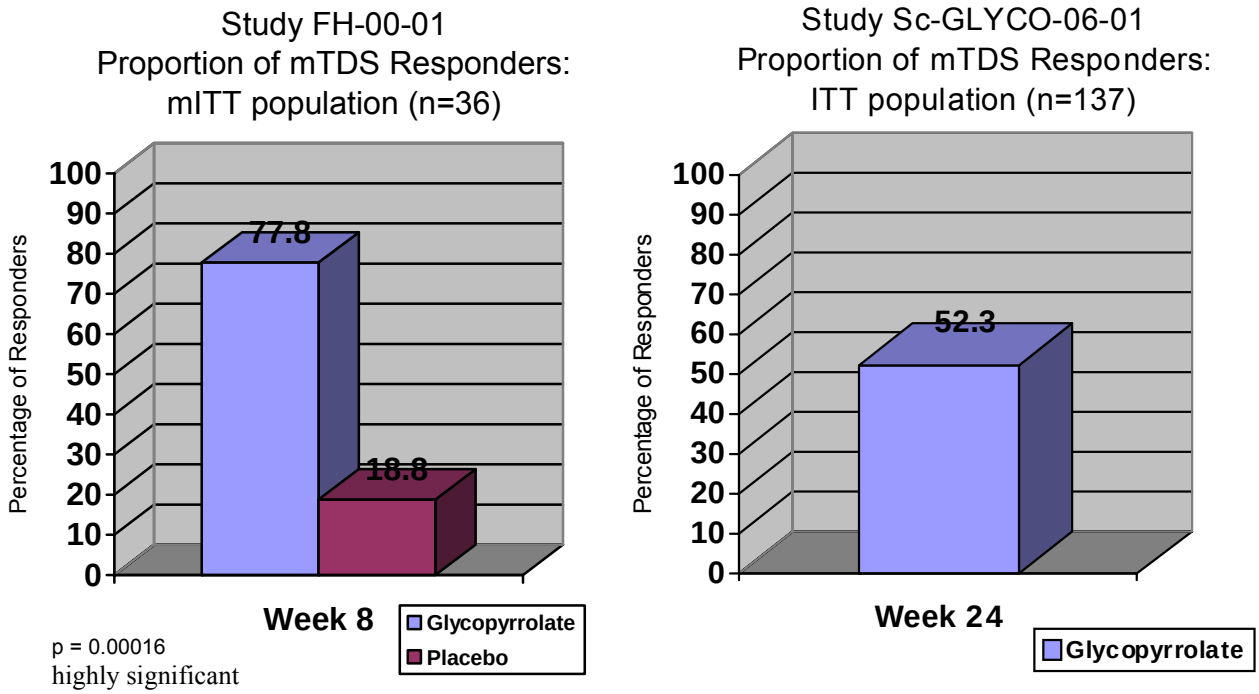
Caregivers completed the scale during prespecified, discrete days of the trials. Baseline scores were recorded at home during two consecutive days prior to drug assignment; the remaining scoring was performed during days 14, 28, 42, and 56

(Weeks 2, 4, 6, and 8) for the placebo-controlled trial and during days 28, 56, 84, 112, 140 and 168 (corresponding to 4, 8, 12, 16, 18 and 24 weeks) for the open label study.

During each of the scoring days, the caregivers performed four evaluations. The first was conducted at 7 AM, prior to the first daily dose of glycopyrrolate; the remaining evaluations were recorded 1 – 2 hours after the three daily doses: at 9 AM, 3 PM, and 9 PM. The mTDS score for each evaluation day was calculated by using the mean of the last three daily assessments and rounding to the nearest tenth decimal place. The baseline mTDS score for each subject is defined as the last day's mTDS assessment before first dose of study medication. For each subject, the change in score from the baseline score to the score at the last evaluation of the trial was calculated. Each subject who improved by 3 units or more was classified as a responder. The pre-specified test of statistical significance was the percentage of responders in the glycopyrrolate group compared to those in the placebo group.

Below is a set of graphs showing the proportion of responders in both phase 3 trials. Study FH-00-01 (on the left) is the placebo-controlled trial, in which the highly significant difference (p=0.0016) between glycopyrrolate responders (77.8%) and placebo group responders (18.8%) is displayed. The graph on the right shows the proportion of responders (52.3%) in trial Sc-GLY-06-01, the open label trial of 24 weeks duration. Although there is no placebo group in that trial with which to compare or perform statistical testing, the similarity of the result to the first study is useful in corroborating the effect at Week 24, the last visit of the open label trial. It is also noteworthy that the proportion of responders is still high at the end of the six month open label trial.

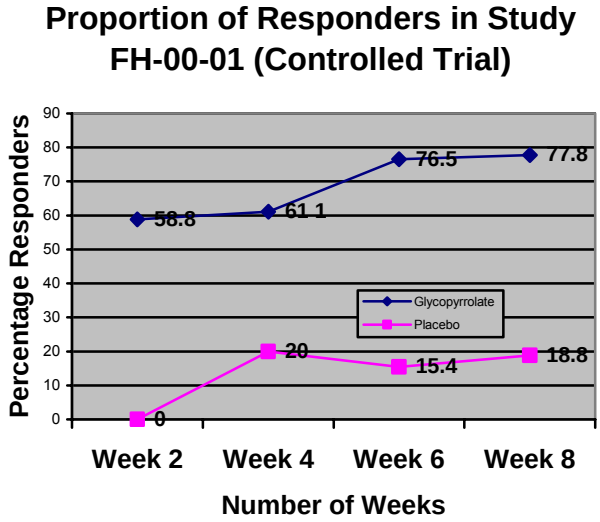
Figure 1: mTDS Responders

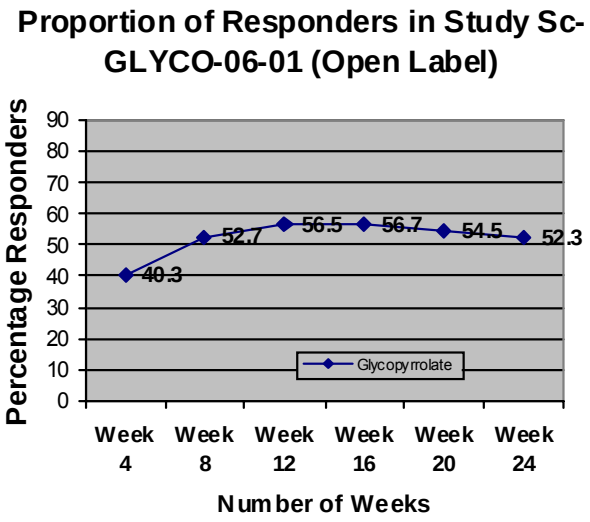


Efficacy Pattern over Time

Because the pre-determined statistical testing of the primary outcome variable as shown above displays only the final mTDS reading compared to the baseline mTDS reading, it is worth examining the pattern of response that also includes the results of the mTDS at several points throughout the trials. Below is a set of graphs that display the proportion of responders in both phase 3 trials at each time point during which the TDS was measured. Note the increase in effect after the Week 4 visit in both trials. This may be explained by recognizing that during the first four weeks of each trial, the dose began low and was titrated upwards between baseline and Week 4. After Week 4, the final dose is maintained, which in most cases was much higher than the starting doses.

Figure 2: mTDS Scores by Visit





Validity of Primary Outcome Variable

Regarding the validity of the mBRS as the primary outcome measure, formal comments were solicited by the Division from the Study Endpoint and Labeling Division (SEALD), due to their expertise in measurements that are not investigator-reported, as is the case in both the primary and secondary efficacy parameters in this NDA. Their comments about the mTDS are useful in that they identify this type of assessment as a "reporter-observed outcome," which has elements of a Patient-Reported Outcome, but due to the cognitive impairment of the subjects, is not patient-reported. This type of secondary reporting must meet certain criteria for validity. The SEALD reviewer stated that it is not acceptable for an observer to report another person's response directly, i.e., someone else's level of pain; however, it is appropriate for subjects who cannot respond for themselves to have observers report on events or behavior that can be observed. In this case, the mTDS scale does just that, with numbers on the scale corresponding to the amount of wetness that is observed on the subjects' clothing and body.

The TDS has a long history of use for evaluating drooling. It first appeared in the literature in 1989 (Camp-Bruno, JA. *Efficacy of benztropine therapy for drooling.* Dev Med Child Neurol. 1989: 31: 309-319) and based upon a current PubMed search, has appeared since in twenty-two journal articles. In the Camp-Bruno article, the authors discuss the development and testing of the TDS. They point out that they created it in order to address several unmet needs of drooling measures at that time:

1) Direct measures of salivary flow-rates and volume are feasible, but irrelevant, while quantitative collection of drooled saliva is relevant but impractical; and
2) Since drooling is highly variable across and within patients over time, an average drool value derived form repeated daily measurements is necessary. Prior to the TDS, most scales had evaluators rate "level of improvement" after drug administration rather than degree of drooling at several time points before and after drug administration.

In their paper, Camp-Bruno et al helped to establish validity with demonstration of both high retest and high correlation between the TDS and more objective time-sampling stream. The original TDS scale measured only the degree of drooling (dry, mild, moderate, severe and profuse); this scale was modified shortly after its introduction to accommodate frequency of drooling as well. The original five categories of dry, mild, moderate, severe and profuse were expanded to nine, with all categories except dry being split into two – occasionally and frequently.

In addition to its widespread use and sound design, the TDS was specifically recommended by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (see Section, 2.6 of this review: Regulatory History) as an appropriate primary outcome variable. It was also agreed upon as an acceptable primary outcome measurement by DDDP during formal meetings. Along those lines, the Division staff specifically recommended that the sponsor modify their primary outcome variable by classifying responders to the mTDS as those with an improvement of three units or more. (b) (4)

In FH-00-01, one only subject dropped out due to lack of efficacy. This subject was in the placebo group. In Sc-GLYCO-06-01, two subjects dropped out due to lack of efficacy. As was noted above, as an open label trial, efficacy results are only supportive and will not be used in the labeling or any promotional materials; therefore, this small number of dropouts over the six months duration is not problematic and does not warrant further discussion. The analysis on dropouts from both trials will be discussed fully in Section 7.3.3: *Dropouts and/or Discontinuations*.

