CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022571Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-571**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Glycopyrrolate**
Medical Division	**DDDP**	**Drug Class**	**Anticholinergic**
OCP Reviewer	**Edward D. Bashaw, Pharm.D.**	**Indication(s)**	**(b) (4) (chronic (b) (4) severe) drooling in pediatric patients.**
OCP Team Leader	**n/a**	**Dosage Form**	**Oral Solution 1mg/5mL**
Pharmacometrics Reviewer	**Jee Eun Lee, Ph.D.**	**Dosing Regimen**	**Three Times Daily**
Date of Submission	**Sept. 2nd, 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Sciele Pharma, Inc.**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**July 28th, 2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:	**X**	**2**		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**			The indication is a pediatric indication
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**x**	**2**		
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		Robinul (glycopyrrolate) Oral Tablets
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		Food Effect and Relative BA were evaluated in the same study
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		**4**		
Total Number of Studies		**7**		

On **initial** review of the NDA/BLA application for filing:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Oral Solution, no BA issues
2	Has the applicant provided metabolism and drug-drug interaction information?	X			By supplying approved labeling from Robinul and literature
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			The proposed dose was based initially on the previously approved products and the PRN nature of the dosing
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Addressed as part of the Pharmacometrics component.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Within the limitations imposed by the disease state
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed			X	Pediatric indication

	effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __No____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please see Recommendation section at the end of filing memorandum.

E. Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology-3

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology

PRODUCT (Generic Name):	Glycopyrrolate Oral Solution 1mg/5mL
PRODUCT (Proposed Brand Name):	PENDING
NDA:	22-571
TYPE:	505(b)(2)
PROPOSED INDICATIONS:	(b) (4) (chronic (b) (4) severe) drooling in pediatric patients
SUBMISSION DATES:	9/2/2009
SPONSOR:	Sciele Pharma, Inc. (Shionogi)
PRIMARY REVIEWER: PHARMACOMETRIC REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D. Jee Eun Lee, Ph.D.
OCP DIVISION:	DCP III

Overview

Glycopyrrolate is a synthetic anticholinergic agent. 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, tracheobronchial, and pharyngeal secretions. Sciele acquired the rights to these products from the innovator (A.H. Robins) and is the current sponsor of the Robinul and Robinul Forte Tablet NDAs.

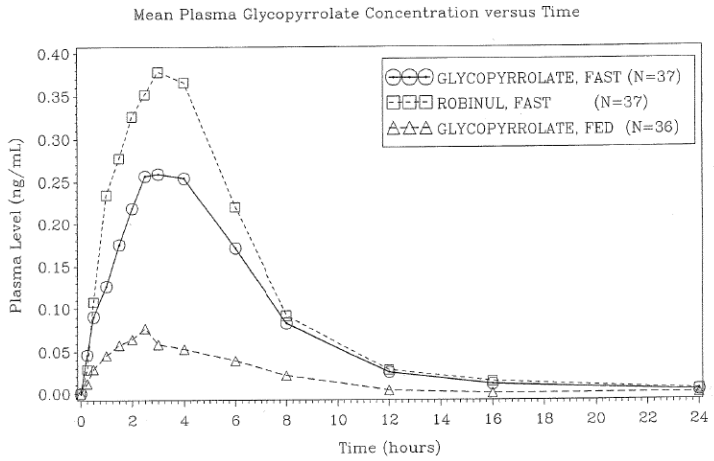
Clinical Pharmacology Studies (submitted)

The sponsor has completed three clinical studies with glycopyrrolate for the proposed indication. Two were efficacy and safety studies, and one was a pharmacokinetic study (FH-00-02). The pivotal efficacy trial (FH-00-01) and an open-label, long-term, safety study (SC-GLYCO-06-01) form the basis for the efficacy and safety evaluation of glycopyrrolate oral solution. Pharmacokinetic evaluations include a bioavailability and food effect study (FH-00-02) and a population PK trial (performed as part of SC-GLYCO-06-01).

Study FH-00-02

This study was an open-label, randomized, single-dose, three-treatment, three-period crossover study designed to compare the bioavailability of the test formulation (glycopyrrolate oral

solution) to the marketed tablet product (Robinul®) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects.



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

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

The results the pk trial (FH-00-02) demonstrated that the oral solution is not bioequivalent to the approved tablets. Surprisingly, the oral solution was 26% ***less bioavailable*** (AUC) than the marketed tablets! When given with a high fat diet the oral bioavailability of the solution declined in adult subjects by approximately 75%. Only limited population pk data was collected in study SC-GLYCO-06-01, the results of which are in general agreement with the healthy adult data.

Population PK Analysis

The population pk analysis was centered on samples collected from study Sc-GLYCO-06-01. This was a multi-center, open-label, 24-week study to assess efficacy and safety of glycopyrrolate oral solution in pediatric patients aged 3-18 years with cerebral palsy or other neurologic conditions. PK samples were collected in 36 patients in this study.

The goal of the PK portion of the trial was to obtain a total of five samples (one pre-dose and four post-dose) per subject, one in each of five windows relative to a morning dose. The four post-dose samples were targeted to bracket T_{max}.

This data was analyzed by the sponsors consultant using a pop pk model developed from the published literature and results from the healthy adult subject data from Study FH-02.

Analytical Methods
Concentrations of glycopyrrolate in human plasma were measured using specific LC/MS/MS methods. There were no glycopyrrolate concentrations measured in any fluids other than plasma. The assay used for the Phase I pharmacokinetic study, FH-00-02, was developed and validated by (b) (4) The lower limit of quantitation (LLOQ) of the assay was 10 pg/ml.

Recommendation and Filing Issues
At this time there are no filing issues from a clinical pharmacology standpoint and the application should be filed.

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

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

/s/

EDWARD D BASHAW

07/27/2010

Original submission of filing memo could not be located in DARRTS, this copy is be re-loaded into the file.

Clinical Pharmacology Review

PRODUCT (Generic Name):	Glycopyrrolate Oral Solution 1mg/5mL
PRODUCT (Proposed Brand Name):	PENDING
NDA:	22-571
TYPE:	505(b)(2)
PROPOSED INDICATIONS:	(b) (4) (chronic (b) (4) severe) drooling in pediatric patients
SUBMISSION DATES:	9/2/2009
SPONSOR:	Sciele Pharma, Inc. (Shionogi)
PRIMARY REVIEWER: PHARMACOMETRIC REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D. Jee Eun Lee, Ph.D.
OCP DIVISION:	DCP III

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Glycopyrrolate is a synthetic anticholinergic agent. 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, tracheobronchial, and pharyngeal secretions. Sciele acquired the rights to these products from the innovator (A.H. Robins) and is the current sponsor of the Robinul and Robinul Forte Tablet NDAs.

One of the pharmacologic actions of all anti-cholinergic agents is the reduction of secretions secondary to cholinergic stimulation. IV and to a lessor extent oral glycopyrrolate has over the years been used as a pre-operative medication to facilitate intubation by decreasing secretions. Due to its efficacy in this indication it has found additional "off-label" usage for the management of drooling associated with neurodevelopmental conditions. A limitation of its use, beyond the lack of an approved indication, is that the current oral dosage forms are tablets, thus there is a limited dosing flexibility. The oral solution that is the subject of this NDA was developed to address this flexibility and to provide an approved product for this indication. This Sponsor was granted "orphan drug" designation by the FDA in June 2006 for the indication "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients".

The sponsor has completed three clinical studies with glycopyrrolate for the proposed indication. Two were efficacy and safety studies, and one was a pharmacokinetic study (FH-00-02). The pivotal efficacy trial (FH-00-01) and an open-label, long-term, safety study (SC-GLYCO-06-01) form the basis for the efficacy and safety evaluation of glycopyrrolate oral solution. Pharmacokinetic evaluations include a bioavailability and food effect study (FH-00-02) and a population PK trial (performed as part of SC-GLYCO-06-01).

The results the pk trial (FH-00-02) demonstrated that the oral solution is not bioequivalent to the approved tablets. Surprisingly, the oral solution was 26% ***less bioavailable*** (AUC) than the marketed tablets! When given with a high fat diet the oral bioavailability of the solution declined in adult subjects by approximately 75%. Only limited population pk data was collected in study SC-GLYCO-06-01, the results of which are in general agreement with the healthy adult data.

1.01 A Note On Off-Study Deaths

During the review of the NDA the FDA became aware of 3 patients that died in Study Sc-GLYCO-06-01 within 30 days of the last dose of study drug. Patient 1403 died of multi-organ failure, 2 days after the last dose of study drug, Patient 1709 died of aspiration pneumonia, 4 days after the last dose of study drug, and Patient 2906 died of anoxic encephalopathy, 20 days after the last dose of study drug. As this is an unusual occurrence (3 deaths out of 125 subjects), the population pk dataset was examined to see if any of the subjects had participated in the pk sampling. Two of these subjects were

included in the pop pk dataset and their data was examined separately for any trends in their data, none was found that could account for the deaths (see Pharmacometrics Review).

1.1 Recommendations

From a Clinical Pharmacology standpoint, the sponsor has met the requirements under 21 CFR 320 and the application is acceptable given the "orphan" nature of the indication and the ethical difficulties in conducting a definitive pk study in developmentally delayed subjects. What is unanswered is whether or not there could be gastrointestinal manifestations of cerebral palsy (or other neurologic conditions in which this drug could be used) that could alter absorption (e.g., differences in GI transit time or inappropriate timing of exocrine secretions into the GI tract). Because the indication is non-specific, and even if limited to one diagnosis such as cerebral palsy (which is a spectrum disorder that does not have one presentation), it is difficult to see how this information could be obtained in a more definitive manner.

1.2 Phase 4 Commitments

None

1.2.1 Special Labeling Comments

The current package insert for Robinul tablets does not contain any oral pk data (with regards to either fed for fasted information). As the sponsor of this NDA is also the current NDA holder for the oral tablet, the tablet portion of study FH-02 should be incorporated into the current package insert for the Robinul tablets.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Finding

1.3.1 Clinical Condition

An oral solution formulation was developed by the sponsor for use in pediatric patients with "pathologic" drooling (sialorrhea-an unintentional loss of saliva from the mouth). This condition is normal in infants but usually stops by 15 to 18 months of age. Pathologic drooling is a problem for developmentally disabled individuals, particularly those with cerebral palsy or other neurologic conditions. In the majority of these individuals, drooling is caused by neuromuscular dysfunction, hypersecretion, sensory dysfunction or motor dysfunction. In children with cerebral palsy and other neuromuscular conditions, drooling is primarily due to oral motor dysfunction. Estimates of prevalence of moderate to severe sialorrhea in the developmentally disabled population range from 10% to 37%.

1.3.2 Glycopyrrolate

As noted in the executive summary, glycopyrrolate is an old drug that has been used for many years orally and via IV for its anticholinergic properties. In the operating room setting it is used as part of the anesthesia prep to decrease oral secretions prior to intubation. In the clinic, it was formerly used as a treatment for ulcers prior to the

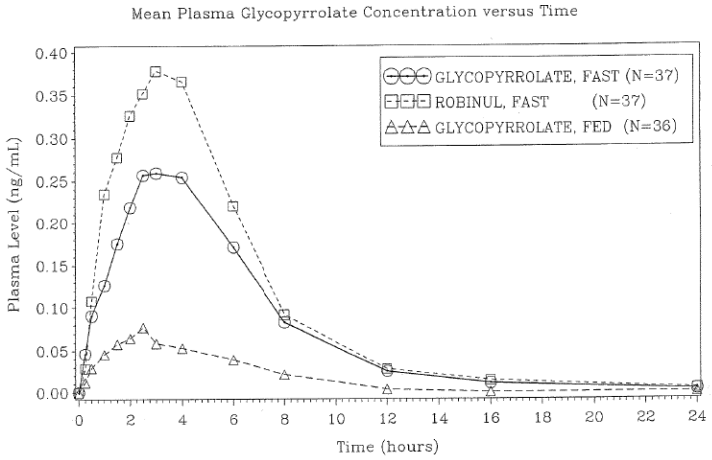
development of H2 and proton pump inhibitors both of which have supplanted its use for this indication.

In this NDA the sponsor has submitted the clinical pharmacology results of 1 study in healthy adult subjects and in an open label clinical trial in which population pk samples were obtained. Additionally, the sponsor used the published results of IV glycopyrrolate to assist in the development of pk/pd model. The population pk aspects of this NDA are covered in the appended Pharmacometrics Report.

1.3.2.1 Single Dose PK

Study FH-00-02

This study was an open-label, randomized, single-dose, three-treatment, three-period crossover study designed to compare the bioavailability of the test formulation (glycopyrrolate oral solution) to the marketed tablet product (Robinul®) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects.



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

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

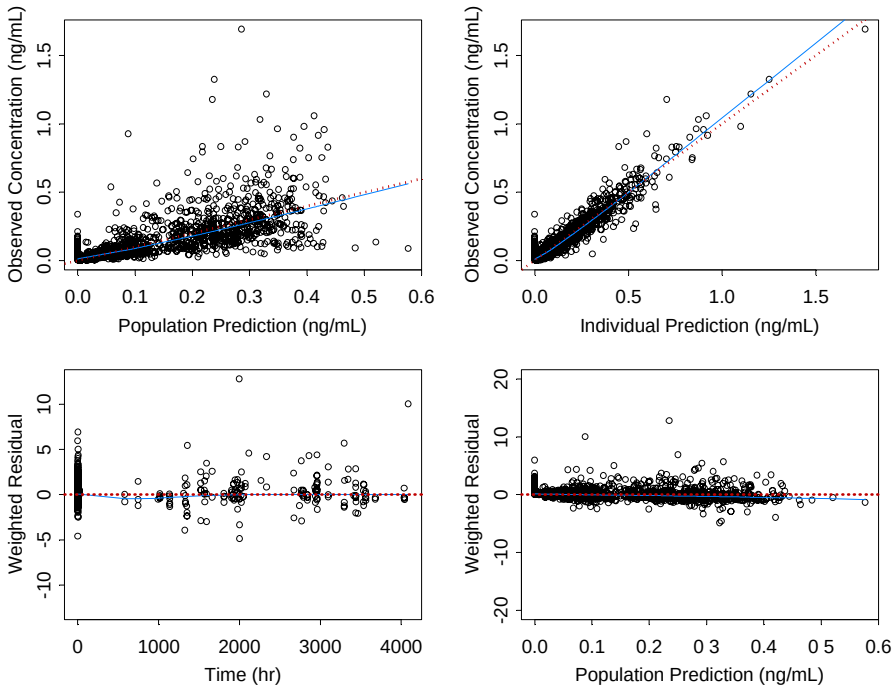
As noted previously the data was remarkable for the lower bioavailability of the oral solution. No explanation or hypothesis was put forward by the sponsor to explain these differences.

1.3.2.2 Population PK (excerpted from the Pharmacometrics Review)

The population pk analysis was centered on samples collected from study Sc-GLYCO-06-01. This was a multi-center, open-label, 24-week study to assess efficacy and safety of glycopyrrolate oral solution in pediatric patients aged 3-18 years with cerebral palsy or other neurologic conditions. PK samples were collected in 36 patients in this study.

The goal of the PK portion of the trial was to obtain a total of five samples (one pre-dose and four post-dose) per subject, one in each of five windows relative to a morning dose. The four post-dose samples were targeted to bracket T_{max}.

This data was analyzed using a pop pk model developed from the published literature and results from the healthy adult subject data from Study FH-02. Using the reviewers modified model, the following graphical estimates of the observed versus predicted data were obtained.



In general the following conclusions obtained from the analysis (see final appended review for details.)

- 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.

1.3.3 General Conclusions

From both the adult data, and the pop pk analysis, the pharmacokinetics of the oral solution form of glycopyrrolate are highly variable. The adult data was surprising in that the tablet formulation revealed a somewhat less variable dosage form than the oral solution form. The pop pk data was relatively scant in nature given the observed variability and problems were encountered in obtaining convergence in the model. As such while general conclusions were drawn with regards to linearity and estimates of clearance, there was not total agreement on the final analysis.

This is an imperfect dataset with regards to the information available in what can only be classified as a variable population. Glycopyrrolate will, however, not be dosed on pharmacokinetics but on pharmacodynamics (i.e., suppression of drooling and the appearance of adverse events).

As noted earlier, there were 3 deaths that occurred following conclusion of study Sc-GLYCO-06-01(the pop pk study). Analysis of the dataset for any linkage or trend was undertaken as part of the pop pk analysis and no association was found, although admittedly this was a small dataset.

Given the complexity of the population and the years of experience with this drug via the IV route, and is current off label use in this population, no additional Clinical Pharmacology information is needed at this time.

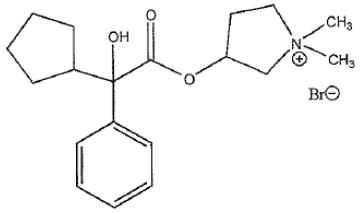
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product

Drug Substance and Formulation

Glycopyrrolate is a synthetic anticholinergic agent. It is a quaternary ammonium salt with the following chemical name: 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide. The molecular formula is C19H28BrNO3 and the molecular weight is 398.33. Its structural formula is as follows:



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.

The composition of the clinically studied is identical to the to-be-marketed formulation:

Quantitative Composition for Glycopyrrolate Oral Solution

Ingredients	Function	Quality Standard	Concentration per unit of Glycopyrrolate Oral Solution	IIG Level[1]
Glycopyrrolate	Active	USP	0.02	N/A
Sorbitol Solution	(b) (4)	USP	(b) (4)	
Glycerin		USP		
Citric Acid		USP		
Sodium Citrate		USP		
Saccharin Sodium (b) (4)		USP		
Propylene Glycol		USP		
Methylparaben		NF		
Propylparaben		NF		
Natural and Artificial Cherry Flavor (b) (4)		Internal		
Purified Water		USP		
[1] Oral Solution (b) (4)				

N/A = Not applicable

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Drooling, or sialorrhea, is an unintentional loss of saliva from the mouth. This condition is normal in infants but usually stops by 15 to 18 months of age. This is a problem for developmentally disabled individuals, particularly those with cerebral palsy or other neurologic conditions. In the majority of individuals, drooling is caused by neuromuscular dysfunction, hypersecretion, sensory dysfunction or motor dysfunction. In children with cerebral palsy and other neuromuscular conditions, drooling is primarily due to oral motor dysfunction.

A number of methodologies to control or diminish sialorrhea in children with neurological dysfunction have been used including oral motor or behavioral therapy, orthodontic appliances, acupuncture, drug therapy, injection of botulinum neurotoxin, irradiation, and surgery to reduce or inhibit gland function.

Anticholinergics block the neurotransmitter acetylcholine in the central and the peripheral nervous system. The classic example and protypical agent is atropine. Anticholinergics are administered to reduce the effects mediated by acetylcholine on acetylcholine receptors in neurons through competitive inhibition. Therefore, their effects are reversible.

Anticholinergic agents block parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Glycopyrrolate has anticholinergic blocking activity and is currently approved as both an IV solution and oral tablets for the following indications:

ROBINUL Injection (NDA 17-558)

In Anesthesia: Robinul Injection is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and

free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. When indicated, Robinul Injection may be used intraoperatively to counteract surgically or drug induced or vagal reflexes associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants.

In Peptic Ulcer: For use in adults as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated.

ROBINUL and ROBINUL FORTE (NDA 12-827)

Robinul tablets are scored, compressed white tablets engraved HPC 200. Each tablet contains: Glycopyrrolate, USP……..1 mg

Robinul Forte tablets are scored, compressed white tablets engraved HORIZON 205. Each tablet contains: Glycopyrrolate, USP…….2 mg

Indications- For use as adjunctive therapy in the treatment of peptic ulcer

Off-label use of commercially available oral glycopyrrolate tablets has been shown in literature trials to be helpful in the management of drooling associated with neuro-developmental conditions. Commonly, fixed dose glycopyrrolate tablets have been used off-label for the treatment of this indication. On 9 June 2006, this sponsor was granted orphan drug designation for the indication "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients" by the Office of Orphan Products Development for oral glycopyrrolate solution (1 mg per 5 mL).

2.1.3 What are the proposed dosage and route of administration?

The product is supplied as clear cherry-flavored oral solution, 1mg/5mL. At the current time, an "optimal" dose is unknown in this indication and dosing varies widely from patient to patient due to both the severity and variability of the disease itself overlaid with any pharmacokinetic variability with this product. Doses are often initiated at approximately 0.01-0.02 mg/kg three times daily and titrated in increments of 0.02 mg/kg every 5-7 days. According the sponsor, (b) (4) The package insert will include a "Caregiver Manual" that describes the clinical signs and symptoms of anticholinergic toxicity along with advice on management and when to contact a physician. The maximum recommended dosage is 0.1 mg/kg three times daily.

The solution should be administered at least approximately one hour before or after meals (as feasible given the clinical setting) since food reduces plasma levels by approximately 75% in healthy adult subjects.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor has completed three clinical studies with glycopyrrolate for the proposed indication. Two were efficacy and safety studies, and one was a pharmacokinetic study. The pivotal efficacy trial (FH-00-01) and an open-label, long-term, safety study (SC-GLYCO-06-01) form the basis for the efficacy and safety evaluation of glycopyrrolate oral solution. Pharmacokinetic evaluations include a bioavailability and food effect study (FH-00-02) and a population PK trial (performed as part of SC-GLYCO-06-01).

FH-00-01

This was a multicenter, randomized, double-blind, eight-week study designed to assess the safety and efficacy of oral glycopyrrolate oral solution (1 mg per 5 mL) compared with placebo in the management of problem drooling associated with cerebral palsy or other neurologic conditions in 36 children (3 through 16 years of age). Patients were randomly assigned to receive either oral glycopyrrolate oral solution or matching placebo oral solution three times daily (TID). Doses of glycopyrrolate oral solution were titrated to an optimal tolerated response for each study participant. Five dose levels (0.02 mg/kg TID, 0.04 mg/kg TID, 0.06 mg/kg TID, 0.08 mg/kg TID, and 0.1 mg/kg TID) were evaluated in this study.

Sc-GLYCO-06-01

This was a multi-center, open-label, 24-week study to assess efficacy and safety of glycopyrrolate oral solution in pediatric patients aged 3-18 years with cerebral palsy or other neurologic conditions. PK samples were collected in 36 patients in this study.

After a 2-day washout of other drooling medications, patients underwent a titration period to determine their optimal dose of glycopyrrolate in terms of the balance of efficacy and excessive anticholinergic effects. . Five dose levels (0.02 mg/kg TID, 0.04 mg/kg TID, 0.06 mg/kg TID, 0.08 mg/kg TID, and 0.1 mg/kg TID) were evaluated in this study.Patients then entered a maintenance period for the remainder of the 24-week study; during this period, the dose was not changed unless indicated clinically.

The goal of the PK portion of the trial was to obtain a total of five samples (one pre-dose and four post-dose) per subject, one in each of five windows relative to a morning dose. The four post-dose samples were targeted to bracket T_{max}. The Pharmacometics review of this data is contained in the appendix along with the Team Leader memo with regards to labeling.

Study FH-00-02

This study was an open-label, randomized, single-dose, three-treatment, three-period crossover study designed to compare the bioavailability of the test formulation (glycopyrrolate oral solution) to the marketed tablet product (Robinul®) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects. The drug was administered as a single dose, and subjects

were monitored for 24 hours after drug administration. A pre-dose blood sample followed by serial post-dose blood samples was drawn. Pharmacokinetic parameters were derived from the plasma concentration versus time profile and included Cmax, Tmax, AUC0-∞, AUC0-24hrs using noncompartmental analysis methods. Additional PK parameters (T1/2 and kel) were estimated for descriptive purposes.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, concentrations of glycopyrrolate in human plasma were measured using specific LC/MS/MS methods. There were no glycopyrrolate concentrations measured in any fluids other than plasma. The assay used for the Phase I pharmacokinetic study, FH-00-02, was developed and validated by (b) (4)
The lower limit of quantitation (LLOQ) of the assay was 10 pg/ml.

While the metabolic fate of glycopyrrolate is unknown, studies with the injectable formulation given IM showed that over 80% of the administered dose was recovered in urine and the bile as unchanged drug and half the IM dose is excreted within 3 hrs.

2.2.3 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was the responder rate, which was based on change in the modified Teacher's Drooling Scale (mTDS) as administered by the parent/caregivers, from Baseline to Week 8.