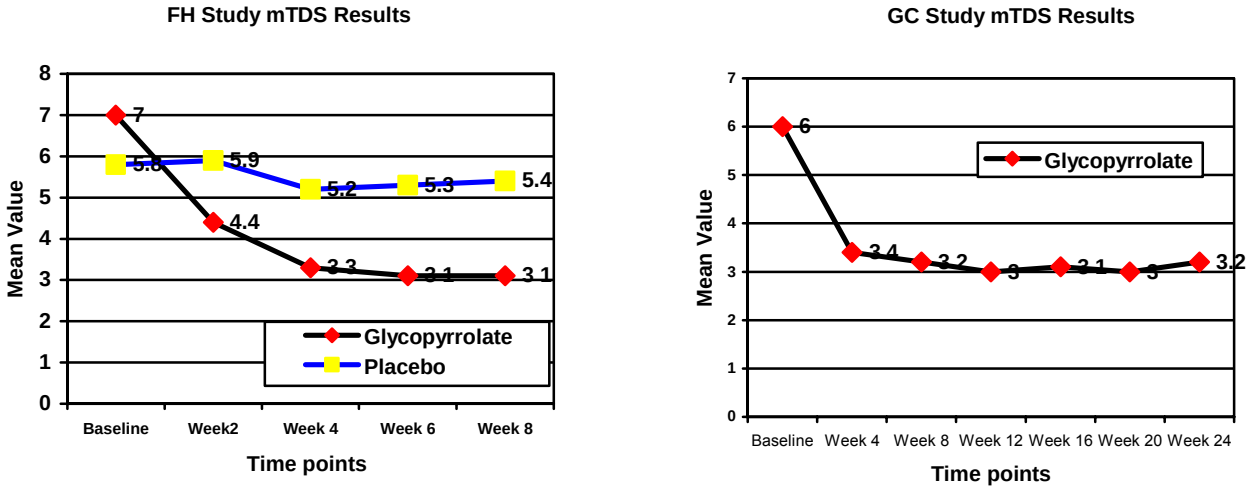
6.1.5 Analysis of Secondary Endpoints(s)

As planned in the protocol, secondary efficacy endpoints include:

1. *Results of the mTDS obtained at individual time points for parent/caregiver assessments.*
2. *Caregiver's and Physician's Global Assessments.*
3. *Caregiver's VAS assessment of improvement.*

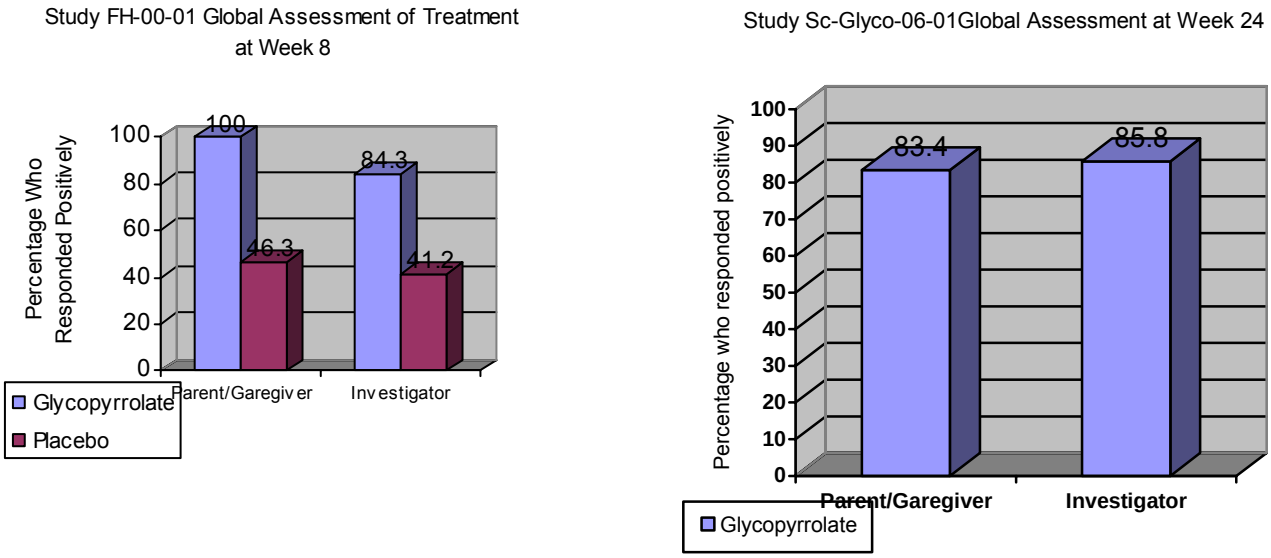
Each of these endpoints will be discussed briefly, in order.

Figure 3: Results of the mTDS at individual time points



The graphs above show the mean values of the mTDS at each time point during which they were measured (note that in this scale, improvement is a decrease in numeric value). The graph on the left, for the placebo-controlled trial, is consistent with the pattern discovered in the primary analysis – the improvement is dramatic over the titration period from baseline until Week 4, and the effect is maintained until the end of the trial. The placebo group, on the other hand, shows no change. In the graph of the open label trial (on the right), the same pattern is evident, and it also shows that the effect was maintained throughout the 6-months duration.

Figure 4: Parent/Caregiver's and Investigator's Global Assessment of Treatment



At the end of the study at Week 8, both the parent/caregiver and the investigator completed a global assessment of the overall treatment using a 5-point scale. The patient/caregiver and investigator completed the assessment by choosing the number that corresponded to whether they agreed or disagreed with the statement:

> "This is a worthwhile treatment" (1= strongly agree, 2= agree, 3 = neutral, 4 = disagree, 5= strongly disagree).

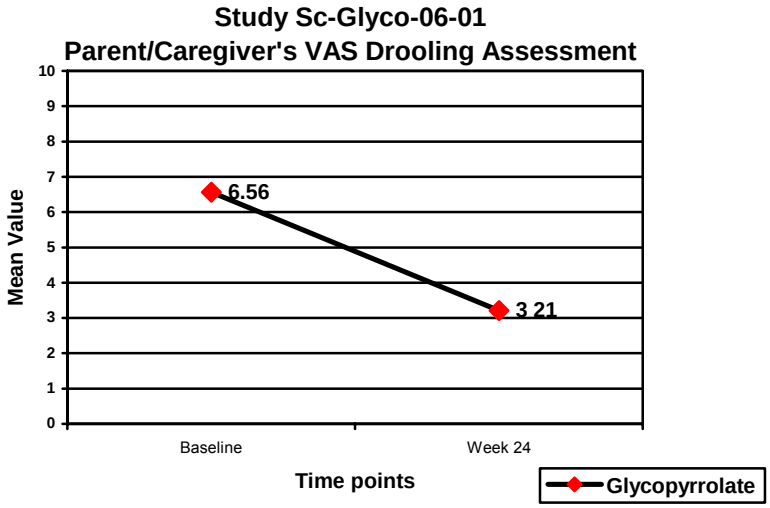
The intent of the global assessment was to obtain the parent/caregiver's and the investigator's overall evaluation of glycopyrrolate liquid for the treatment of drooling, including benefits and adverse effects, during the entire duration of the study.

At Week 8 (the last visit) of Study FH-00-01, 84% of physicians and 100% of parent/caregivers agreed that treatment with glycopyrrolate was worthwhile, while only 41% of physicians and 56% of parent/caregivers thought the placebo was worthwhile ($p \leq 0.014$; Fisher's Exact)

At Week 24 (the last visit) of Study Sc-GLYCO-06-01, 83% of parent/caregivers and 86% of the investigators agreed that the treatment with glycopyrrolate was worthwhile.

The SEALD team reviewed this global outcome variable and deemed it not "content valid". This means that the term "worthwhile" does not describe a well-defined effect of treatment. (b) (4)

Figure 5: Visual Analog Scale (VAS):
Parent/Caregiver's Assessment of Extent of Drooling for the Day



During the open-label study only, the parent/caregiver performed VAS assessments on the same days that mTDS assessments were obtained. The purpose of the 10 cm "Parent/Caregiver's Assessment of Extent of Drooling for the Day" VAS assessment (0 = normal; 10 = extremely wet) was to provide an overall assessment of the extent of drooling for that day. The VAS was obtained at the end of the Baseline day and at the end of the day prior to the last visit at Week 24 (Visit 8). The change from Baseline in VAS assessment was calculated as the Baseline VAS assessment minus the post-Baseline VAS assessment. A positive change was indicative of improvement in symptoms and a negative change reflected a worsening of symptoms. The mean VAS score was reduced from 6.56 at Baseline to 3.21 at the end of 24 weeks of treatment with glycopyrrolate liquid.

(b) (4)

In the open label study, there is no comparator group, so any improvement over baseline cannot be corrected for background improvement that is often discovered during clinical trials. In addition, VAS scales are difficult to use, unless anchored with easy-to-comprehend explanations and guides to help gauge where the mark along the line should be. Nonetheless, the trend of this outcome is consistent with the other outcomes; even on a poorly conceived scale, the results show that parents/caregivers noted an improvement in drooling in subjects when taking glycopyrrolate, as compared to the baseline measurement before taking the drug.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

The following subgroups were analyzed for the MITT population:

- Age group (≥3 to ≤11 years, ≥12 to ≤18 years)
- Gender (Male and Female)
- Race (White, Black or African-American, Other)
- Weight for Age Percentile (≤5th Percentile, >5th Percentile)

In the table below, the primary endpoint for the placebo-controlled trial, proportion of Responders at Week 8, is listed for both the test group and the placebo group, as stratified by age, gender, race and weight. Although the sample size is small, the overall trend does not suggest any differences between subgroups. In Study FH-00-01, the response rate at Week 8 was slightly higher in patients of 12 years or older (83.3%) than in younger patients (75.0%), in female patients (100.0%) than in male patients (66.7%) and for patients above the 5th weight percentile (90.9%) compared to patients below the 5th weight percentile (57.1%) while no clinically relevant tendencies could be revealed for race (due to the low number of black and other races) or the 3 dose categories. Although Study Sc-GLYCO-06-01, the open-label trial (b) (4) for completeness, a similar subgroup analysis is shown in the table as well. No clinically relevant tendencies with regard to response rate could be revealed for subgroup analyses in this trial either.

Table 10: Proportion of Responders Stratified Demographically

Week 8 [a]	FH-00-01 Glycopyrrolate Liquid (1 mg per 5 mL) N = 19	Sc-GLYCO-06-01 Glycopyrrolate Liquid (1 mg per 5 mL) N = 137	Placebo N = 17
Overall			
Total Subjects	19	137	17
Responders	14 (73.7%)	59 (43.1%)	3 (17.6%)
Subgroups by age			
Patients ≥ 3 to ≤ 11 years (N)	12	69	12
Responder	9 (75.0%)	29 (51.8%)	2 (18.2%)
Patients ≥ 12 to ≤ 18 years (N)	7	68	5
Responder	5 (83.3%)	30 (53.6%)	1 (20.0%)
Subgroups by gender			
Male patients (N)	13	77	9
Responder	8 (66.7%)	31 (50.0%)	2 (25.0%)
Female patients (N)	6	60	8

Responder	6 (100.0%)	28 (56.0%)	1 (12.5%)
Subgroups by race			
White (N)	16	98	10
Responder	11 (73.3%)	42 (51.2%)	1 (11.1%)
Black or African-American (N)	2	29	7
Responder	2 (100.0%)	15 (65.2%)	2 (28.6%)
Other (N)	1	10	0
Responder	1 (100.0%)	2 (28.6%)	0
Subgroups by weight for age percentile			
≤ 5% patients	8	70	7
Responder	4 (57.1%)	31 (49.2%)	2 (28.6%)
> 5 % patients	11	61	10
Responder	10 (90.9%)	27 (60.0%)	1 (11.1%)

Stratification by drooling severity

In Study FH-00-01, the percentage of patients with profuse or severe drooling was substantially reduced after 8 weeks of treatment with glycopyrrolate oral solution. The percentage of patients with profuse drooling was 41.2% at Baseline compared with 0% after 8 weeks of treatment with glycopyrrolate oral solution. Similarly, the percentage of patients with severe drooling (35.3%) at Baseline was substantially reduced to 0% at 8 Weeks.

In Study GC, the percentage of patients with profuse drooling was 21.6% at Baseline compared with 2.3% after 24 weeks of treatment with glycopyrrolate liquid. Similarly, the percentages of patients with severe (36.6% to 8.3%) and moderate (32.1 % to 25.6%) drooling were substantially reduced and 15% of patients were no longer drooling at the end of the study.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Due to the need for balancing a therapeutic response with a tolerable adverse events profile, the clinical trials were designed to begin with a low dose, and employ dose titration during the first four weeks, with subjects remaining at their four-week dose for the rest of the trial. The data collected during both clinical trials regarding the dose changes over time support the success of the titration scheme in reaching the optimal dose for subjects.

Several analyses of these data will be examined in the remainder of this section of the review. The first will be the patterns of individual subject's increases and decreases in dosing during the trial. The second set of graphs examines the final dosing and maximal dosing for a normal distribution response.