Modified Teacher's Drooling Scale (mTDS)

The 9-point mTDS scale is:
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

The degree (severity/frequency) of drooling was measured by parents/caregivers on non-school days using the mTDS. The mTDS assessments were conducted at Baseline (on two separate non-school days of the parent/caregiver's choice within the 9-day period of

Day -8 to Day 0, before randomization) and on Days 14 ± 3, 28 ± 3, 42 ± 3 and 56 ± 3 (2, 4, 6, and 8 weeks after randomization).

The endpoint itself, while somewhat subjective, is considered relatively well validated and is commonly used in the evaluation of subjects with cerebral palsy.

2.2.4 Exposure-Response

2.2.4.1 Does this drug prolong the QT or QTc interval?

A specific QT/QTc evaluation was not conducted for this product. A consult was submitted to the IRT/QT team. The following questions/conclusions were extracted from the IRT/QT review written by Suchitra Balakrishnan, MD.

QUESTION POSED BY REVIEW DIVISION
Specifically, does DCRP agree that the data do not suggest a further need for monitoring through a PMC or PMR? Please also review the following sections of the proposed PI pertaining to cardiac events: 1) Section 4, Contraindications; 2) Section 5.5 General Anticholinergic Effects; and 3) Table 1: Adverse events, which includes "Heart Rate Increased."

Response #1 QT Assessment for Glycopyrrolate

- While there are limitations in studies FH-00-01 and Sc-GLYCO-06-01 because of sparse ECG collection and absence of time matched PK sampling, the data along with the post-marketing experience suggest that large effects on the QT or other ECG intervals are unlikely.
- Exposure (Cmax and AUC data) with multiple dosing of glycopyrrolate is unavailable. The clinical pharmacology review for the NDA is still pending. If the review team concludes that, since exposures in the pediatric population with multiple dosing of the oral solution is similar to or lower than with the approved products a TQT study would not be required. On the contrary if higher exposures is expected or if the population PK analysis is inconclusive, it may be reasonable to have the sponsor conduct a TQT study as a post-marketing commitment.

Response #2 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 tachycardic 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-GLYCO-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 (see section 4.1.3). However, we defer to the OSE opinion for incidence of symptomatic cardiac arrhythmias and tachycardia with off-label use in this population.

- The sponsor has not proposed any labeling related to ECG effects. Unstable cardiovascular status is listed under contraindications. Tachyarrhythmias and tachycardia are listed under general anticholinergic effects (warning and precautions) and in the adverse reactions (clinical trials and post-marketing experience) section. We do not have any additional comments in this regard; the proposed labeling seems reasonable.

Clinical Pharmacology Conclusions on QT

From a Clinical Pharmacology standpoint, there is no objective evidence to require additional QT evaluations at this time based on the data at hand. This is based on the observation from the accumulated data that the exposure (admittedly in healthy subjects) is less with the new solution compared to the marketed tablet. In addition, the observed plasma half-life of 3hrs is such that with TID dosing there would be minimal accumulation. As noted in the IRT/QT consult, anticholinergic agents by their very nature can cause cardiac affects including reports of QT_c prolongation. However, given the long history of safe use of both the IV and oral formuations and the lack of significant indications in either the OSE AERS database (as cited in the IRT/QT review) and the published literature there does not seem to be a need for a PMC/PMR to further pursue this issue.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

The single dose pharmacokinetics of oral glycopyrrolate solution were determined an open-label, randomized, single-dose, three-treatment, three-period crossover study. It was designed to compare the bioavailability of the test formulation (glycopyrrolate oral solution) to the marketed tablet product (Robinul) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects. A total of 39 subjects were randomized to one of six treatment sequences.

Variable	Statistic or Category	Value
Age	N	39
	Mean	27.26
	Std Dev	7.21
	%CV	26.4
	Minimum	18
	Median	25
	Maximum	43
Weight	N	39
	Mean	155.41
	Std Dev	22.21
	%CV	14.3
	Minimum	115
	Median	156
	Maximum	205
Height	N	39
	Mean	68.28
	Std Dev	3.24
	%CV	4.7
	Minimum	62
	Median	68
	Maximum	75

Variable	Statistic or Category	Value
Gender	MALE	25 (64%)
	FEMALE	14 (36%)
Ethnicity	CAUCASIAN	11 (28%)
	BLACK	25 (64%)
	ASIAN	3 (8%)
Frame Size	SMALL	2 (5%)
	MEDIUM	34 (87%)
	LARGE	3 (8%)

Of the 39 subjects, a total of 35 subjects received all three treatments. Subject 016 failed to report to the facility for period III on the assigned date. Subject 017 was withdrawn from the study by the investigator due to a positive toxicology screen (alcohol) at entry of period II. Subject 029 voluntarily withdrew during period I and subject 033 was withdrawn by the investigator for ingesting Motrin prior to entry of period II. Subjects 011, 029 and 033 were replaced with subjects 117, 129 and 133 as the original subjects had not completed at least two periods of the study. Samples from all subjects receiving any drug were analyzed and the data included in the pharmacokinetic analyses. All subjects receiving any drug are included in safety assessments.

The three test treatments were administered alternatively according to the randomization screen following a 10 hr fast in the fasted legs and immediately after consuming the standard FDA High Fat breakfast in the fed leg. The mean pharmacokinetic parameters are presented below:

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

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

Of interest in the data is the apparent poor performance of the oral solution relative to the oral tablet. There was an observed difference of 26% between the mean AUC0-24hr for the glycopyrrolate oral solution (fasted) and the Robinul tablets. This is especially

surprising that the normal expectation is that oral solutions represent the most bioavailable oral formulation. Given that Robinul tablets represent a formulation that is over 30yrs old, it strongly suggests that the original formulators either did their job well or that there is some unique interaction between the GI tract and the oral solution that is resulting in a slower absorptive phase.

With regards to the effect of food on the oral solution, the mean AUC0-24hr for the glycopyrrolate oral solution (fasted) was more than 4.5-fold higher than the mean AUC0-24hr after the glycopyrrolate oral solution (fed). Results for area under the curve extrapolated to infinity were similar.

Evaluation of the data using the two 1-sided test demonstrated, not surprisingly, that none of the treatments could be considered bioequivalent. The implication of this data is that once an individual dose is determined, the administration relative to meals should be consistent to avoid loss of effect and the potential to increase the oral dose due to a perception of loss of effect-when in fact it is loss of bioavailability.

	Geometric Mean Ratio (%)*			
Parameter	Estimate	90% Confidence Interval		
Liquid Fasted vs. Robinul Fasted				
Cmax	76.99	65.39	→	90.64
AUC(0-t)	71.44	61.46	→	83.04
AUC(inf)	71.65	62.06	→	82.73
Liquid Fed vs. Liquid Fasted				
Cmax	26.26	22.34	→	30.86
AUC(0-t)	24.54	21.15	→	28.48
AUC(inf)	28.91	25.08	→	33.33

*Based on analysis of natural log-transformed data.

Due to the design of the study, there was not a comparison of the effect of food on the oral tablet, nor does the current package insert for Robinul contain any oral pk data (with regards to either fed for fasted information). One element that should be pursued is that as the sponsor of this product is also the current NDA holder for the oral tablet, the tablet portion of this study should be incorporated into the current package insert for the Robinul tablets.

2.3 Intrinsic Factors

Classical intrinsic factors were not evaluated for glycopyrrolate. Currently the IV formulation is approved for use in infants down to 1 month of age. Use below 1 month of age is not recommended (b) (4)

The following information, for background, was extracted from the currently approved IV package insert (verbatim) from the FDA/NIH DAILY MED website (label dated 8/06).

> Gender: Gender differences in pharmacokinetics of glycopyrrolate have not been investigated.

Renal Impairment: In one study glycopyrrolate was administered IV in uremic patients undergoing renal transplantation. The mean elimination half-life was significantly longer (46.8 minutes) than in healthy patients (18.6 minutes). The mean area-under-the-concentration-time curve (10.6 hr-µg/L), mean plasma clearance (0.43 L/hr/kg), and mean 3-hour urine excretion (0.7%) for glycopyrrolate were also significantly different than those of controls (3.73 hr-µg/L, 1.14 L/hr/kg, and 50%, respectively). These results suggest that elimination of glycopyrrolate is severely impaired in patients with renal failure.

Hepatic Impairment: Pharmacokinetic information in patients with hepatic impairment is unavailable.

Pediatrics: Following IV administration (5 µg/kg glycopyrrolate) to infants and children, the mean T1/2 values were reported to be between 21.6 and 130.0 minutes and between 19.2 and 99.2 minutes, respectively.

2.4 Extrinsic Factors

As with the intrinsic factors, specific extrinsic factors were not evaluated.

The following information, for background, was extracted from the currently approved IV package insert (verbatim) from the FDA/NIH DAILY MED website (label dated 8/06).

Drug Interactions: The concurrent use of glycopyrrolate injection with other anticholinergics or medications with anticholinergic activity, such as phenothiazines, antiparkinson drugs, or tricyclic antidepressants, may intensify the antimuscarinic effects and may result in an increase in anticholinergic side effects.

Concomitant administration of glycopyrrolate injection and potassium chloride in a wax matrix may increase the severity of potassium chloride-induced gastrointestinal lesions as a result of a slower gastrointestinal transit time.

2.5 General Biopharmaceutics

2.5.3 Food Effect

The effect of food was assessed as part of study FH-02. As previously described, this study was an open-label, randomized, single-dose, three-treatment, three-period crossover study designed to compare the bioavailability of the test formulation (glycopyrrolate oral solution) to the marketed tablet product (Robinul®) under fasted conditions and to compare the bioavailability of the test formulation under fasted and fed conditions in healthy subjects, using the FDA high fat breakfast. Although not required to, the study did not evaluate the effect of food on the pharmacokinetics of the Robinul tablet-a comparison that, given the poor performance of the solution under fasted conditions, could have been quite instructive.

The results of the effect of food on AUC and Cmax are summarized below, please note that in the legend where (F) is part of the name of the variable that denotes the presence of food.

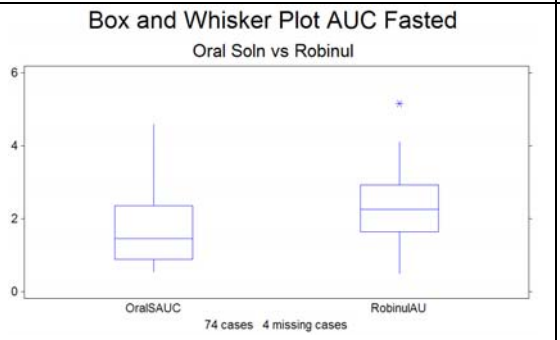
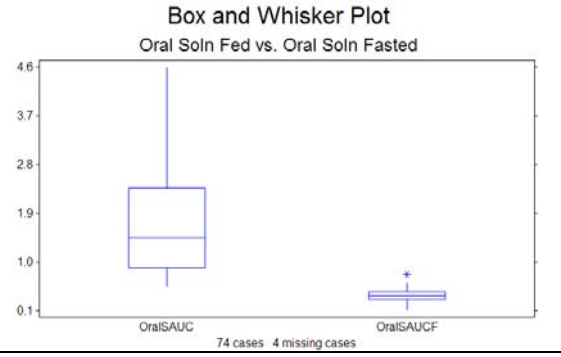
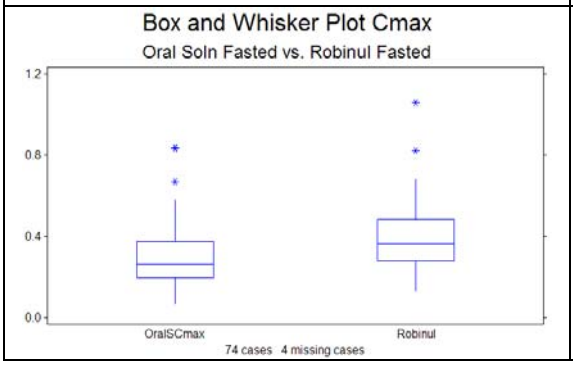
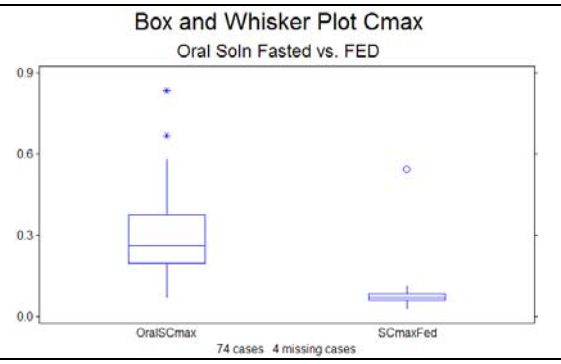
AUC 0-t Comparisons	
Oral Soln vs. Robinul Tablet	Oral Soln. Fasted vs. Fed
	
Cmax Comparisons	
Oral Soln vs. Robinul Tablet	Oral Soln. Fasted vs. Fed
	

Table 1: 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.