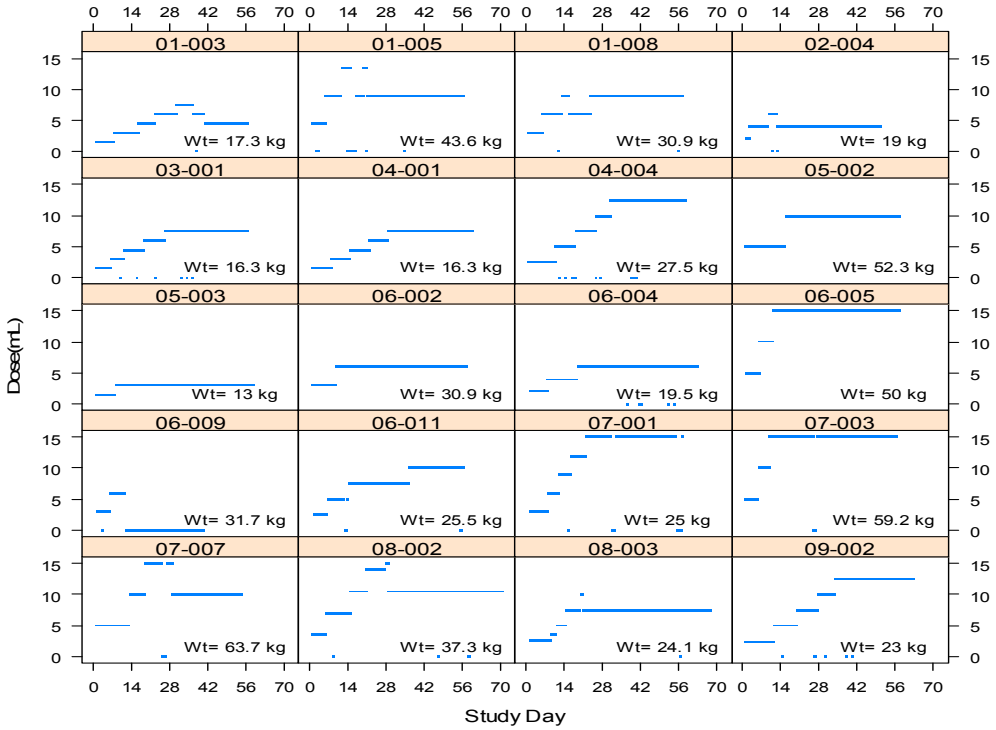
The set of charts on the following page were created from the sponsor's data by the Biostatical reviewer assigned to this NDA. They show the dose for each subject at each

point during the placebo-controlled trial. The trial began with a low dose based upon body weight of .02 mg/kg. Adverse events were recorded at home throughout the trial by the caregiver on a sheet similar to a diary, but with focused questions on signs and symptoms of adverse events (mBRS scale, which will be discussed in detail in the Safety section of this review). Every week during the titration period, Weeks 1 through 4, these recorded events were evaluated by the investigator ; if adverse events, in the opinion of the investigator, did not prevent it, the initial dose was doubled at Week 2, tripled at Week 3 and quadrupled at Week 4.

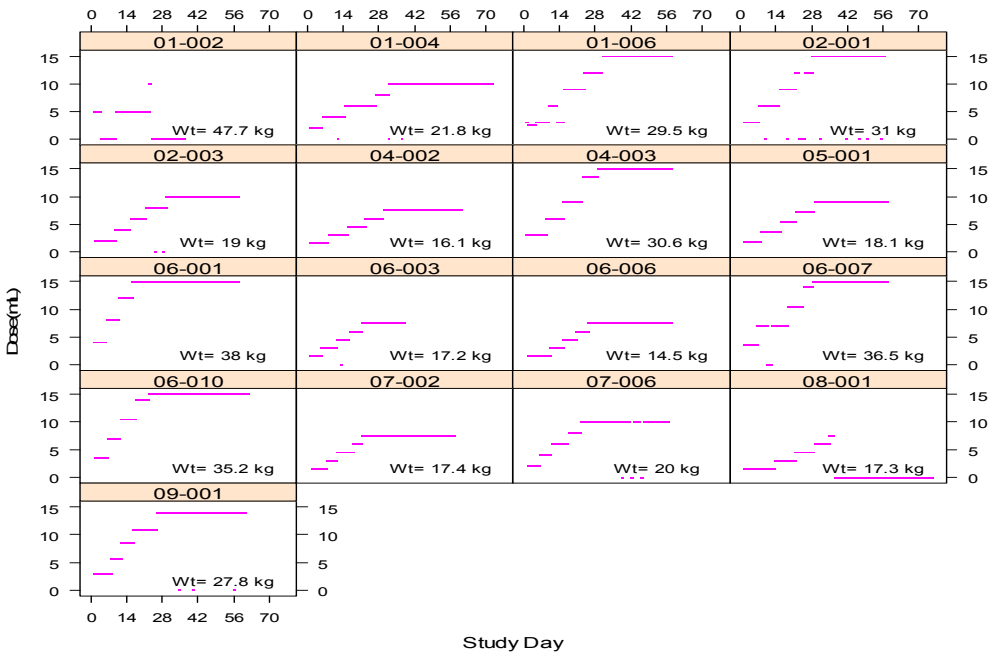
Of note in these charts is that dosing increased during the titration periods in the subjects randomized to glycopyrrolate, with some reaching the maximum dose and remaining there, some reaching the maximum dose but decreasing to a lower one, and some never reaching the maximum dose. Specifically, the end dose for five patients was the maximum level for their weight, one patient was at dose level 4, two patients were at dose level 3, and one was at dose level 2. On the other hand, as expected, the placebo subjects nearly all progressed to the maximum and stayed there, since there was no effect, either therapeutic or adverse event-related that would prevent them from escalating the dose to the maximum.

Table 11: Dose Titration for Glycopyrrolate and for Placebo

Study FH-00-01: Subjects randomized to glycopyrrolate



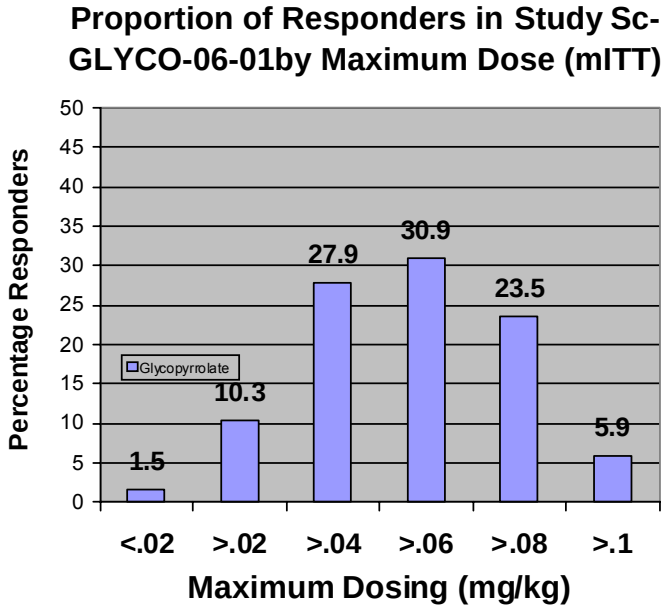
Study FH-00-01: Subjects randomized to placebo

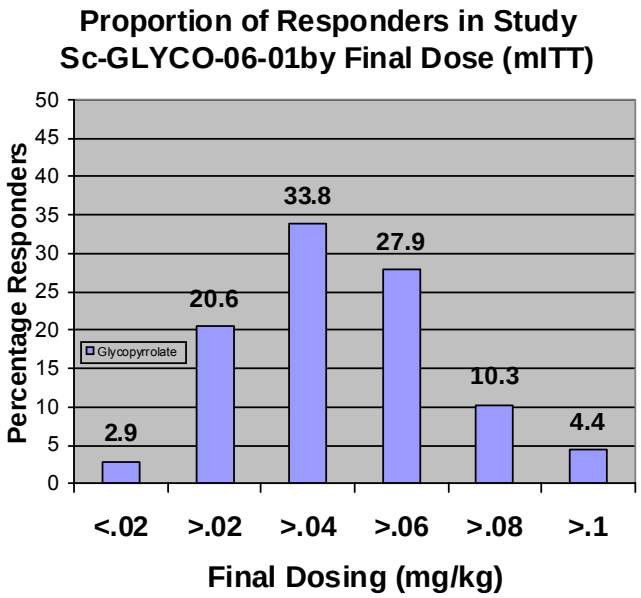


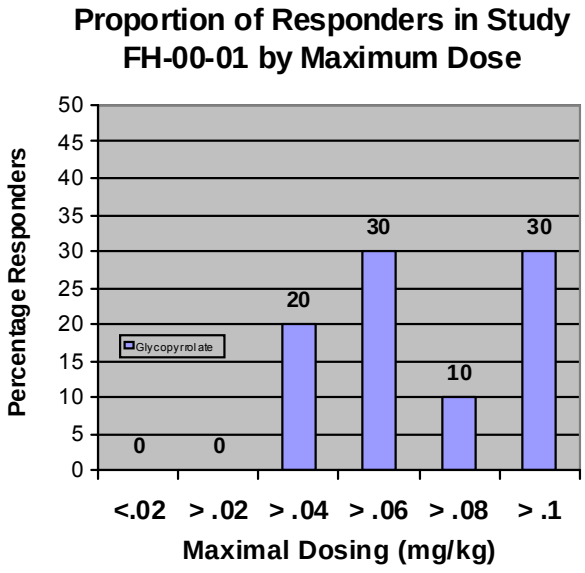
In the next set of figures, this reviewer compiled the data submitted by the sponsor into a set of graphs that demonstrate the distribution of subjects by final dosing that is highly consistent with a normal distribution. In a situation in which normal variation in response is expected, such as response to a drug, a bell shaped curve will result with the majority of subjects responding in the middle of the curve and equal outliers in response (higher than expected, or lower than expected) on both ends. When adjusted for weight of subjects, as was accomplished by setting the x-axis to dosing in mg/kg, it can be seen that this is exactly what the final titrated dosing in the subjects achieved.

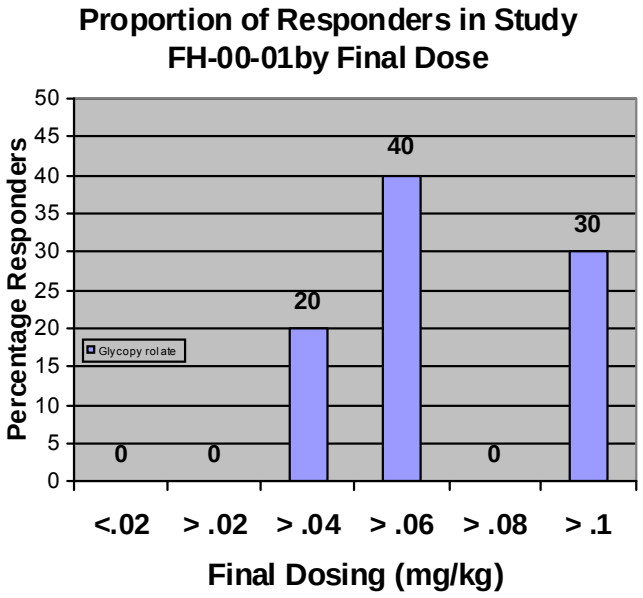
Note that the top two bar graphs show both the final dose and the maximum dose during the titration period for the open label study. They both show normal curves, but the maximum dose is shifted slightly to the right, compared to the graph of the final (optimal) dose. Although this is consistent with the efficacy being tied in to the dosing, the AE profile resulted in subjects lowering the maximum dose to one with a better balance. The lower two graphs in this series was constructed based upon the placebo-controlled trial. Because only 17 subjects were on drug during the 8 weeks of this trial, a normal distribution is seen, but there are too few subjects to see as clearly a trend. Although placebo-controlled trials are preferred to draw conclusions, in this case, the far greater number of subjects and lengthier duration makes the open-label study results on dosing more robust than the lower one. Nonetheless, both are consistent with the dose-titration plan being effective and capable of reaching an optimal response.