It is very clear from this data that food significantly depresses the availability of glycopyrrolate from the oral solution (as noted above, there is no corresponding data for the oral tablet in this study). Although the sponsor did construct 90% confidence intervals around the data, visual inspection of both the mean data and the box-whisker plots are sufficient to demonstrate that food has a marked effect on the absorption of glycopyrrolate and the timing of meals vis a vis administration should be controlled to produce maximal and/or reproducible effects.

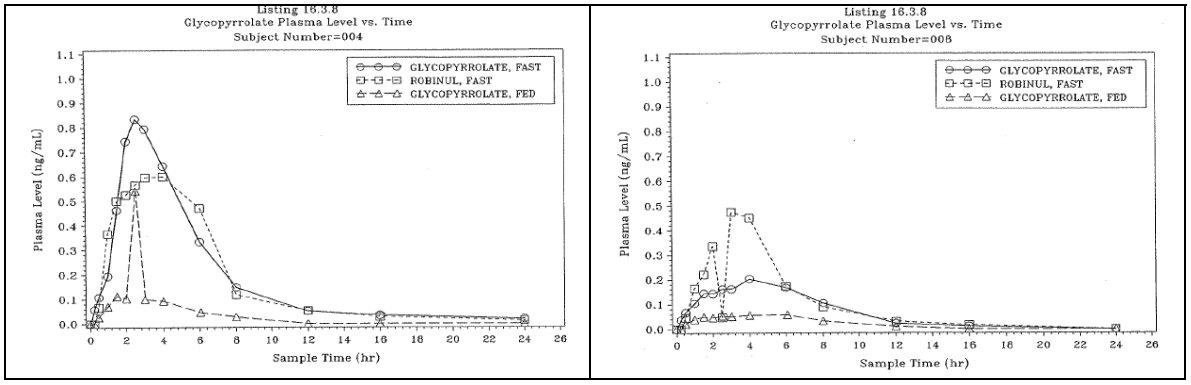
2.6 Analytical Section

The analytical review to this NDA is complicated by the number of different companies that have been involved in the development of this project and the time involved. As previously mentioned the original sponsor was a company named First Horizon. They were the ones responsible for the healthy subject pk study FH-002. This study was performed in 2002. At that time they used a liquid chromatography *l* tandem mass spectrometry (LC/MS/MS) method for the determination of glycopyrrolate in heparinized human plasma was validated using [redacted] (b) (4) as the internal standard.

The more recent study Sc-GLYCO-06-01 conducted by Sciele used a different LC/MS/MS system using [redacted] (b) (4) as an internal standard (IS).

The performance characteristics of the two methods are somewhat different; these are covered in more detail in the appendix. In general both methods appear to be adequately validated. Having said that, there does appear to be some difficulty in the data analysis portion of the FH-002 study.

Upon visual inspection of the concentration time profiles, various anomalies were found:



In both of these subjects at the same timepoint there are obvious spurious samples, one in the oral solution fed and one in the oral tablet fasted. The possibility that these timepoints represent real data is impossible, given the amount of reversible mass transport these concentration swings represent. The sponsor makes no mention either in the original study report in 2002 or in the 2009 NDA submission. Examination of raw data profiles shows some similar "deviations". While on the whole they do not seem to have affected the overall results of the trial, the deviations are random, they do point to a lack of detailed evaluation of the data by the sponsor and their consultants.

Because of the population nature of study Sc-GLYCO-06-01 a similar examination of the data is not possible.

Analytical Conclusions

Although it appears that there was a lack of some rigor in the examination of the raw data from study FH-002 by both the original sponsor and the current sponsor (and their attendant consultants), the overall analytical control of the study does not show any significant deviations from proper procedures.

The analytical methods used in both Clinical Pharmacology studies FH-002 and Sc-GLYCO-06-01 are acceptable.

2.7 Labeling

The proposed label for glycopyrrolate combines information from the oral solution, and Robinul® oral tablet and IV formulations. During the labeling portion of this review a difference of opinion was voiced between the Pharmacometric Reveiwer and Team Leader. Their differences are spelled out in the attached supervisory memo and review. In general the differnces hinge on two statements in the label:

1.) (b) (4)

Dr. Lee is of the opinion that this is not a true statement while Dr. Jadhav feels it is supported by the bulk of the available data from the IV product and the associated modeling. As primary reviewer, I have considered both positions, (b) (4)

I have decided to include the wording of Dr. Jadhav in this section but to re-order it in the absorption section as I do not believe that it is the most important take home mention in the absorption section and does not merit inclusion in the first paragraph.

2.) In the elimination section of the label there is a difference of opinion as to how variability should be expressed

(b) (5)

(b) (5)

In considering this I took into consideration what the objective of this information would be to me as a clinical pharmacist. First and foremost I would like a clear understanding of variability. (b) (5) If, the goal here is to demonstrate variability-then range is a more effective presentation to the general clinician.

The Clinical Pharmacology labeling recommendation is provided below:

Absorption

Absorption of [TRADENAME] (fasting) was compared to the oral tablet (b) (4) The Cmax after (b) (4) administration was 23% lower compared to tablet administration and the AUC0-inf was 28% lower after (b) (4) administration. Mean Cmax after (b) (4) administration in the fasting state was 0.318 ng/mL, mean AUC0-24 was 1.74 ng.hr/mL. Mean time to maximum plasma concentration for [TRADENAME] was 3.10 hours and mean plasma half-life was 3.0 hours.

A high fat meal was shown to significantly affect the absorption of glycopyrrolate oral solution (10 mLs, 1 mg/5 mL), in healthy adults. The mean Cmax under fed high fat meal conditions was approximately 74% lower than the Cmax observed under fasting conditions. Similarly, mean AUC0-T was reduced by about 78% by the high fat meal compared with the fasting AUC0-T. Pharmacokinetic results (mean ± SD) are described in Table 2. A high fat meal markedly reduces the oral bioavailability of [TRADENAME]. Therefore, [TRADENAME] should be dosed at least one hour before or two hours after meals.

Table 2. Pharmacokinetic parameters (mean±SD) for [TRADENAME], fasting and fed

	Cmax ng/mL (n)	Tmax hours (n)	AUC_{0-T} ng·hr/mL (n)	AUC_{0-Inf} ng·hr/mL (n)	T½ hours (n)
Fasting	0.318 ± 0.190 (n=37)	3.10 ± 1.08 (n=37)	1.74 ± 1.07 (n=37)	1.81 ± 1.09 (n=37)	3.0 ± 1.2 (n=37)
Fed	0.084 ± 0.081 (n=36)	2.60 ± 1.12 (n=36)	0.38 ±0.14 (n=36)	0.46 ± 0.13 (n=35)	3.2 ± 1.1 (n=35)

After oral administration to children ages 7-14 years undergoing general anesthesia, mean bioavailability of glycopyrrolate was low (approximately 3%) and highly variable between subjects (range 1.3 to 13.3% absolute bioavailability; n=6 children) compared to IV exposure. Similarly, low and variable oral bioavailability is seen in adults (b) (4)

Distribution
After I.V. administration, glycopyrrolate has a mean volume of distribution in children aged 1 to 14 years of approximately 1.3 to 1.8 L/kg , with a range from (0.7 to 3.9L/kg). In adults aged 60-75 years, the volume of distribution was lower (0.42 L/kg +/- 0.22).6

Metabolism
In adult patients who underwent surgery for cholelithiasis and were given a single I.V. dose of tritiated glycopyrrolate, approximately 85% of total radioactivity was excreted in urine and < 5% was present in T-tube drainage of bile. In both urine and bile > 80% of the radioactivity corresponded to unchanged drug. These data suggest a small proportion of I.V. glycopyrrolate is excreted as one or more metabolites.

Elimination
Approximately 65-80% of an I.V. glycopyrrolate dose was eliminated unchanged in urine in adults.8,9 In two studies, after I.V. administration to pediatric patients ages 1-14 years, mean clearance values ranged from 1.01- 1.41 L/kg/hr (range 0.32 – 2.22 L/kg/hr).5,7 In adults, I.V. clearance values were 0.54 ± 0.14 L/kg/hr. (b) (4)

Subpopulations
Pediatrics
(b) (4)

Gender
Population pharmacokinetic evaluation of adults and children administered I.V. or oral glycopyrrolate did not identify any effect of gender on glycopyrrolate clearance or systemic
exposure.

Race
The pharmacokinetics of glycopyrrolate by race has not been characterized.

Elderly
Glycopyrrolate pharmacokinetics have not been characterized in the elderly.

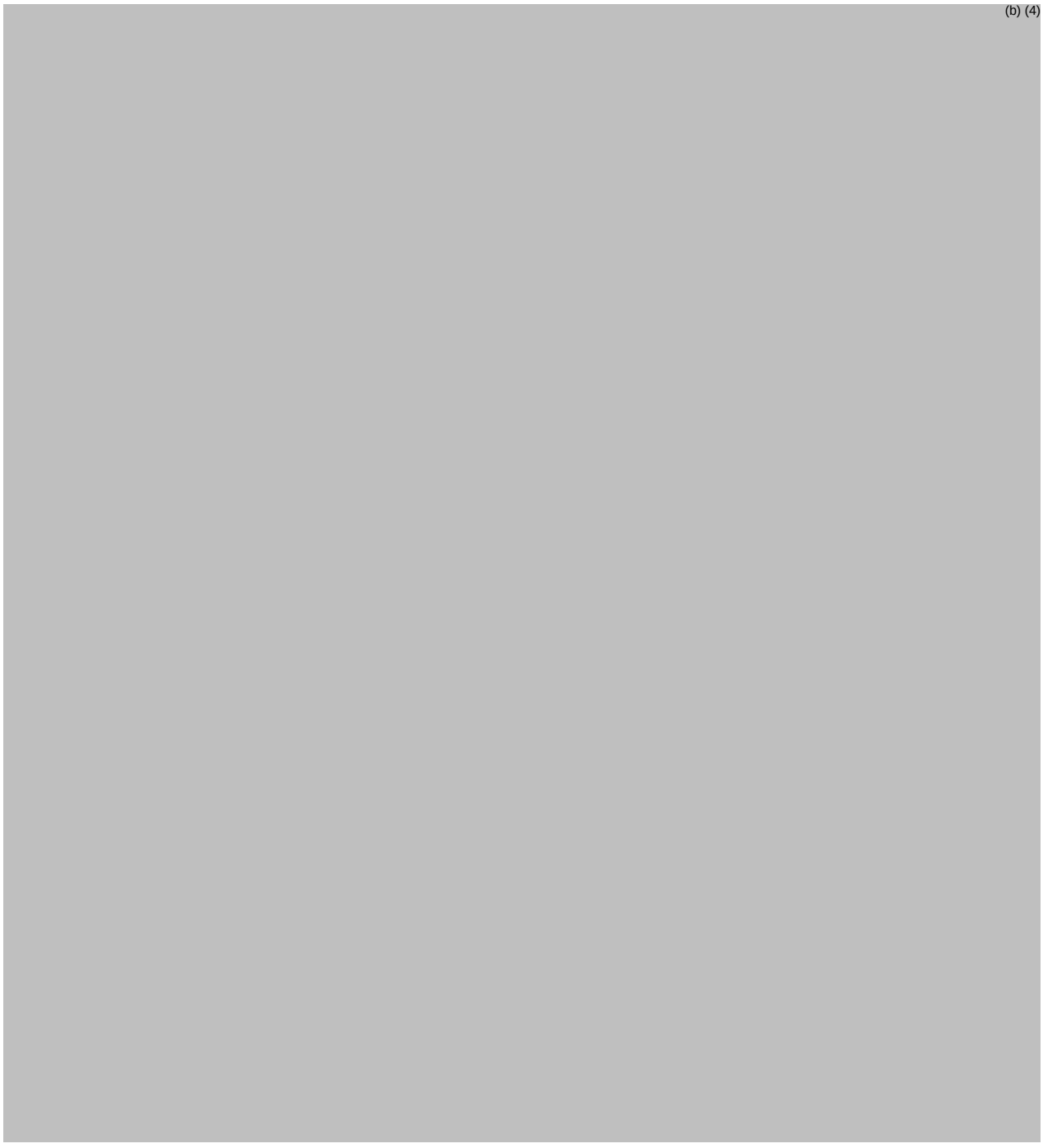
During the closure of the review process, attention was given to the drug-drug interaction potential of glycopyrrolate. In the draft labeling from the sponsor the following text was located in the "HIGHLIGHTS" section of the label:

Of interest is that while the highlights section cross-references a section 7, no such section is provided by the sponsor in their proposed label (section 7 being the Drug Interactions Section)

Following additional discussions with the reviewing Medical Officer, Dr. Fred Hyman, the following text was developed for both the "Highlights" and Drug Interactions sections of the label.