Figure 6: Proportion of Responders Grouped by Maximum and Final Dose









When considered in combination, the results from these two studies support the recommendation that once an initial dose has been selected, clinical signs can be used to titrate dosing for each child. This is further supported by the results of the pharmacokinetics evaluation, which was summarized in Section 4.4.3 of this review.

The pharmacokinetics results showed that body weight is the only covariate that needs to be considered when selecting an initial dose of glycopyrrolate.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In both studies, the proportion of responders increased continuously throughout the titration periods. In Study Sc-GLYCO-06-01, improvement continued until its peak at 56.7% by Week 16 was observed, and the response rate remained stable through Week 24. The stable efficacy response of glycopyrrolate oral solution throughout the trials was also found in the subgroup analyses. Overall, the results indicate that the efficacy of oral glycopyrrolate is maintained at least over the course of an 8-week pivotal trial and the 24- week open-label trial, suggesting that there is no development of tolerance to the efficacious effect of oral glycopyrrolate in this patient population.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Primary safety data were gathered from the two phase 3 studies conducted under this IND - a double blind controlled study (FH-00-01) and an open label study (Sc-GLYCO-06-01). To a lesser degree, a phase 1, pharmacokinetics study in 36 healthy adults is also a primary source of safety data. 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 that was approved under NDA 12-827 in 1961 to treat gastric ulcers, and has been widely used off-label to treat drooling in children with CP. The safety gathered from adverse events databases and drug utilization databases for Robinul is discussed in detail in Section 8.0 of this review, Postmarketing Studies.

The table below provides the length of exposure to glycopyrrolate and range of doses used for the safety evaluation of this NDA. Further discussion of the dosing and its titration during the trials is discussed later in this section of the review.

Table 12: 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

7.1.2 Categorization of Adverse Events

All adverse event terms were coded using the Medical Dictionary for Regulatory All adverse event terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 10.0. The sponsor reported the adverse events during these trials appropriately with Preferred Term (PT) and by System Organ Class (SOC). There was no evidence of overly broad or overly narrow terms being employed. A review of the case report forms for all subjects with serious adverse events verifies that the coding and classification were well matched to the SOC and PT.

As per the protocol of both studies, all SAE's were followed-up until the event resolved, which could include longer than the planned length of the studies. All non-serious AEs were followed until the subjects competed the study.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In this review, the safety data can be pooled to a limited extent, especially when using the data to compute incidence of adverse events. This is for two reasons: 1) the open label trial has no placebo arm and no blinding, which can bias the adverse event reporting; and 2) the placebo trial is eight weeks, whereas the open label trial is six months, resulting in a greater time period during which adverse events may occur. The placebo arm of Study FH-00-01 allows for comparing normal background rates of AE's in subjects who are closely matched for baseline characteristics and are following the same protocol for the same duration. The comparisons between these two groups are useful in establishing causality by controlling for background events. The open-label pivotal trial is much longer at 6 months, and has a study population on drug that is five times as great as the controlled trial, both factors which will allow for eliciting of more AEs; however, background AE's over the same time and with the same sample size is unknown, making a causal relationship between drug and AE's in that trial inconclusive.

In order to examine pooled data for both trials, but still allow for individual examination by trial, safety data from studies FH-00-01 and Sc-GLYCO-06-01 are presented both separately and pooled as follows:

- FH-00-01 glycopyrrolate oral solution (1 mg/5 mL)
- Sc-GLYCO-06-01 glycopyrrolate oral solution (1 mg/5 mL)
- Pooled glycopyrrolate oral solution (1 mg/5 mL), and
- Placebo.

The total safety population consists of patients from the FH-00-01 study who were randomized to study drug and who received at least one dose of study drug, and patients from the Sc-GLYCO-06-01 study who received at least one dose of study drug.

7.2 Adequacy of Safety Assessments

Overall, the assessments conducted by the sponsor and submitted to this NDA are adequate to support safety. The safety plan is challenging, as the target population is cognitively impaired, necessitating most of the adverse event monitoring in conjunction with the subject's parent or caregiver. In addition, most of the subjects were already affected by multiple and often serious concomitant medical conditions (described in detail in the Demographics section of this review, 6.1.2). Fortunately, the adverse events associated with anticholinergic drugs are well understood and predictable. In the remainder of this section, further detail will be provided regarding safety evaluations used in the clinical development, and how the sponsor captured the adverse events within the limits of the subjects' cognitive impairment.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequacy of Overall Clinical Experience

Size and Duration of Trials
The clinical program for ascertaining the safety of the glycopyrrolate solution included the same two phase 3 studies that have been previously described in detail. In addition, a phase 1 pharmacokinetics study was conducted in 36 adults, each given one dose of glycopyrrolate liquid. In summary, the phase 3 studies consisted of one placebo controlled study of 38 subjects, 20 of whom were on active drug for 8 weeks; and a 6-month open-label study of 137 subjects. All subjects who received at least one dose of study drug were monitored for safety throughout the trial and for 30 days after the trial ended. Because this drug needs to be titrated based upon both the effectiveness of the drug and subjects' responses to the associated anticholinergic adverse events, the trial design had dose titration as a part of the protocol. The results from the pharmacokinetics study will be briefly discussed in the safety section of this review.

Ideally, studies with larger sample sizes and longer duration would have been preferable to the two submitted; a larger number of subjects on the placebo controlled trial would have helped to better identify drug-related AE's compared to background AE's. Regarding the totality of subject exposure in both trials, the International Conference on Harmonization guidance for industry E1A, *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions* recommends 300 subjects for 6 months for a chronic use drug. However, the Division agreed with the sponsor during a 2004 meeting (See Regulatory History Section of this review, 2.5.1) that 100 evaluable subjects who were in a well designed study for six months should be adequate to confirm the chronic safety profile in this patient population.

During each of the pivotal trials, the sponsor monitored adverse events through investigator-conducted physical examinations, laboratory measurements, ECG, adverse events recording, and review of the caregivers diary adverse events reporting. The caregivers completed a detailed diary (on a three-times-per-week basis) which required them to complete a specific checklist of anticholinergic associated adverse events, as well as other general signs of other adverse events. A separate cardiac trial was conducted within the open-label clinical trial to evaluate for proarrhythmic effects. This is fully described in Section 7.4.4 of this review.

To supplement the two trials, and draw on the long history of off-label glycopyrrolate use, the sponsor supplied additional glycopyrrolate safety data from AERS and other reporting systems on the marketed glycopyrrolate formulations. The AERS search captured data for at least the past 30 years (the earliest report captured for glycopyrrolate tablets within the AERS database was from 1978), and with a usage of

over (b) (4) during the period 2002 – 2007 alone, the denominator of subject-years is quite extensive. This is discussed in full detail in Section 8.0 of this review, Post Marketing Data.

Demographics
The trials enrolled an adequate number of various demographic subsets and individuals with pertinent risk factors. Since the subjects used for the safety evaluation are the same as those evaluated for efficacy, refer to Section 6.1.2 of this review, entitled, Demographics, which provides tables and summarizes in detail the pertinent characteristics of subjects in both pivotal trials. Of primary interest to the safety testing is that differences can be examined within the safety data for any signs of a different safety responses between the various races, age groups, degree of severity of cerebral palsy (as determined largely by degree of mobility and feeding tube status). All of the demographic and other baseline characteristics are described in the narratives of all serious adverse events that occurred in either trial. See section 7.3 of this review, Major Safety Results.

7.2.2 Explorations for Dose Response

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 located in 7.1.1 of this review summarizes exposure to study drug. Of note is that 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. In particular, it is worth noting that the mean daily dose of glycopyrrolate for subjects in Study FH-00-01 the mean daily dose 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 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. *It appears as though in both trials, one placebo-controlled with an 8-week duration and one open label trial of 6 months duration with a more medically compromised*

population, the final dosing followed a normal distribution with the average subject in each receiving a final dose of approximately 0.05 mg/kg, which is the midpoint of the titration range (italics to add emphasis).

Mean percent compliance with the study drug regimen in Study FH-00-01 was similar for glycopyrrolate oral solution-treated (94%) and placebo-treated (92%) patients. The proportion of patients who were ≥ 70% compliant with the study drug regimen in Study FH-00-01 was 95% for glycopyrrolate oral solution-treated patients and 83% for placebo-treated patients. The mean total dose of study drug was 256.5 mg for patients in Study FH-00-01. The mean daily dose (mg/kg) of glycopyrrolate oral solution received by patients in Study FH-00-01 was 0.1513 mg/kg. At 3 doses per day, the average individual dose was therefore 0.0504 mg/kg, which is the mid-range of the allowable titration ranges of 0.01 mg/kg to 0.1 mg/kg. The mean duration of glycopyrrolate oral solution dosing was 57.3 days in Study FH-00-01. The duration of dosing range for most glycopyrrolate oral solution-treated (90.0%) and placebo (83.3%) patients in Study FH-00-01 was > 50 to ≤ 100 days.

7.2.3 Special Animal and/or In Vitro Testing

As the active substance, glycopyrrolate is well characterized pharmacologically. No adverse reactions or clinical findings emerged during clinical development that necessitated special testing.

7.2.4 Routine Clinical Testing

Safety was evaluated with the following clinical testing:

(1) physical examination at Screening and Week 24 in Study Sc-GLYCO-06-01; Week 8 in Study FH-00-01)
(2) 12-lead ECG at Screening, Weeks 4, 12, and 24 in study Sc-GLYCO-06-01; Week 8 in study FH-00-01)
(3) clinical laboratory evaluations (blood chemistry, hematology, and urinalysis) at Screening and Week 24 in Sc-GLYCO-06-01; Week 8 for Study FH-00-01; and
(4) vital sign measurements, which were recorded at Screening and Weeks 1, 4, 8, 12, 16, 20, and 24 in Study Sc-GLYCO-06-01; during Weeks 1,2,4,6, and 8 during Study FH-00-01)

If a subject prematurely terminated from the study earlier than the last scheduled visit, the safety assessments were performed at the time of discontinuation from the study.

Specific laboratory testing included:

1. Hematology: Hb, Hct, RBC, WBC, differential WBC count, (i.e., neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelets.

2. Serum biochemistry: creatinine, BUN, sodium, potassium, chloride, bicarbonate, glucose, alkaline phosphatase, ALT, AST, GGT, total bilirubin, calcium, phosphorus, uric acid, cholesterol, total protein, albumin.

3. Urinalysis: dipstick (leukocytes, protein, blood, glucose, ketones); if abnormal: microscopic sediment examination (erythrocytes, leukocytes, bacteria, casts, epithelial cells).

4. TSH and free T4 (in nonverbal, non-mobile patients): to screen for hyperthyroidism which can exist undetected in nonverbal, non-mobile patients.

5. Urine or blood pregnancy test: (if applicable).

The sponsor defined clinically significant events in their protocol as the following:

"Hematology values, blood chemistry values, urine values, and seizure grades that worsen more than one toxicity grade from baseline will be considered clinically significant (e.g., Grade 0 at baseline worsens to Grade 2, or Grade 1 at baseline worsens to Grade 3.)"

The sponsor also acknowledged in their protocol that this patient population has a relatively high prevalence of seizure disorder. Therefore, the baseline seizure grade was established by the patient's history from the parent/caregiver before the subject started the trial. Changes in those values from baseline were analyzed at the end of the study.