==========

This contraindication was actually contained in the original label provided by the sponsor but it was buried deep within the labeling-even though it was classified as a contraindication.



In the original list of drugs provided by the sponsor in their list of Drug Interactions the following drugs have been deleted as the published literature does not indicate that the

"interactions" would be of a clinically significant magnitude. Accoding to the sponsor the information for these interactions came from the 2010 Drug Interactions FACTS. Reproduced below is part of the individual interaction monographs provided by the sponsor. These "interactions" are part of the general anti-cholinergic section of the reference.

(b) (4)

3 Pages have been Withheld in Full immediately following this page as B4 (CCI/TS).

APPENDIX

Memorandum

From: Pravin Jadhav, Team Leader, Division of Pharmacometrics
To: Dennis Bashaw, Director, Division of Clinical Pharmacology
Concurrence: Joga Gobburu, Director, Division of Pharmacometrics

RE: Labeling claims based on population pharmacokinetic analysis- NDA 22-571

The sponsor is seeking labeling claims based on population PK analysis. This review pertains to describing the PK of glycopyrrolate with respect to its dose-proportionality and dependence on body size for pediatrics. The review summarizes areas of scientific and technical disagreements between Primary Pharmacometrics Reviewer (Dr. Jee Eun Lee) and Team Leader on those labeling recommendations (Part I of Pharmacometrics Review; draft received on 05/07/2010). The review also provides revised recommendations for labeling.

Sponsor's labeling claim #1: (b) (4)

Dr. Lee's position: (b) (4)

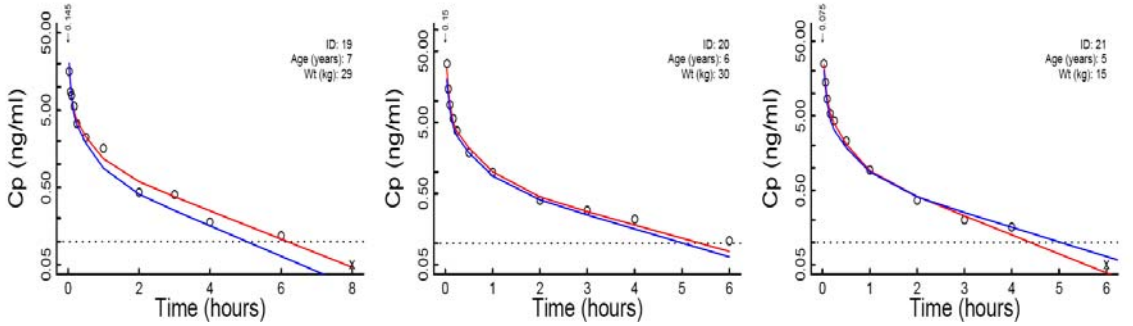
Considering totality of evidence from three pediatric studies (Turku #1, Turku #2 and SC-GLYCO-06-01), current glycopyrrolate labeling and population pharmacokinetic modeling performed by the sponsor, (b) (4)

1. (b) (4) According to Robinul IV label[1], AUC of 8.64 ug•hr/L was observed after 6 ug/kg glycopyrrolate IV dose. In the FH-00-02 study in adults, a 2000 ug (28.5 ug/kg for a 70 kg individual) single dose of glycopyrrolate oral formulations resulted in AUC of 1.81 ug•hr/L (Fed; oral solution), 0.46 ug•hr/L (Fasting; oral solution), and 2.46 ug•hr/L (Fasting; tablet) corresponding to absolute bioavailability of 4.5%, 1.14%, and 6.1%, respectively. The results are consistent (b) (4) using data from a crossover study (Turku #2) in children (50 ug/kg oral dose). (b) (4)
2. Glycopyrrolate concentrations observed in pediatric studies using 5 ug/kg IV doses (Turku #1 and Turku #2) were 20 fold higher than concentrations observed in SC-GLYCO-06-01 after 20-100 ug/kg oral solution doses. The

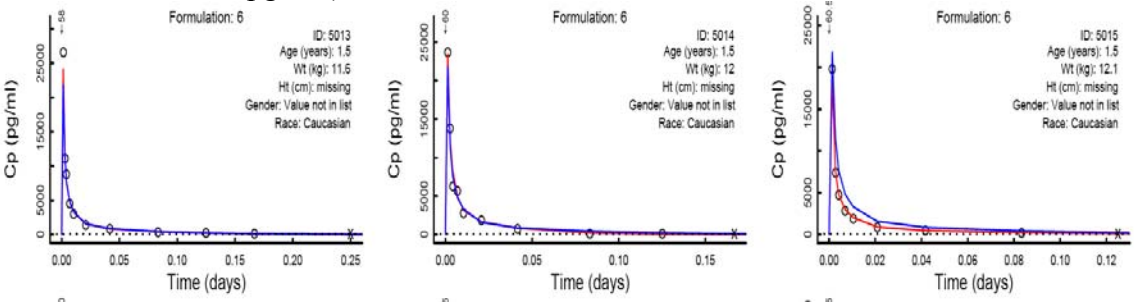
[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/017558s053lbl.pdf

concentrations observed in SC-GLYCO-06-01 are as high as 1.7 ng/mL (sparse sampling). We have experience up to 34.3 ng/mL (about 20-fold higher to that observed in pediatrics) from the Turku#1 and Turku#2 studies after IV dosing. The concentrations in SC-GLYCO-06-01 are likely to be observed after the recommended doses. The concentrations observed in FH-00-02 study in adults were reasonably similar (range 0.005-1.06 ng/mL) to concentrations observed in SC-GLYCO-06-01. The following are representative graphs from two pediatric studies (Turku #1 and Turku #2) and FH-00-02 study in adults.

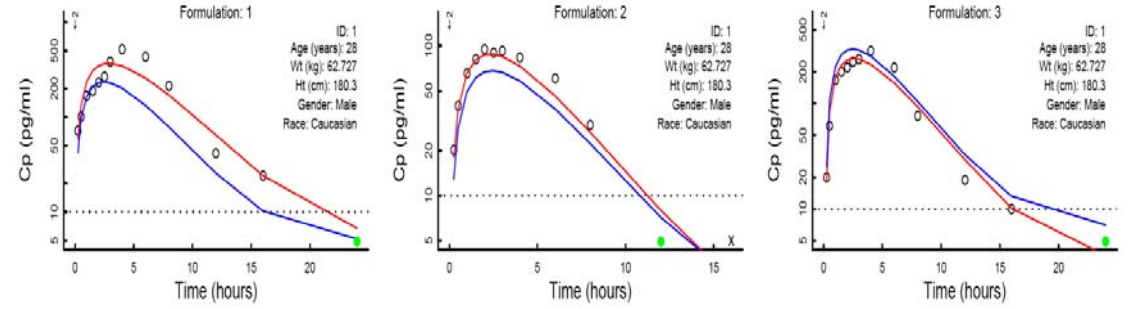
Turku #1: Rautakorpi 1994 Glycopyrrolate IV data



Turku#2: Rautakorpi 1998 Glycopyrrolate IV data (please note different concentration units; pg/mL)



FH-00-02 study in adults (Oral administration)



Based on these graphs, there is no evidence of non-linearity at 20 fold higher concentrations in pediatrics and similar concentrations in adults compared to expected clinical concentrations in pediatrics. For example, if glycopyrrolate followed nonlinear pharmacokinetics, the initial decline in the plasma concentrations would have been slower at high concentrations, compared with that at low concentrations. In other words, the rate of elimination would not be directly proportional to the plasma concentration. There is no such visual

evidence in concentration-time profiles for glycopyrrolate after IV and oral administration.

3. Further, the sponsor was able to describe the observed PK using a dose-proportional pharmacokinetic model in the SC-GLYCO-06-01 study. A similar model successfully described data obtained from Turku #1 and #2 studies. As noted above, the latter studies include 20 fold higher concentrations than those observed in the SC-GLYCO-06-01 study. The model described the pharmacokinetic data from IV and Oral administration in pediatrics and adults reasonably well.

(b) (4)

Sponsor's labeling claim #2: (b) (4)

Revised Labeling Recommendations:

(**Revisions**: Green)

(b) (4)

1 Page has been Withheld in Full immediately following this page as B4 (CCI/TS).

Office of Clinical Pharmacology:
Pharmacometric Review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is the weight-based dose adjustment scheme proposed in the label reasonable?

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.

Are the proposed labeling statements based on population pharmacokinetics analyses acceptable?

(b) (4)

Recommendations

1. Initial dose selection based on body weight is reasonable. The maintenance dose should be based on titration scheme performed in the trial.
2. (b) (4)
3. Apparent clearance estimated from population PK analysis should be reported along with a range as well as point estimate to provide the results of the analysis with its limitation.

Label Statements

The propose label includes statements in 12.3.

(b) (4)

(b) (4)

The proposed label includes statements in special population subsection for pediatrics,

(b) (4)

Pertinent regulatory background

Summary of the application

Sponsor: Sciele Pharma, Inc.
Application type: 505(b)(2)
Drug Name: Glycopyrrolate Oral Solution
Strength: 1 mg/ 5 mL

Background of the application

This submission relies on the FDA's previous findings of safety and effectiveness for the listed drug Robinul (glycopyrrolate) Injection 0.2 mg/mL, via cross reference to NDA 17-558, sponsored by Baxter Healthcare as well as Robinul (glycopuyrrolate) Injection 0.2 mg/mL via cross reference to NDA 14-764, sponsored by A.H. Robins. Moreover, the sponsor is the owner of Robinul and Robinul Forte (glycopyrrolate) Tablets 1 mg and 2 mg (NDA 12-827). 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, tracheobronchial, and pharyngeal secretions.

Glycopyrrolate is a medication of the muscarinic anticholinergic group. It is a synthetic amine with no central effects and is available in oral and intravenous forms. In anesthesia, glycopyrrolate injection can be used as a preoperative medication in order to reduce salivary, tracheobroncial, and pharyngeal secretions, as well as to decrease the acidity of gastric secretion. It is also used in conjunction with neostigmine, a neuromuscular blocking reversal agent, to prevent neostigmine's muscarinic effects such as bradycardia.

Drooling, or sialorrhea, is an unintentional loss of saliva from the mouth. This condition is normal in infants but usually stops by 15 to 18 months of age. However, for developmentally disabled individuals, particularly those with cerebral palsy or other

neurologic condition may have continuous drooling at later age. In the majority of individuals, drooling is caused by neuromuscular dysfunction, hyper-secretion, sensory dysfunction or oranatomic (motor) dysfunction. In children with cerebral palsy and other neuromuscular conditions, drooling is primarily due to oral motor dysfunction. Drooling can result in perioral chapping and maceration with secondary infection, irritation and maceration of facial skin, dehydration due to chronic loss of fluids, increased risk of aspiration, wetness and odor of clothing, social embarrassment, lowering of self-esteem and limitation of vocational opportunities.

Off-label use of commercially available oral glycopyrrolate tablets has been shown in literature trials to be helpful in the management of drooling associated with neuro-developmental conditions. Commonly, fixed dose glycopurrolate tablets have been used off-label for the treatment of this indication.

On 9 June 2006, glycopyrrolate was granted an orphan drug designation for the indication "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients" by the Office of Orphan Products Development.

The sponsor has completed three clinical studies with glycopyrrolate for the proposed indication: Two efficacy and safety studies and one pharmacokinetic study. The pivotal efficacy trial (FH-00-01) and an open-label, long-term safety study (SC-GLYCO-06-01) form the basis for the efficacy and safety evaluation of the oral solution.