7.2.5 Metabolic, Clearance, and Interaction Workup

Specific in vitro and in vivo testing was not performed on glycopyrrolate to identify enzymatic pathways responsible for clearance of the drug. The anticholinergic activity of glycopyrrolate is well characterized and its general effects on all muscarinic receptors are known. Approximately 85% of glycopyrrolate is excreted unchanged in the urine and bile. Drug-drug interactions as well as consideration of metabolism in individuals with renal or hepatic impairment are discussed in appropriate sections of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Glycopyrrolate is an anticholinergic drug, pharmacologically very similar to atropine; the significant difference is that glycopyrrolate does not cross the blood-brain barrier, whereas atropine does. As such, the common adverse events for this product are well known and include xerostomia, dry skin, blurred vision, cycloplegia, mydriasis, photophobia, anhidrosis, urinary hesitancy and retention, tachycardia, palpitations, xerophthalmia and constipation. As a result, the sponsor was advised during their

development phase to choose a monitoring tool that would evaluate these potential class effects.

Toward that end, during both trials, the sponsor used a scale that was recommended by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (see Regulatory History) with the intent of helping caregivers to observe carefully for adverse events. This scale, the modified Behavioral and Medical Rating Scale (mBMRS) was first described by Camp-Bruno in the same paper as the TDS was described. It objective is to uncover expected cholinergic affects as well as subtle adverse events by probing for both signs and symptoms of adverse events. For both studies conducted for this NDA, the mBMRS was used by both the parent/caregiver and the investigator to identify possible AE-related behaviors and physiological effects in patients taking glycopyrrolate oral solution.

The mBMRS measures how much the patient has experienced certain symptoms on an assessment day using the following scale: 1 = not at all; 2 = just a bit; 3 = quite a bit; and 4 = very much. The sponsor then presented the scores as the average of the non-missing responses to the 28 pre-specified symptoms recorded at each visit. The behavioral and symptom subscales were calculated as the mean of the first 12 and last 16 symptoms, respectively, as ordered on the CRF. The sponsor defined a positive change as improvement and a negative change as worsening. During both trials, caregivers administered and recorded the results of the mBMRS three times weekly during the entire trial. In addition, during the assessment visits, the investigator also administered the mBMRS at Visits 4, 5, 6 and 7.

Below are the 28 items in the mBRS:

1. Restless, Overactive
2. Excitable, Impulsive
3. Disturbs Others
4. Fails to finish things, Short attention span
5. Constantly fidgeting
6. Inattentive, Easily distracted
7. Demands must be met immediately
8. Cries often and easily
9. Mood changes quickly and drastically
10. Temper outbursts
11. Overly serious, sad or sensitive
12. Change in coordination
13. Fearful
14. Diarrhea
15. Constipation
16. Drowsy
17. Nasal Congestion
18. Vomiting
19. Irritable
20. Dry Mouth
21. Difficulty Urinating
22. Flushing of the skin on the face or body
23. Headache
24. Blurred Vision
25. Heart Palpitations
26. Increased Heart Rate
27. Skin Rash
28. Skin Hives

In response to a formal consult about this scale, the SEALD team concluded that the mBMRS is not a content valid scale. Specifically, the problem with the content of this

scale is that many of the items listed cannot be reported with accuracy by the caregiver or parent; only observable items can be reported with any confidence. For example, heart palpitations or increased heart rate is not observable, and parents were not trained to accurately make these assessments. Similarly, headache, blurred vision, dry mouth, and nasal congestion can only be guessed by an outside observer. More objective observations such as diarrhea, vomiting, and flushing of the skin are acceptable items for such a scale. Therefore, although only the clearly observable items in this scale are valid for reporting, this scale is nonetheless a useful adjunct to open-ended adverse events questioning in focusing the caregivers to specifically look for those symptoms of interest. (b) (4)

7.3 Major Safety Results

7.3.1 Deaths

Table 13: Summary of Deaths

Patient ID	Preferred Term	Severity	Outcome	Relationship
Sc-GLYCO-06-01 glycopyrrolate oral solution				
1403	Multi-organ failure	Severe	Death	Not related
1709	Pneumonia aspiration	Severe	Death	Unlikely
2906	Anoxic encephalopathy	Severe	Death	Not related

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 dose of study drug. Although none of the three subjects were taking glycopyrrolate at the time of death, all three had symptoms that lead to their death while they were on the study drug. Patient 1403 died of multi-organ failure which was precipitated by septicemia from a urinary infection after 3 weeks of glycopyrrolate use. Patient 1709 died of aspiration pneumonia after being on drug for 3 months, and Patient 2906 died of anoxic encephalopathy after being on drug for 4 months.

In the remainder of this section, a brief narrative of the events leading to death is presented, with attention to the medical history of each of these subjects and the likely causes of death. In addition, there is pharmacokinetics and laboratory data available for two of the three subjects, 1709 and 2906, which was reviewed as a part of the Clinical Pharmacology review and summarized here as well. The conclusion of these histories and the clinical pharmacology data is that there is no evidence to conclude that glycopyrrolate is causally related to any of the deaths.

Summary 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, there is no evidence to support that the multi-organ failure was related to treatment with glycopyrrolate liquid.

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 seizures
- Profound mental and motor retardation
- MIC-KEY Gastrostomy Feeding Tube.
- Gastroesophageal reflux disease (GERD)
- Controlled reactive attachment disorder (RAD)
- 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 was titrated over four weeks to the maximum allowable dose of 15 mL (0.086 mg/kg). After being on 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. There is no evidence of causal relationship between the event of aspiration pneumonia and treatment with glycopyrrolate liquid.

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.

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
- Grade1 seizures

- Osteoporosis
- Gastroesophageal reflux disease
- recurrent strep
- spinal fusion
- bilateral hip replacement
- bilateral ureter implant

Concomitant medications:

dantrolene, ranitidine hydrochloride, clonidine, baclofen, metoclopramide hydrochloride, carnitine, alendronate sodium, macrogol, budesonide, valproate semisodium, carbamazepine, naproxen sodium, guaifenesin, diazepam, Fleets enema, and bisacodyl.

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.

Comparison of incidence of deaths during trials to overall mortality rates:
Although there is very little support for a relationship between glycopyrrolate exposure and any of the three deaths in close proximity to the end of the trial, a consult was sent to CDER's Division of Epidemiology (DEPI) that requested an examination of mortality data from databases for individuals with cerebral palsy. These results were requested in order to see if the three deaths that occurred during these trials were excessive. The results reflect that the three deaths shortly after the period of the study is within reason of expected background mortality rates of individuals of similar ages with similar conditions.

The placebo controlled trial was small and of 8 weeks duration. During that time, or shortly after the end of the trial, none of the 17 subjects on placebo or the 14 on glycopyrrolate died. Looking next at the open label trial of 137 subjects on glycopyrrolate for a 6-month period and follow-up, 3 deaths occurred within one month of the end of the trial. No further deaths occurred in the population which was examined for six months of follow-up. Converting the total exposure of the drug to a mortality rate, it was calculated by DEPI as 45 per 1000 person years. Because this point estimate was based upon only 3 deaths during a short period of time, the 85% confidence interval is from 15 to 140 deaths per 1000 person years. DEPI's search of mortality databases found that for a similar population of age-adjusted CP individuals with cognitive impairment, quadriplegia and a feeding tube, the expected mortality rate is 36-39 deaths per 1000 years.

Therefore, the rate is similar to what is expected, and is considered within the limits of a background mortality incidence for this population. Although the background mortality rate for the CP population may appear high for a young population, it must be noted that the population recruited for this trial had more medical complications as a result of the severity of their CP. Mortality increases in CP patients significantly when factors such as lack of mobility and feeding tube are added. Children with milder CP were not accepted for these trials, as the moderate to severe drooling required for entry is associated with more severe CP.

7.3.2 Nonfatal Serious Adverse Events

The table below lists all subjects included in the safety population who experienced nonfatal SAEs. 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 (defined as definitely, probably, or possibly related) to treatment with glycopyrrolate oral solution.

Table 14: Subjects in Safety Population with Serious Adverse Events

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

In the controlled trial, no subjects on placebo reported an SAE, and one glycopyrrolate-treated patient experienced an SAE. Approximately eight days after receiving his last dose of study drug, Patient 8002, who had a history of generalized epilepsy and complex partial seizures, experienced an episode of generalized tonic-clonic seizure activity that spontaneously resolved after 11 minutes.

In the open-label trial, 11 subjects reported SAE's.

1. Subject 0502 was a 6 year old white male was on study drug for 4 months when diagnosed with pneumonia and treated successfully with antibiotics. The event resolved without sequela and the subject resumed glycopyrrolate and completed the study.
2. Subject 0807 was a 3 year old white female who experienced increased salivation and irritability after being on drug for 3 weeks. She was diagnosed with esophageal candidiasis and successfully treated with fluconazole. The parents decided not to resume treatment as a result.
3. Subject 1304 a 4 year old Hispanic, African American male was on study drug for one week when he was found to have elevated sodium levels during routine physical examination with his physician. The subject was given intravenous fluids to treat dehydration, and the event resolved without incident. The investigator decided to withdraw the subject from the trial after discovering that the subject had a long history of hypernatremic dehydration prior to entering the trial.
4. Subject 1503 was a 3 year old white male who was on study drug 2.5 months when diagnosed with otitis media. He was taken off medication for 3 days, and then resumed and completed the study.
5. Subject 1601 was a 10 year old African American male who was on study medication for 2 weeks when diagnosed with lithium toxicity. He was hospitalized until his lithium results were stable, and then discharged; the caregiver was given instructions regarding the dosing of the lithium. The subject resumed glycopyrrolate and completed the study with no additional incidents.
6. Subject 1901 was a 16 year old girl of mixed race, who was on the study for two days when her parents reported nystagmus. Upon ophthalmologic evaluation, the physician informed the parents that she had the same level of nystagmus prior to initiating the drug. Since nystagmus is an identified adverse events associated with glycopyrrolate use, the parents decided to withdraw from the trial.
7. Subject 2806 was a 6 year old white female who had a medical history of mixed seizure disorder. She was on glycopyrrolate for six weeks when she presented to the emergency room with a seizure. During the hospital visit, it was discovered that her ventricular catheter needed replacement. The events resolved without sequela and the subject restarted the study drug and remained on the trial without further incident.
8. Subject 2810 was a 16 year old white male who was on drug for three months before being admitted to the hospital for pneumonia. Treatment with antibiotics was instituted and the subject was returned home after one day. The study drug was resumed and the subjects completed the study.
9. Subject 2910 was a 16 year old white male who as on drug for one month before reporting a seizure. Concomitantly, he had an elevated temperature and right facial cellulitis. He was treated with antibiotics and lorazepam and

discharged after four days. He had a long history of seizures. He continued to take glycopyrrolate even during the hospital stay and completed the trial

10. Subject 3006 was a 16 year old African American female, who was on drug for four months when she presented to the emergency room with what was diagnosed as pneumonia. The event resolved in two days and the subject continued with glycopyrrolate on the trial.
11. Subject 3505 was a 7 year old white female who was taking glycopyrrolate for 3 months when she was admitted to the hospital for abdominal distension. Abdominal x-ray indicated no fecal retention, constipation, volvulus or obstruction, and stool cultures were negative. However, the physician decided to removed the child from the study as decreased gastrointestinal motility is a well known anticholinergic effect.

7.3.3 Dropouts and/or Discontinuations

Table 15: AE listing for Dropouts

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 pain	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	Gastrointestinal motility disorder	Recovered	Moderate	Yes	Possible

The table above lists the patients who discontinued prematurely due to an AE. Of the 21 patients who discontinued treatment because of an AE, 16 patients (15 in the pooled glycopyrrolate oral solution group and 1 in the placebo group) terminated the study early because of an AE, three patients had an AE with a fatal outcome, and two patients withdrew consent to participate in the study (patient/parent decision) because of an AE. Sixteen of the 21 patients (76%) had AEs that were considered related (defined as definitely, probably, or possibly related) to treatment with study drug.

Gastrointestinal AEs were the most common type of AE; otherwise no trend in the types of event that led to treatment discontinuation was apparent. Vomiting and constipation each led to treatment discontinuation for three patients and abnormal behavior led to discontinuation for two patients. All other AEs that led to treatment discontinuation were reported in one patient each.

7.3.4 Significant Adverse Events

For both clinical studies reported in this NDA, the System Organ class (SOC) with the highest frequency of AEs was Gastrointestinal followed by General Disorders. Within the SOCs, the frequency of preferred terms was slightly different between the studies. The primary reason for the differences in frequency across the studies is attributed to the small number of patients treated in the FH-00-01 study (n=20) compared with the larger. population treated in SC-GL YCO-06- 01 (n=137). There are no signals of meaningful differences between the two studies. (from 2.5.5.7).

7.3.5 Submission Specific Primary Safety Concerns

This section pertains to a specific safety issue that may have an impact on labeling. It is worth noting in this section that there was some concern about caregivers being vigilant to observe the children for adverse events. Although the caregiver does not raise the dose of the drug without consulting with the child's physician, the physician will need to rely on a discussion with the parent/caregiver to evaluate any adverse events that may be significant. When the results of the mBMRS were examined from the caregivers' diaries at home and with the investigator's mBMRS during a clinic visit, the caregivers identified a significantly greater number of AE's than the investigators.

For example, of all the AEs reported in Study SC-GLYCO-06-01, 24.7% were identified by the parent/caregiver using the mBMRS and 1.8% by the Investigator using the mBMRS. Of all the AEs reported in Study FH-00-01, 39.9% were identified by the parent/caregiver using the mBMRS and 4.5% were identified by the Investigator using the mBMRS. Based upon this analysis, the caregivers in this trial were extremely vigilant in reporting any adverse events to their physician.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Parents/caregivers were trained on how to identify potential adverse effects associated with glycopyrrolate liquid and on how to facilitate glycopyrrolate liquid dosage adjustment. A training manual for parents/caregivers, which the caregiver read and discussed with the investigator, was written for this purpose.

The most frequently observed treatment-emergent adverse event (TEAE) was constipation, an expected event. Overall, 21.7% of the pooled population had constipation. The other most frequently observed gastrointestinal system TEAEs were vomiting (19.1%) and diarrhea (17.2%). Dry mouth was reported for 14.6% of the pooled population. Other system organ classes were affected as noted in the table below. Although the placebo controlled trial had a small enrollment, note that the percentage of subjects in the placebo group also reported similar symptoms.

Table 16: 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%)

Of these commonly occurring adverse events, nearly all were of mild or moderate severity. The following table lists all severe adverse events during both trials, and it can be seen that none of the incidences rises above 1% with the exception of constipation in the FH-00-01 study (10%), Dry mouth (5%), vomiting (5%), flushing (5%) and convulsion (5%). With the extremely small sample size for Study FH-00-01, it is prudent

to look at these events in the 6-month open label study which followed 137 subjects on drug. In that trial, there were no reports of extreme constipation, dry mouth, vomiting, or flushing, or convulsion. The only event in the open label trial that rose about 1% for severity is pyrexia at 1.5% (none in the placebo-controlled trial). As characteristic anticholinergic outcomes, these findings are within expectations.

Table 17: Severe AE's

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
Abdominal pain	0	1 (0.7%)	1 (0.6%)	0
Abdominal tenderness	0	1 (0.7%)	1 (0.6%)	0
Constipation	2 (10.0%)	1 (0.7%)	3 (1.9%)	0
Diarrhoea	0	1 (0.7%)	1 (0.6%)	0
Dry mouth	1 (5.0%) 0 1		(0.6%)	0
Vomiting	1 (5.0%) 0 1		(0.6%)	0
Pyrexia	0	2 (1.5%)	2 (1.3%)	0
Pneumonia	0	1 (0.7%)	1 (0.6%)	0
Procedural pain	0	1 (0.7%)	1 (0.6%)	0
Therapeutic agent toxicity	0	1 (0.7%)	1 (0.6%)	0
Ventriculoperitoneal shunt malfunction	0	1 (0.7%)	1 (0.6%)	0
Hypokalaemia	0	1 (0.7%)	1 (0.6%)	0
Hyponatraemia	0	1 (0.7%)	1 (0.6%)	0
Convulsion	1 (5.0%) 0 1		(0.6%)	0
Dysgeusia	0	1 (0.7%)	1 (0.6%)	0
Hydrocephalus	0	1 (0.7%)	1 (0.6%)	0
Nystagmus	0	1 (0.7%)	1 (0.6%)	0
Abnormal behaviour	0	1 (0.7%)	1 (0.6%)	0
Dyspnoea	0	1 (0.7%)	1 (0.6%)	0
Respiratory distress	0	1 (0.7%)	1 (0.6%)	0
Flushing	1 (5.0%) 0 1		(0.6%)	0
Hypotension	0	1 (0.7%)	1 (0.6%)	0

The following section describes in detail the adverse events in the placebo controlled trial only, in order to compare the AE profile in the glycopyrrolate subjects to the AE profile in the placebo group:

All 20 patients in the glycopyrrolate group and 16 of 18 patients in the placebo group experienced AEs. Most AEs were mild to moderate in severity; five glycopyrrolate-treated patients experienced AEs considered severe. No AE in either treatment group was judged to be definitely related to study drug. The mBMRS instrument was used by

both the Investigator and parents/caregivers in identifying medication-associated symptoms, but parents/caregivers relied on the mBMRS much more heavily. Parent/caregivers used the scale to report AEs for 13 glycopyrrolate-treated patients and 9 placebo-treated patients compared with Investigators who reported 3 AEs for patients in the glycopyrrolate group and 3 in the placebo group. Furthermore, parents/caregivers used the mBMRS for identifying AEs across a variety of System Organ Classes while Investigators primarily used it for AEs coded to gastrointestinal disorders and nervous system disorders.

The majority of patients, regardless of treatment, had no change from Baseline for any item of the mBMRS at any post-baseline visit. However, of those glycopyrrolate-treated patients who did have a change, results trended toward a clinical improvement over time so that by Week 4 and Week 6 more patients had changes reflecting improvement from Baseline for 12 of the 28 mBMRS questions compared with patients having increases reflecting deterioration in condition for seven and eight questions, respectively. The cumulative effect was that the number of items for which patients had a response indicating improvement increased from 11 at Week 2 to 14 at Week 8. By comparison, of the placebo treated patients who had a change from Baseline, responses showed no consistent trend. The cumulative effect for the placebo group was mixed: improving from 11 at Week 2 to 15 at Week 4, then decreasing to 10 at Week 6 but increasing to 14 at Week 8.

Examination of hepatic, renal, or pancreatic AEs
The following TEAEs associated with disorders of hepatic function were each observed for one patient in the pooled glycopyrrolate population: increased alanine aminotransferase, increased blood albumin, and increased blood bilirubin.

Dysuria, reported for nine patients (5.7%), was the most frequently reported TEAE associated with renal function for the pooled glycopyrrolate-treated population. Decreased urine output and urinary retention were each observed for six patients (3.8%) in the pooled glycopyrrolate population and hypernatraemia and bladder distention were each observed for two patients (1.3%). The following renal TEAEs were each reported for one patient (0.6%) in the pooled glycopyrrolate population: bacteria urine, decreased blood potassium, hyponatremia, metabolic acidosis, hematuria, and abnormal urine odor. Increased lipase, associated with disorders in pancreatic function, was observed for one patient (0.6%) in the pooled glycopyrrolate population.

Table 18: Treatment Emergent Adverse Events Associated with Disorders in Hepatic, Renal, or Pancreatic Function: Open Label and Controlled Trials

Organ System 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
Hepatic function				
Alanine aminotransferase increased	0	1 (0.7%)	1 (0.6%)	0
Blood albumin decreased	0	1 (0.7%)	1 (0.6%)	0
Blood bilirubin increased	0	1 (0.7%)	1 (0.6%)	0
Renal function				
Urine output decreased	1 (5.0%)	5 (3.6%)	6 (3.8%)	1 (5.6%)
Bacteria urine	0	1 (0.7%)	1 (0.6%)	0
Blood potassium decreased	0	1 (0.7%)	1 (0.6%)	0
Hypokalemia	0	3 (2.2%)	3 (1.9%)	0
Hypernatraemia	0	2 (1.5%)	2 (1.3%)	0
Hyponatraemia	0	1 (0.7%)	1 (0.6%)	0
Metabolic acidosis	0	1 (0.7%)	1 (0.6%)	0
Dysuria	0	9 (6.6%)	9 (5.7%)	0
Urinary retention	3 (15.0%)	3 (2.2%)	6 (3.8%)	0
Bladder distention	0	2 (1.5%)	2 (1.3%)	0
Hematuria	0	1 (0.7%)	1 (0.6%)	0
Urine odor abnormal	0	1 (0.7%)	1 (0.6%)	0
Pancreatic function				
Increased lipase	0	1 (0.7%)	1 (0.6%)	0

7.4.2 Laboratory Findings

All clinical laboratory test results, from central and local laboratories, were reported in or converted to a standard set of units for pooled analysis. If central and local laboratory measurements were available for the same patient on the same day, only the central laboratory values were summarized and analyzed. The normal reference ranges for all clinical laboratory tests reported by local and central laboratories were supplied by the respective laboratory performing the tests. For applicable tests, the laboratory performing the tests defined laboratory values as low, normal, or high (L, N, or H) relative to normal reference ranges for the patient's age and sex. Baseline for laboratory data was defined as the Visit 1/Screening value. For applicable tests, the change from baseline was calculated as the post-baseline value minus the baseline value

Hematology:
Clinically Significant Abnormalities

No notable changes in mean hematology parameters values in any treatment group were observed between baseline and end-of-study. A total of three patients (two patients from Study FH-00-01 and one from Study Sc-GLYCO- 06-01) had hematology values that worsened more than one toxicity grade from baseline (e.g., Grade 0 at baseline worsened to Grade 2, or Grade 1 at baseline worsened to Grade 3). The following patients had clinically significant laboratory values:

Patient 8003 from Study FH-00-01, was a 15-year-old, white female in the glycopyrrolate group. The patient had readings of 11.3 gm/dL hemoglobin and 3.73 M/UL red blood cell count at Screening. Week 8 test results showed the patient had 3.79 M/UL RBC, 110 K/UL platelet count, 18% neutrophils, 48% lymphocytes, and 26% monocytes. The moderately elevated lymphocyte and monocyte counts, and the moderately decreased neutrophil and red blood cell counts were reported as AEs. These four hematological AEs were considered not related to study drug, and all were ongoing at the end of the study.

Patient 2003, from Study FH-00-01, was a 4-year-old, African-American male in the placebo group. The patient had a neutrophil count of 38.8% at Screening followed by a reading of 22.8% neutrophils at Week 8. The decreased neutrophil count was reported as a mild AE unlikely to be considered related to study drug. An unscheduled follow-up assessment detected 25.9% neutrophils.

Patient 0801, from Study Sc-GLYCO-06-01, was a 16-year-old, white female in the glycopyrrolate group. Hematology test results indicated that she had a platelet count of 390,000/µL at baseline and 67,000/µL at Week 24/Exit Visit.

Serum Chemistry

Based on safety data, there were no obvious trends or safety concerns with regard to the effect of glycopyrrolate on chemistry values. A total of three patients (two patients from Study FH-00-01 and one from Study Sc-GLYCO-06-01) had chemistry values that worsened more than one toxicity grade from baseline (e.g., Grade 0 at baseline worsened to Grade 2, or Grade 1 at baseline worsened to Grade 3). Brief descriptions of these events are provided below.

Patient 6001, from Study FH-00-01, was a 14-year-old, African-American female in the placebo group. The patient had an abnormal free T4 level of 0.64 ng/dL at Screening, but it was within the normal range (0.75 ng/dL) at Week 8. The patient was reported to have the AE of mild acquired hypothyroidism, and this event was considered not related to study drug.