Thirty eight patients were enrolled in FH-00-01 study and 103 patients were enrolled in SC-GLYCO-06-01 study. The Agency recommended evaluating the pharmacokinetics of glycopyrrolate oral solution in the target patient using population PK approach and agreed that these data could be obtained from a subset of patients in SC-GLYCO-06-01.

The pharmacokinetics evaluations in the population PK report included a bioavailability and food effect study (FH-00-02) and a population PK trial (performed as part of SC-GLYCO-06-01).

Reviewer's notes regarding data:

(1) One dose level was administered to adult subjects. The dose proportionality of PK cannot be confirmed from adult data.

(2) The results in pediatric trials are confounded due to the lack of information on whether the drug was administered to children with or without food. The food effect observed from adult data was significant (Study FH-00-02). FH-00-02 study in adults had three arms; fed with high fat, fasted, and the reference drug (Robinul). The relative bioavailability of oral solution to the reference drug for each arm was markedly different based on food status (fasted-72% and fed- 21%). However, due to the lack of information, the interpretation for the apparent clearance in pediatrics is complicated.

(3) The absolute bioavailability of glycopyrrolate estimated from 6 children was reported in literature is ranging 1.3%~13.3% (Rautakorpi P et al., 1998).

Summary of the sponsor's population PK analysis

The sponsor's analysis includes two parts.

(1) First part: Two historical studies (Turku#1 and Turku#2) in pediatric patients conducted in Finland were analyzed. In Turku#1, 26 children aged 2 months-12 years were given glycopyrrolate 5 mcg/kg as an intravenous bolus. In Turku#2, six children aged 7-14 years were dose with glycopyrrolate on two occasions: once orally (50

mcg/kg) and once intravenously (5 mcg/kg). Then a pooled analysis of these two studies was conducted. This analysis focused on determining the optimal means to calibrate the pharmacokinetic characteristics for body size.

(2) Second part: An analysis for a crossover study conducted by Sciele (formerly First Horizon) in healthy adults (FH-00-02) was performed to develop a structural model for the systemic pharmacokinetics of the drug and to develop absorption models from the three states. Finally the pediatric study (Sc-GLYCO-06-01) with chronic moderate to severe drooling was pooled with the adult data. Again, this analysis was confounded by the fed status in children: although pediatric patients were instructed a fast briefly before dosing on days in which samples would be obtained, this was not documented. Thus, "fasting" pediatric data is not strictly comparable to either children and adults could be a function of age and/or body size or a function of fed status.

The analysis 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.

Results of Sponsor's Analysis

(1) First part:

The Turku#1 and Turku#2 studies yielded similar results for the systemic pharmacokinetics of glycopyrrolate. For each, a 3-compartment linear model described the systemic pharmacokinetic characteristics of glycopyrrolate. For the second study, a first-order absorption model with an absorption lag was applied to describe the data for oral dosing. A model in which the systemic parameters were normalized by body weight was preferred statistically and by goodness-of-fit plots.

Reviewer's comments: The above analysis was based on limited information. There were several key pieces missing from the data about how the clinical trials were actually conducted. Most importantly, the information on the actual dosing regimen in pediatric patients was not available. The investigators provide conflicting information with respect to the preparation of the oral formulation: either the IV formulation or tablets dissolved in juice. Furthermore, there is no validation report for the assay and the pharmacokinetic data provided by the investigators were questionable. (b) (4)

Further, the absolute bioavailability reported in the label was obtained from the analysis for Turku#2 study. The number of subjects participated in the study was too small (n=6) so the absolute bioavailability should be interpreted with caution.

(2) Second part:

Although three-compartment model was used in earlier analysis (first part), first-order absorption, two-compartment with lag time model was introduced as the optimal model for the pooled adult and pediatric data. None of the NONMEM runs with the pooled data converged successfully. A failure to converge may indicate inability to fit the limited quantity of pediatric data. The pediatric samples were small in number. Furthermore, the information on whether the drug was administered with or without food was not available for the pediatric data. Therefore, adequate assessment of pharmacokinetics was hindered.

(3) Final Model chosen:

A pooled analysis of adult and pediatric studies with Sciele's liquid glycopyrrolate formulation indicates that scaling the systemic pharmacokinetic parameters by either measured body weight or body weight raised to the 0.7 power removed any residual effects of age and/or body size (or other covariates). When pharmacokinetic parameters were allometrically scaled by body weight or body weight raised to the 0.7 power, the same scale was applied to all parameters.

Table 1. Sponsor's Model and Its Parameter Estimates

Model normalized by weight (optimal model which the sponsor reports PK values from)
$CL=TVCL*(Weight/70\ kg)*ETA_{CL}$
$V1=TVV1*(Weight/70\ kg)*ETA_{V1}$
$CLRA=TVCLRA*(Wegith/70kg)*ETA_{CLRA}$
$V2=TVV2*(Weight/70\ kg)*ETA_{V2}$

Model normalized by weight ratio raised to the 0.7 power
$CL=TVCL*(Weight/70\ kg)^{0.7}*ETA_{CL}$
$V1=TVV1*(Weight/70\ kg)^{0.7}*ETA_{V1}$
$CLRA=TVCLRA*(Wegith/70kg)^{0.7}*ETA_{CLRA}$
$V2=TVV2*(Weight/70\ kg)^{0.7}*ETA_{V2}$

Parameter	Estimate	ω(IIV)*	Description
CL/F (L/hr)	759	0.287	Apparent clearance
V1/F (L)	1920	0.354	Apparent central volume of distribution
CLRA (L/hr)	292	0 FIXED	Distribution clearance between central and peripheral compartment
V2 (L)	21400	0 FIXED	Peripheral volume of distribution
KA1(/hr)	0.409	0.108	First order absorption rate constant for glycopyrrolate at fasted state
LAG1	0.0766	0 FIXED	Absorption lag time for glycopyrrolate at fasted state
BIO1	0.707	0.223	Bioavailability for glycopyrrolate at fasted state
KA2	0.384	0.153	First order absorption rate constant for glycopyrrolate at fed state
LAG2	0 FIXED	0 FIXED	Absorption lag time for glycopyrrolate at fed state
BIO2	0.21	0.16	Bioavailability for glycopyrrolate at fed state
KA3	0.436	0.000116	First order absorption rate constant for Robinul at fsted state
LAG3	0.156	0 FIXED	Absorption lag time for Robinul at fasted state
BIO3	1 FIXED	0 FIXED	Bioavailability for Robinul at fsted state
KA4	1 FIXED	0 FIXED	First order absorption rate constant for glycopyrrolate from Finland study
LAG4	0 FIXED	0 FIXED	Absorption lag time for glycopyrrolate from Finland study
BIO4	1 FIXED	0 FIXED	Bioavailability for glycopyrrolate from Finland study
KA5	0.222	0 FIXED	First order absorption rate constant for glycopyrrolate in pediatrics
LAG5	0 FIXED	0 FIXED	Absorption lag time for glycopyrrolate in pediatrics
BIO5	0.384	0.525	Bioavailability for glycopyrrolate in pediatrics
SIGMA1	0	NA	Proportional error for Finland study
SIGMA2	0	NA	Additive error for Finland study
SIGMA3	0.0828	NA	Proportional error for adults
SIGMA4	0.00001	NA	Additive error for adults
SIGMA5	0.127	NA	Proportional error for pediatrics

SIGMA6	0.00001	NA	Additive error for pediatrics

* IIV: Inter-individual variability

The final model was chosen based the objective function value which was obtained from the two-compartment, first-order absorption with lag time which was allometrically scaled by body weight, and some parameters including the pediatric absorption lag time was fixed (Table 1).

Having adjusted for body size, there is no evidence of other covariate effects (age, race, lab values, etc.); however, the small samples size might have limited the ability to detect other covariate effects.

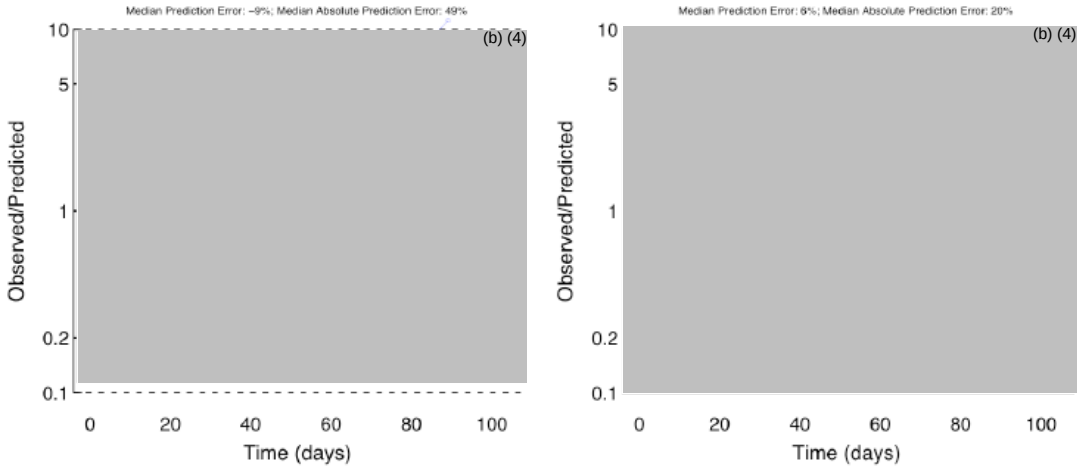


Figure 1. Ratio of observed to population predicted concentrations of glycopyrrolate for pediatric patients for the optimal model*. Each line represents values for an individual subject. The BQL value used in the analysis is displayed with a red dot (Source: Figure 11 from the sponsor's report).

The sponsor reported that any test one over the other model was not feasible because neither model converged nor nested to each other. The sponsor also accepted that the failure of NONMEM runs with pediatric patient data to converge could invalidate the results. The report concluded that despite the quantity of data in pediatric patients being limited. The analyses suggested that the systemic exposure in children was comparable, having adjusted for body size via either weight or weight raised to the 0.7 power, to the exposure in fed adults. The report addressed further that dosing adjustments after the initial dose could then be made based on clinical signs of efficacy (coupled, as necessary, with adverse events).

Reviewer's comments:

(1) The sponsor made a few attempts to achieve successful convergence. For example, the effect of BQL handling methods was evaluated by modifying models, allometric scaling was applied to all pharmacokinetic parameters.

(2) The reviewer simplified the model by reducing parameters. The reviewer chose one-compartment first order absorption model and added correlation between clearance and volume of distribution in the model. Furthermore, the reviewer's model employed conventional allometric scaling method. (See Reviewer's Analysis).

Reviewer's Analysis Part I

Introduction

Although the optimal model the sponsor developed was not converged, the proposed label includes statements based on the population PK analysis. The reviewer reanalyzed the data using the sponsor's model to properly address the results in the label.

Objectives

Analysis objectives are:

1. To evaluate the relationship between drug exposure and weight to examine weight-based dosing regimen proposed in the label
2. To examine the population pharmacokinetics model to support pharmacokinetic parameters in the label

Methods

Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
SC-GLYCO-06-01	Pooled PK data for healthy adults and pediatric patients	\\cdsesub1\EVSPROD\NDA022571\0000\m5\datasets\sc-glyco-06-01-poppk\analysis\sciele-pk

Software

NONMEM VI, S-Plus 7.0

Models

(1) The correlation between concentration and body weight was examined by generating concentrations 0~2 hour postdose were plotted against body weight.

(2) The model was modified by changing the scaling factor. Clearance parameters were normalized by body weight with allometric exponent of 0.75 and volume of distribution parameters were normalized by body weight.

(3) The concentrations do not range for multiple magnitudes thus only additive error model was also attempted for the residual error model.

(4) Since correlation between apparent clearance and apparent volume was expected because of bioavailability in each parameter, it was added in the model.

(5) One outlier concentration point from adult data (subject ID 6004) was removed.

(6) After several runs with two-compartment model, the contribution of peripheral compartment was observed to be not significant. Thus the model was simplified to one-compartment with first-order absorption and the inter-individual variability for lag time was removed.

(7) The goodness-of-fit to compare the sponsor's model and the reviewer's model was performed.