Patient 8001, from Study FH-00-01, was a 10-year-old, African-American male in the placebo group. Clinical chemistry analysis revealed the patient had 151 mmol/L sodium, 114 mmol/L chloride, and 19 mmol/L bicarbonate at Screening. Unscheduled repeat values showed abnormal values of 108 mmol/L chloride and 14 mmol/L bicarbonate. Further follow-up testing indicated that none of his values were clinically significantly abnormal.

Patient 0805, enrolled in Study Sc-GLYCO-06-01 was a 10-year-old, white male in the glycopyrrolate group. Chemistry test results indicated that he had a blood calcium level of 9.2 mg/dL at baseline and 7.2 mg/dL at Week 24/Exit Visit.

Urinalysis

There are no safety concerns relative to urinalysis results in the safety database. A total of one patient (Study FH-00-01) had urinalysis values that worsened more than one toxicity grade from baseline (e.g., Grade 0 at baseline worsened to Grade 2, or Grade 1 at baseline worsened to Grade 3). A brief description is provided below.

Patient 9002, in Study FH-00-01, was a 9-year-old, white female in the glycopyrrolate group. Urinalysis showed the patient had 10 to 29 mg/dL protein, 1+ leukocytes, 10 leukocytes and one erythrocytes under high-powered field (HPF), 3+ epithelial cells, and 1+ bacteria in her urine at Screening. By Week 8 she was reported to have 100-299 mg/dL protein, trace ketones, 3+ leukocytes, 123 leukocytes using a HPF, 4+ epithelial cells, and 1+ bacteria. Results at an unscheduled assessment indicated trace leukocytes, one leukocyte and one erythrocyte using HPF, and 1+ epithelial cells.

7.4.3 Vital Signs

Changes from baseline to end of study for systolic and diastolic blood pressure, pulse rate, respiration rate, temperature, were examined. A moderate increase from baseline in mean systolic blood pressure was reported for the pooled glycopyrrolate oral solution-treated population (3.4 mmHg). A small decrease from baseline in mean diastolic blood pressure was reported for the pooled population (-0.3 mmHg). A small increase from baseline in mean pulse rate was reported for the pooled population (1.9 beats/min). No notable changes from baseline to end of study in mean respiratory rate or mean body temperature were observed. Increases from baseline in mean body weight values were observed in the pooled population (1.15 kg) and may be attributed to normal growth of the population over a 6 month study period.

7.4.4 Electrocardiograms (ECGs)

Glycopyrrolate, as an anticholinergic, is expected to increase the heart rate. In anticipation of the need to address cardiac effects, the sponsor incorporated ECG analysis into both the placebo-controlled trial and the open label trial on 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. The sponsor acknowledges that the sample size was small and minimal ECG frequency employed, but state that the data do not suggest that glycopyrrolate should have a clinically marked increase in QTc duration. To verify the sponsor's conclusions, a formal consult was issued from DDDP to the Interdisciplinary Review Team for QT Studies Consultation, located within the Division of Cardio-Renal Products (DCRP), to review the QT assessment for glycopyrrolate and also evaluate other effects of glycopyrrolate related to tachycardia/tacharrhythmias. The group was also asked if the data provided a sufficient evaluation of the cardiac outcomes for safety, or whether additional monitoring through a PMC or PMR was recommended. Towards that end, 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 using MedDRA Preferred Terms linked to Higher Level Terms "Ventricular arrhythmias and cardiac arrest", "Cardiac conduction disorders", "rate and rhythm disorders" and "supraventricular arrhythmias". Preferred Terms related to QT prolongation were also included (syncope, convulsion, electrocardiogram QT prolonged).

The 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.

Further conclusions from the consult include the following:
TQT Assessment for Glycopyrrolate
Exposure (Cmax and AUC data) with multiple dosing of glycopyrrolate is unavailable. However, the population pharmacokinetics data revealed that plasma levels for glycopyrrolate solution are 25% lower than that of the marketed tablet. Therefore, a TQT study is not required.

Effects of glycopyrrolate related to tachycardia/tachyarrhythmia's

- Consistent with its anticholinergic properties, glycopyrrolate increased the heart rate in the placebo controlled study (FH-00-01) by 10.5 bpm and had a variable effect in ScGLYCO-06-01. While there was a significant number of tachycardia outliers, only two subjects in FH-00-01 (compared to 1 in placebo group) had tachycardia reported as an AE and one subject 1403 in Sc-GL YCO-06-01 had a supra-ventricular arrhythmia but the case was confounded because of

comorbidities (chronic respiratory. failure, UTI with sepsis) and concomitant medications.

- Compared to adults, children (except those with underlying heart disease or right heart failure secondary to chronic aspiration) are likely more tolerant of this HR increase since they have higher heart rates at baseline compared to adults and this seems consistent with the MGPS data mining analysis results of fewer events in the pediatric age group.
- The sponsor has not proposed any labeling related to ECG effects. Unstable cardiovascular status is listed under contraindications. Tacharrhythmias and tachycardia are listed under general anticholinergic effects (warning and precautions) and in the adverse reactions (clinical trials and post-marketing experience) section. Therefore, the proposed labeling seems reasonable.

For additional details on the review of the ECG Study, refer to the DCRP/Interdisciplinary Review, a part of this NDA's action package.

7.4.5 Special Safety Studies/Clinical Trials

As was described in the table of Safety Studies in Section 5.1 of this review, a phase 1 pharmacokinetics trial of 36 healthy adults was conducted as Protocol FH-00-02, which included safety measurements. For completeness, the safety findings will be presented in this section. Because this study consisted only of one dose of the glycopyrrolate liquid after fasting, and a second dose of glycopyrrolate liquid given after a fatty meal one week later, this study was not designed and is not capable of eliciting changes in health measures over sufficient time for an outcome to develop. In addition, the population used in this trial is all adults whereas the target population for this NDA is pediatric patients.

Glycopyrrolate liquid administered under fasting and fed conditions and Robinul tablets administered to fasting subjects were safe and well tolerated by healthy male and female volunteers. There were a total of 93 treatment-emergent adverse events and all but one were mild in severity. None of the events was severe in nature. Headache and dry mouth were the most frequently reported events but were only reported by 19% and 11% of the subjects, respectively.

Clinical laboratory values were obtained from screening to discharge. Four subjects exhibited decreased globulin; results for all four subjects returned to within reference range during the study or upon repeat testing following discharge. Four subjects had abnormal urinalysis results; there was no observable trend for any parameter to increase or decrease over time throughout the study.

The investigator performed a physical examination during the screening process, at entry of each period and upon. discharge for each subject. The few abnormalities that were noted were not clinically significant. A 12-lead electrocardiogram was obtained at

screening, at entry of each period and at discharge. None of the subjects exhibited clinically significant abnormal electrocardiogram results during the study.

Vital signs (supine blood pressure, pulse and temperature) were measured during screening, at entry of each period, pre-dose and following drug administration at 1, 2 and 24 hours. Few abnormalities were noted that did not resolve upon repeat measurement. None of the subjects had changes in measurements of vital signs, which were considered an adverse event. The mean systolic and diastolic blood pressure, pulse and body temperature by treatment were computed at pre-dose, 1, 2 and 24 hours post-dose and examined. There were no remarkable changes in measurements of vital signs during the study.

7.4.6 Immunogenicity

Glycopyrrolate is a well-understood anticholinergic drug, which does not require any examination for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose Titration has been well described in both the safety and efficacy sections of this review. Expected anticholinergic adverse events increase proportionately with dose.

7.5.2 Time Dependency for Adverse Events

No time dependency was noted for the appearance of adverse events in these trials.

7.5.3 Drug-Demographic Interactions

The demographics have been described in both the Safety and Efficacy sections of this review. There were no demographic factors that affected the safety or efficacy of the drug.

7.5.4 Drug-Disease Interactions

As per the recommendations of the Advisory panel, the sponsor enrolled subjects with multiple levels of cerebral palsy and other neurological diseases that result in severe drooling. No specific interactions were noted in the clinical trials submitted to this NDA; however, literature is consistent about contraindications against use of glycopyrrolate in concomitant conditions such as glaucoma; (b) (4) paralytic ileus; (b) (4) unstable cardiovascular status in

acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; and myasthenia gravis. These conditions are listed in the proposed labeling.

7.5.5 Drug-Drug Interactions

Concomitant Medications:
Every subject in this trial was on at last one concomitant medication; the average number of concomitant medications was seven per subject. The most common medications included drugs to prevent constipation; and drugs to control seizures. Specifically, the most common concomitant drugs (≥ 5%) co-administered in patients with cerebral palsy or other neurodevelopmental deficits who participated in the glycopyrrolate development program (n=157), are listed below. These drugs listed have been commonly used with glycopyrrolate in this patient population without evident safety concerns:

- Antiepileptics: carbemazepine (7.0%), clonazepam (13.4%), lamotrigine (12.1%), levetiracetam (23.6%), oxcarbazepine (13.4%), phenobarbital (14.6%), topiramate (12.7%), valproate semisodium (10.8%), valproic acid (7.0%), and zonisamide (5.1%).
- Gastroesophageal reflux and gastrointestinal disorders: metoclopramide (5.7%), ranitidine (10.2%), lansoprazole (21.7%), ondansetron (7.6%), budesonide (16.6%) and dimeticone (5.1%).
- Respiratory disorders: albuterol (salbutamol) (22.9%), levosalbutamol (8.3%), glucocorticoids (fluticasone proprionate [7.0%], mometasone furoate [7.0%]), and montelukast (10.2%).
- Muscle relaxants and anti-spasmotics: baclofen (33.1%), diazepam (28.7%) and lorazepam (14.0%).
- Laxatives: macrogol (43.9%), bisacodyl (14.0%), lactulose (9.6%), and fleet (8.3%).
- Analgesia/anti-inflammatory: acetaminophen (41.4%,), ibuprofen (34.4%), hydrocortisone (5.1%)
- Antihistamines: cetirizine HCL (8.3%), lortadine (10.2%)
- Antibiotics: amoxicillin (14.0%), amoxicillin with clavulanate potassium (8.9%)
- Antipsychotic: risperidone (7.0%)
- Hypertension: clonidine (10.2%)
- Miscellaneous agents: calcium carbonate (13.4%), melatonin (5.7%), certagen (8.3%), multivitamin (5.7%), Hepatitis A vaccine (6.4%), influenza vaccine (7.6%)

Since glycopyrrolate tablets were first marketed in 1961, 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)

The sponsor has proposed labeling language that includes the potential drug interactions that have been described in this section.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not performed.

7.6.2 Human Reproduction and Pregnancy Data

Not performed.

7.6.3 Pediatrics and Assessment of Effects on Growth

The growth and development of the target population for this drug is significantly affected by their cerebral palsy and its comorbidities. No specific assessment of the effect on growth from glycopyrrolate was performed as a part of this submission. However, no reports from either AERS or published literature for the widely off-labeled use of Robinul have been received.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As an anticholinergic, there could be serious adverse events with an accidental overdose. The labeling of the approved drugs with glycopyrrolate contain instructions for overdose, which includes maintaining an open airway, managing hyperthermia, administering neostigmine, or administering activated charcoal as appropriate. The labeling for this drug will carry the same instructions. In terms of potential for overdose, the pharmacology/toxicology studies reviewed results of 8 and 30 times the equivalent human dose in animals, without serious adverse events.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Because glycopyrrolate has been marketed since 1961 in a tablet form for the treatment of gastric ulcers, but widely used off label for treatment of drooling in children, the postmarketing experience is a valuable tool for the safety evaluation of this new dosing form and indication. The oral tablets are indicated for gastric ulcers in adults, and the injectable glycopyrrolate is approved as pre-operative and intraoperative antimuscarinic agent. The oral tablets are crushed and currently used for treating drooling in children with cerebral palsy; the injectable glycopyrrolate has not been reported as being used for this purpose, but the AERS data were examined for it as well. Towards that end, The Division of Pharmacovigilance (DPV) was enlisted through a formal consult from DDDP to help examine AERS data on the already marketed glycopyrrolate-containing drugs. After conducting a complete search of all AERS data to date, they did not identify any new significant safety concerns associated with the use of any formulation of glycopyrrolate in children 0 – 18 years old. In addition they had no additional labeling recommendations at this time, other than the label reflect currently available safety information.