Results

The associations between drug exposure (concentration) and body weight and other demographic factors were examined. (b) (4)

As shown in Figure 2, the concentration does seem to increase as body weight decreases. This graph cannot be interpreted because of the titration to response scheme that was adopted in the trials. The PK samples were collected after visit 3 when the titration was complete. The initial doses for the pediatric patients were determined based on their body weight and then dose-titration was followed by close monitoring of clinical responses of the patients. The non-responders or patients with high clearance could end up with high dose and vice versa. Therefore, the differences in doses do not allow obvious interpretation on the relationship body weight and exposures. The graph between body weight and clearance is more relevant to comment on the relationship.

(b) (4)

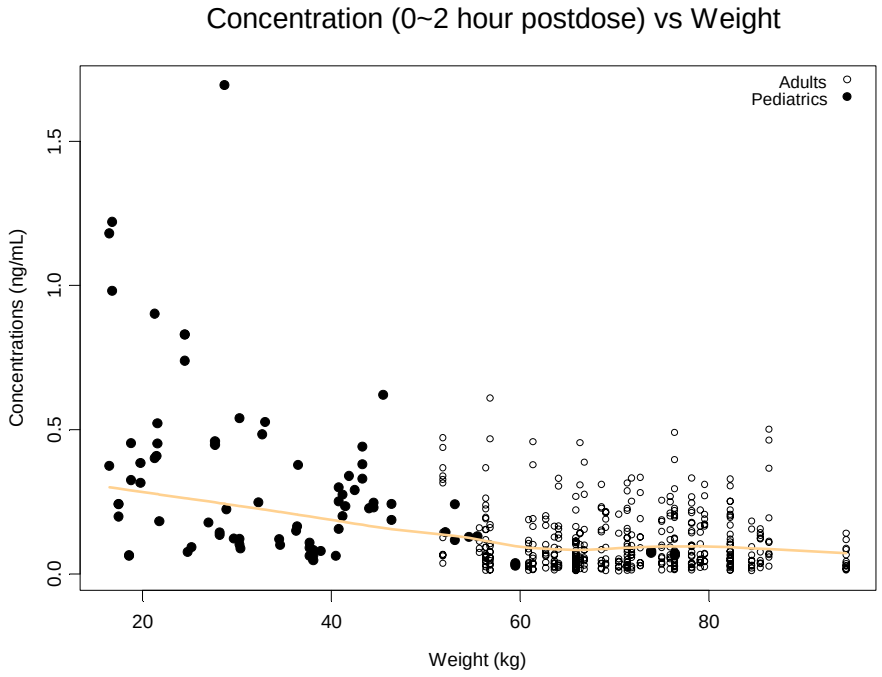


Figure 2. Concentration (0~2 hour postdose) versus weight profile for both adult and pediatric subjects:

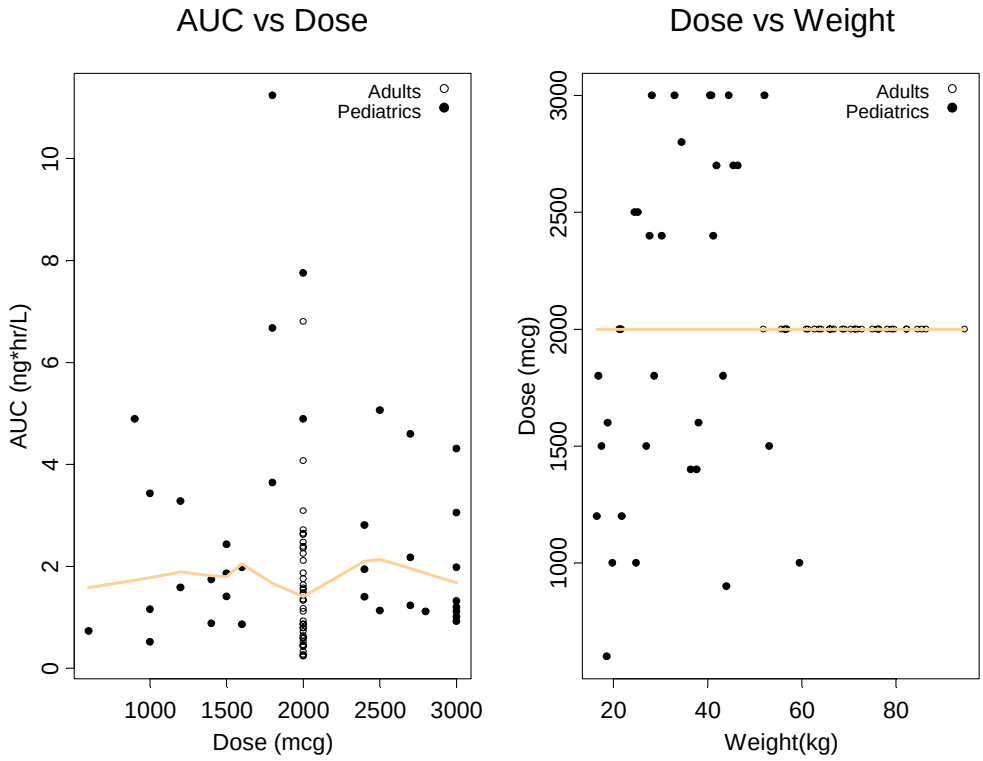
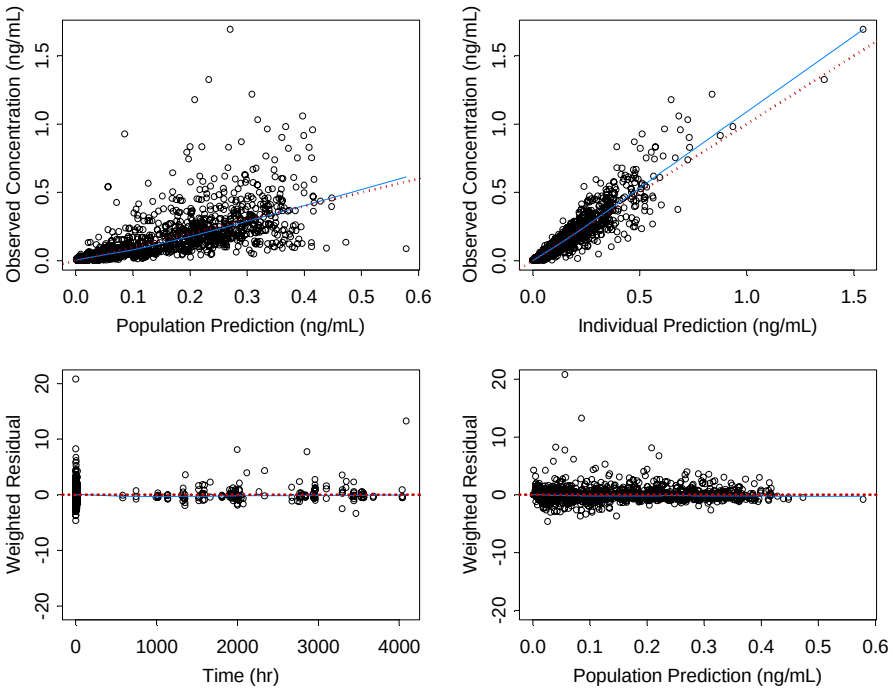


Figure 3. AUC versus dose profile on the left panel shows no significant change across doses. This is mainly because the maintenance doses for the pediatric patients were adjusted by close monitoring of clinical responses.

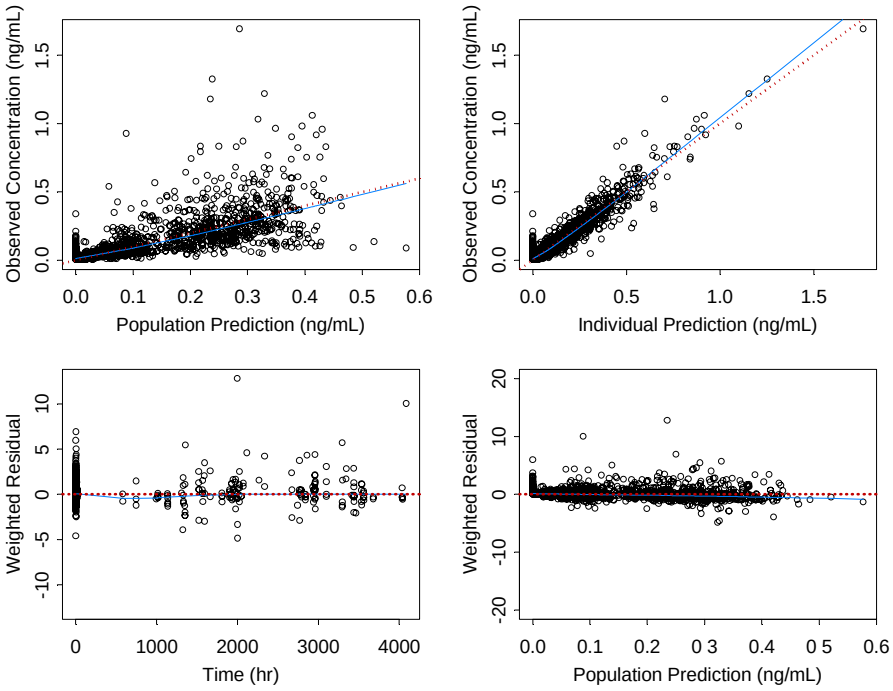
In Figure 3, the reviewer found no relationship between dose and exposure (AUC). The graph is difficult to interpret for similar reasons mentioned above. The non-responders or patients with high clearance could end up with high dose and vice versa. Therefore, it is not surprising to find the lack of relationship.

The concentrations in pediatric patients were obtained at steady state whilst adult concentrations were measured after single dose administration. Therefore, there might be other factors (not measured in the study) could affect estimation of clearance in pediatric patients. For example, the estimation of clearance and relative bioavailability were confounded due to the lack of information on food status in pediatrics. The fed status in adults decreased the exposure over 30% is considered, the apparent clearance estimated for the pediatric patients cannot be comparable to either fed or fasted adult data.

Despite these limitations, it is reasonable to select a starting dose based on body weight and perform titration (as done in the pivotal study) based on the response. For the pharmacokinetic information in the label, the reviewer recommends that the PK parameters estimated from the modified model by the reviewer be reported in the label as a range. The sponsor's model estimate for the apparent clearance 759 L for 70 kg subject ranging 90.3~2776 L/hr in adults and 86.4~1200.9 L/hr in pediatrics whilst the reviewer's modified model estimate for the apparent clearance was 927 L for 70 kg subject ranging 294.0~2291.7 L/hr (5.28 ~ 38.95 L/hr/kg) in adults and 258.1~1150.3 L/hr (8.07 ~ 25.65 L/hr/kg) in pediatrics.



(a) Sponsor's optimal model



(b) Reviewer's modified model

Figure 4. Goodness of fit in comparison of the sponsor's optimal model and the reviewer's modified model. There are slight improvements in predicted concentrations and weighted residual profiles.

Table 3. Reviewer's Modified Model and Its Parameter Estimates

Model normalized by weight ratio raised to the 0.7 power			
$CL=TVCL*(Weight/70\ kg)^{0.75}*ETA_{CL}$ $V1=TVV1*(Weight/70\ kg)*ETA_{V1}$			
Parameter	Estimate	ω(IIV)	Description
CL/F (L/hr)	927	0.192*	Apparent clearance
V1/F (L)	1430	0.679*	Apparent central volume of distribution
KA1(/hr)	0.379	0.054	First order absorption rate constant for glycopyrrolate at fasted state
LAG1 (hr)	0.686	0 FIXED	Absorption lag time for glycopyrrolate at fasted state
BIO1	0.682	0.208	Bioavailability for glycopyrrolate at fasted state
KA2 (/hr)	0.315	0.00002	First order absorption rate constant for glycopyrrolate at fed state
LAG2 (hr)	0.001	0 FIXED	Absorption lag time for glycopyrrolate at fed state
BIO2	0.175	0.00832	Bioavailability for glycopyrrolate at fed state
KA3	0.343	0.00443	First order absorption rate constant for Robinul at fsted state
LAG3	0.284	0 FIXED	Absorption lag time for Robinul at fasted state
BIO3	1 FIXED	0	Bioavailability for Robinul at fasted state
KA4	1 FIXED	0	First order absorption rate constant for glycopyrrolate from Finland study
LAG4	0 FIXED	0	Absorption lag time for glycopyrrolate from Finland study
BIO4	1 FIXED	0	Bioavailability for glycopyrrolate from Finland study
KA5	0.183	0	First order absorption rate constant for glycopyrrolate in pediatrics
LAG5	0 FIXED	0	Absorption lag time for glycopyrrolate in pediatrics
BIO5	0.515	0.525	Bioavailability for glycopyrrolate in pediatrics
SIGMA	0.00324		Additive residual error

* Correlation between ω(CL) and ω(V) was estimated to be 0.00314

The relative bioavailability for glycopyrrolate in fed adults was reported more than 30% lower than that in fasted adults when referenced to Robinul, which is well reflected in the concentration profile on the left panel of Figure 5. These adult data were included in the population PK analysis and served as informative data for pediatric pharmacokinetic parameter estimation. When model-estimated AUC values from the reviewer's model were compared for the three conditions (right panel of Figure 5), they were reasonably well aligned with the concentration profiles. This boxplot provides supportive evidence that the results estimated from the population PK model could be informative when they are reported along with limitations.