DPV searched the entire AERS database with a focus on cases with an outcome of death, cases of tachycardia/supraventricular or ventricular arrhythmia, and adverse events associated with oral glycopyrrolate. Glycopyrrolate is available in oral tablets and injectable form, so both forms were included in the searches. Both the Robinul brand of glycopyrrolate and multiple generics are available, so DPV searched on all brands.

In the oral route of administration, the AERS search turned up a total of 11 cases in children 0 – 18 years of age. Cases were uncovered between the time period 1979 through 2008. Of the 11 cases, none resulted in death, although nine of them were serious in nature. The breakdown of the 11 reports is as follows:

Table 19: AERS Search Results for Glycopyrrolate: 1979 - present

AE	Number of reports	Comments
tachycardia	6	Currently listed in Robinul label
Urinary retention	2	Currently listed in Robinul label
oliguria	1	Currently listed in Robinul label
Urinary track infection	1	
Renal failure	1	Patient was on concomitant cisplatin therapy

Analysis of Off-Label Use in Children
As a further means of evaluating safety, determining a “denominator” for glycopyrrolate use in the target group is highly valuable. Our analyses up to this point have provided safety information about the use of glycopyrrolate liquid during the clinical trials, and the

postmarketing examination of AERS data for glycopyrrolate tablets and injection. However, determining the actual off-label data use about the number of children between the ages of 3 and 16 who have been prescribed glycopyrrolate tablets off-label will allow for approximating the actual postmarketing exposure rate for the past several years of the target group. The sponsor states in their NDA submission that using their sales data, the number of Robinul tablets dispensed in the United States during 2002 – 2007 was (b) (4). This number includes only Robinul and Robinul Forte tablets and does not include generics. The sponsor provided no further data regarding usage by age or CP status.

In order to verify the sponsor's numbers and attempt to further determine the actual use in children between 3 and 16, the Drug Use Team within DEPI were consulted. Drug Use staff analyzed drug marketing data from Intercontinental Marketing Services (IMS Health), SDI, Vector One, and Total Patent Tracker from the years 2002 through 2009. Their data is derived only from US Outpatient Retail Pharmacies. The yearly amount, including both generics and Robinul brand name (b) (4) between 2002 and 2009, starting with (b) (4) prescriptions during the year 2002 and ending with (b) (4) prescriptions during the year 2009. To get an accurate picture of glycopyrrolate use, it is important to include both the Robinul brand name as well as US-marketed glycopyrrolate generics. This is because there was a reversal of brand name use between 2002 and 2009, with generic brands comprising less than (b) (4) of the total glycopyrrolate marketed in 2002, whereas in 2009, (b) (4) of all glycopyrrolate sales were from generic brands. Given that a total of the DEPI data shows a total of (b) (4) prescriptions for the Robinul brand name between 2002 and 2007, this consistent with the sales figures provided by the sponsor of (b) (4), as this would average to (b) (4) tablets per prescription, which sounds reasonable.

Using the data stratified by age, approximately (b) (4) of all glycopyrrolate tablets are prescribed for children between the ages of 3 and 16; during the years 2002 – 2009, the total number of prescriptions dispensed to children between the ages of 3 and 16 was approximately (b) (4), or approximately (b) (4) prescriptions per year. Limited data are available to posit the number of these yearly prescriptions that are specifically used in children with CP. However, some data from office-based physicians were available, which indicated that in this age group, approximately (b) (4) of the usage was for hyperhidrosis, and another (b) (4) may have been conditions related to GI symptoms such as irritable colon. A specific listing for salivary secretion disorder is given as (b) (4); however, the reminder of the figures listed conditions associated with CP such as congenital hemiplegia, quadriplegia, and mental retardation that support approximately (b) (4) of the usage data for children with CP as their primary diagnosis.

The paucity of adverse events data from the AERS and other postmarketing safety data, in combination with a yearly usage of approximately (b) (4) prescriptions in the age group of 3 – 16 in patients with a significant number diagnosed with CP provides strong additional support to the safe use of glycopyrrolate.

9 Appendices

9.1 Literature Review/References

The sponsor included the full papers in the submission of all 29 references that they cited in their submission. Most of these papers were submitted to supplement the safety and efficacy conclusions from the clinical trials. For example, these included review articles on the management of drooling in children with cerebral palsy, literature concerning pharmacokinetics of glycopyrrolate and known anticholinergic effects, including cardiovascular. Articles included data from both human and animal studies. A very useful article was included that described the validation method used for the primary efficacy outcome, the modified Teacher's Drooling Scale.

9.2 Labeling Recommendations

The sponsor's proposed labeling relied heavily on the already approved forms of glycopyrrolate – Robinul tablets and Robinul injection. Much of that information regarding the expected anticholinergic AE's remained unchanged with this new dosing form and target population.

To date, the sponsor has not settled on a final trade name, and it is likely that this matter will not be settled by the action date.

Dose Titration Labeling
The titration schedule that was successfully used during both clinical trials is well supported for the proposed labeled dose. This titration is begun at a dosing of .02 mg/kg three times daily, and is titrated in increments of 0.02 mg/kg every 5 – 7 days. The physician should be contacted before each dose increase, so that that provider can review the adverse events profile for the child with the caregiver. The maximum dosing is 0.1 mg/kg or not to exceed 3 mg per dose, regardless of the child's weight. Because this requires a step of calculations for each dose increase, i.e., converting the child's weight into kg, multiplying the current dosing in mg/kg for that week's dose and converting the mg dosing into the correct volume in mL of solution, it is recommended by this reviewer to include a table in the labeling that was provided to the physicians during the clinical trial (see below). This is much more likely to cut down on medication error.

Table 20: Dose Titration Schedule

Glycopyrrolate Liquid (1 mg/5 mL)
Doses described were given three times daily.

Weight		Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4		Dose Level 5	
Kg	lb	(~0.02 mg/kg)		(~0.04 mg/kg)		(~0.06 mg/kg)		(~0.08 mg/kg)		(~0.1 mg/kg)	
13-17	27-38	0.3 mg	1.5 mL	0.6 mg	3 mL	0.9 mg	4.5 mL	1.2 mg	6 mL	1.5 mg	7.5 mL
18-22	39-49	0.4 mg	2 mL	0.8 mg	4 mL	1.2 mg	6 mL	1.6 mg	8 mL	2.0 mg	10 mL
23-27	50-60	0.5 mg	2.5 mL	1.0 mg	5 mL	1.5 mg	7.5 mL	2.0 mg	10 mL	2.5 mg	12.5 mL
28-32	61-71	0.6 mg	3 mL	1.2 mg	6 mL	1.8 mg	9 mL	2.4 mg	12 mL	3.0 mg	15 mL
33-37	72-82	0.7 mg	3.5 mL	1.4 mg	7 mL	2.1 mg	10.5 mL	2.8 mg	14 mL	3.0 mg	15 mL
38-42	83-93	0.8 mg	4 mL	1.6 mg	8 mL	2.4 mg	12 mL	3.0 mg	15 mL	3.0 mg	15 mL
43-47	94-104	0.9 mg	4.5 mL	1.8 mg	9 mL	2.7 mg	13.5 mL	3.0 mg	15 mL	3.0 mg	15 mL
≥48	≥105	1.0 mg	5 mL	2.0 mg	10 mL	3.0 mg	15 mL	3.0 mg	15 mL	3.0 mg	15 mL

Dispensers
Another issue with the label of note is that during the clinical trials, the sponsor provided each caregiver with a measured plastic dose cup and a measured oral syringe for measuring and dispensing the glycopyrrolate liquid. In the proposed label, the caregivers are instructed to purchase a measured does cup. There has been some discussion regarding whether the sponsor should be co-packaging the dose cup and syringe with the bottle. After a review of currently marketed drugs, it does not appear as though it is typical to require a sponsor to include such measuring devices. There are examples of drugs that are co packaged with their dispensers, and for most, there is a compelling reason. Ophthalmic drops are typically packaged with eye cups and droppers as per 21 CFR 200.50; the reason given in that citation is the need for sterility, which is not the case with glycopyrrolate liquid. Many OTC drugs such as Motrin, Tylenol, especially for children also is co packaged as per a guidance (Guidance for Industry: Dosage Delivery Devices for OTC Liquid Drug Products, November 2009). However, the OTC products are more of a concern because they are not dispensed by a learned intermediary. Given that, the guidance does not require that dosing dispensers be included; it only recommends it. Other compelling reasons to include dispensing with a drug is if:

- High precision is needed for drug;
- Reconstitution is required before use;

- Dosing is unique (vaginal products).

Based on currently marketed drugs, there is often a recommendation in the labeling that the consumer purchase an accurate measuring device, such as in the 2008-approved labeling supplement for promethazine and codeine syrup, NDA 08-306, with the following first paragraph in the Dosage and Administration section of the label: "It is important that Promethazine HCl and Codeine Phosphate Oral Solution is measured with an accurate measuring device (see PRECAUTIONS-Information for Patients). A household teaspoon is not an accurate measuring device and could lead to over dosage, especially when half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate device and can provide instructions for measuring the correct dose."

In the case with this drug, which has been used off label for at least 30 years, has (b) (4) prescriptions filled a year in children with CP, and has had no serious AERS reports that are related to this drug to date, it would be somewhat difficult to conclude that inaccurate dosing is a problem. It is recommended that language similar to that described above for promethazine be included in the glycopyrrolate label.

Medication Guide Discussion
Regarding the need for a Medication Guide or a REMS, this was discussed by the entire review team early in the review process. According to 21 CFR 208 *Part 208—Medication Guides For Prescription Drug Products,* a medication guide is needed if the Agency determines that without distribution of FDA-approved patient information, the drug's use would pose a serious and significant public health concern; i.e., when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products. The regulation elaborates with the following points:

(c) Patient labeling will be required if the FDA determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

One of the evaluations during the clinical trial was the caregivers' understanding of the need to evaluate the children for adverse events in order to establish an optimal dose that provided a significant therapeutic effect with a tolerable adverse events profile. The caregivers read a manual that was very similar to what is proposed in the Patient Package Insert (PPI). The caregivers were tested on the material before reading the manual and after reading the manual. On the average, they scored 15/20 correct

before reading the manual and 16/20 correct after reading the manual, indicating that they were already aware of care for the children prior to training, that there was little room to improve, and that the caregiver manual did not add significantly to their knowledge base.

In addition, during the trials, both the caregivers and the investigators completed the same mBMRS, an enumerated listing of potential adverse events to be checked. The caregivers listed a significant greater number of adverse events in the subjects than the investigators did. This demonstrated that the caregivers, who included parents, foster parents and institutional caregivers, have a good understanding of safety using this drug before reading relevant materials, and have little room to improve significantly more. The results of the clinical trial outcome, which includes a high degree of clinical efficacy; the success of caregivers to titrate successfully to the optimal dose and throughout the 8 week and 6-month duration of the trials; the small number of related SAE's during the trial; and the modest number of dropouts - supports the notion that the caregivers do not require the level of a Medication Guide to ensure that the drug is used safely and effectively.

9.3 Advisory Committee Meeting

There was no advisory committee meeting prior to NDA submission. As was discussed in detail in the Regulatory History Section of this review, 2.6., the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee held a general discussion of the need for a glycopyrrolate liquid shortly after the IND for glycopyrrolate liquid was opened. Refer to that section for the summary including recommendations of that meeting.

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

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