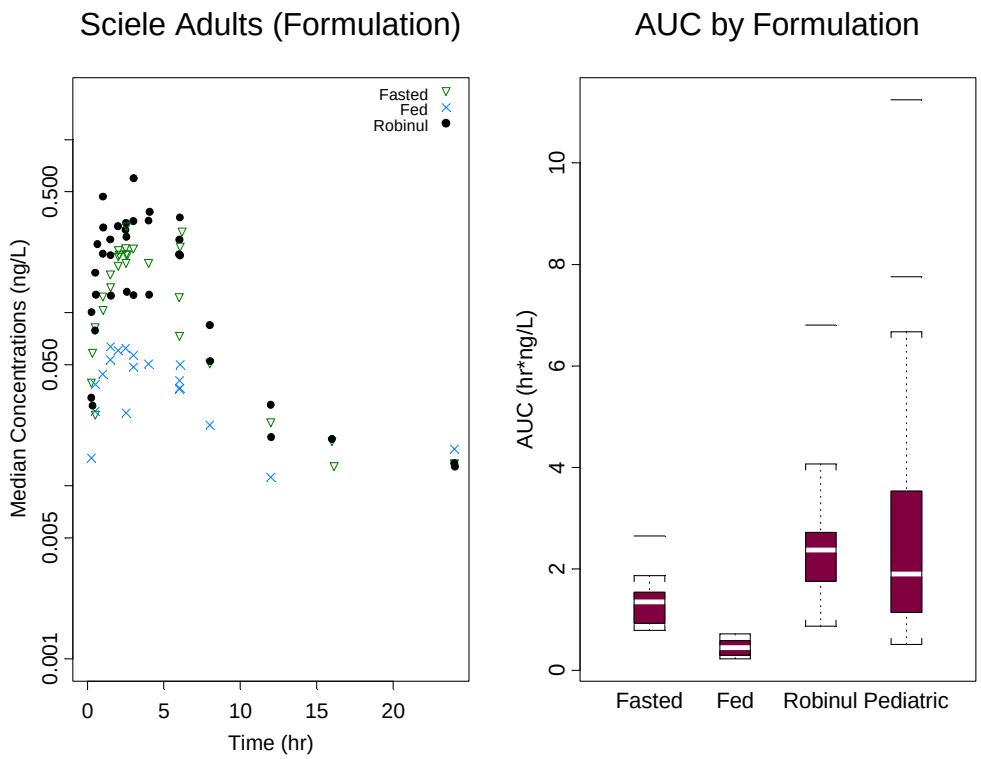


Figure 5. Left: The concentration vs. time profile by formulation/fed/fasted status for adults, Right: Boxplot for calculated AUC from model-estimated CL/F for formulation/fed/fasted status and pediatric patients.

Conclusion

- 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.

Reviewer's analysis part II

Introduction and Objectives

A separate analysis to investigate possible association between deaths and drug exposure was conducted upon the request from the reviewer's team.

Although no deaths were reported for study participants while patients were treated with study drug, three patients died in Study SC-GLYCO-06-01 within 30 days after the last dose of study drug. SUBJECT 1403 died of multi-organ failure two days after the last dose of study drug, SUBJECT 1709 died of aspiration pneumonia four days after the last dose of study drug, and SUBJECT 2906 died of anoxic encephalopathy 20 days after the last dose of study drug. The events of multi-organ failure and anoxic encephalopathy

were considered not related by the sponsor, and the event of aspiration pneumonia was considered unlikely to be related to treatment with glycopyrrolate oral solution also by the sponsor.
Among those three patients, two patients (SUBJECTS 1709 2906) and of them left pharmacokinetic data, thus the reviewer team questioned if there was any association between the incidents and drug exposure.

Methods

All evaluations were conducted based on visual examination on pharmacokinetic data and laboratory data. Upon the limitations of the data, it is difficult to make a clear conclusion by brief visual examinations on the pharmacokinetic data unless there are any significant outliers associated with the dead patients. Being aware of the restriction, the visual examinations on dosing information, physiological conditions such as demographic and laboratory data were performed.

Results and Conclusions

As shown in Figure 3, the maintenance doses administered to many pediatric patients were higher than the single dose administered to adult subjects. The difference is more significant in weight-normalized dose than total dose administered in two populations. Some pediatric patients received 5-times higher weight-normalized doses compared to adults, and 3 subjects including SUBJECT 2906 received above the maximum dose (100 mcg/kg) proposed in the protocol. Although the weight-normalized dose was high for SUBJECT 2906, the concentration profile does not show clear indication that the patients were exposed to drug significantly higher than other patients (Figure 7).
Additionally, physiological conditions such as hepatic functions and renal functions were evaluated using laboratory data (Figure 8). There were no significant signs observed from the physiological conditions associated with clearance either. However, the correlations between the pharmacokinetics and the clinical outcomes are not clearly understood, and there are various unknown physiological factors affecting in the relationships between PK and PD. Upon the limitations of the data, no clear evidence for the association between PK and the deaths was observed. However, the protocol violation for three patients who received above the maximum weight-normalized dose (100 mcg/kg) should be addressed.

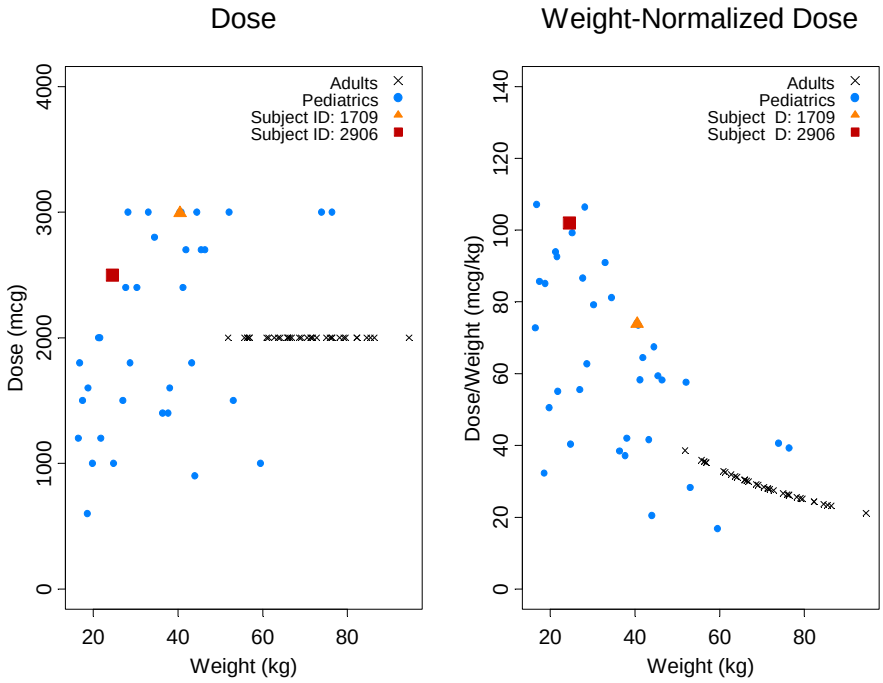


Figure 6. Dose versus weight and weight-normalized dose versus weight profiles featuring two pediatric patients who died after the clinical trial.

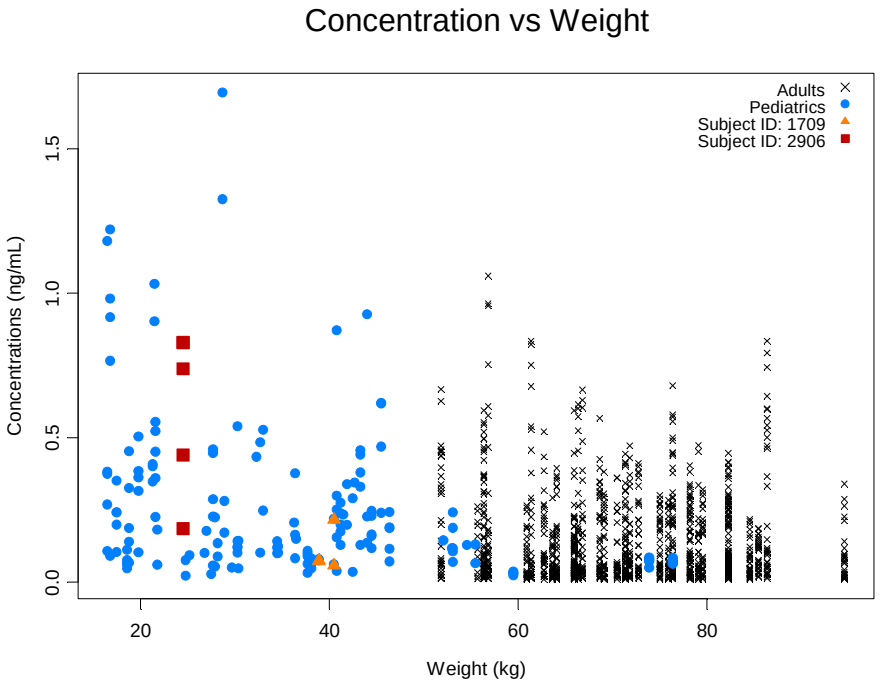
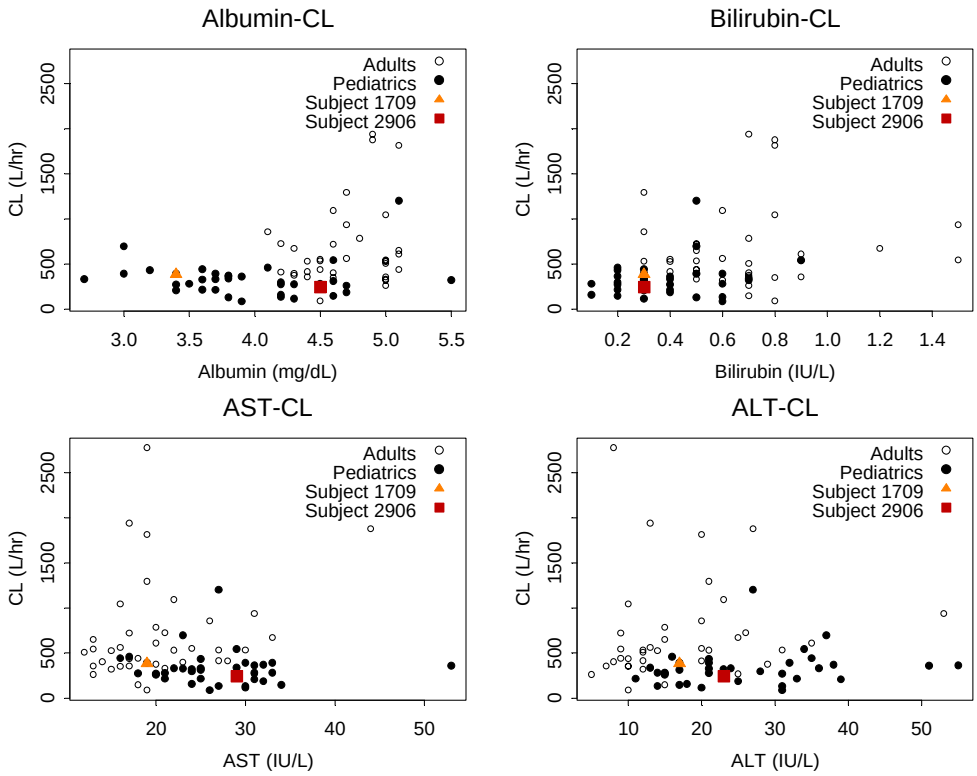
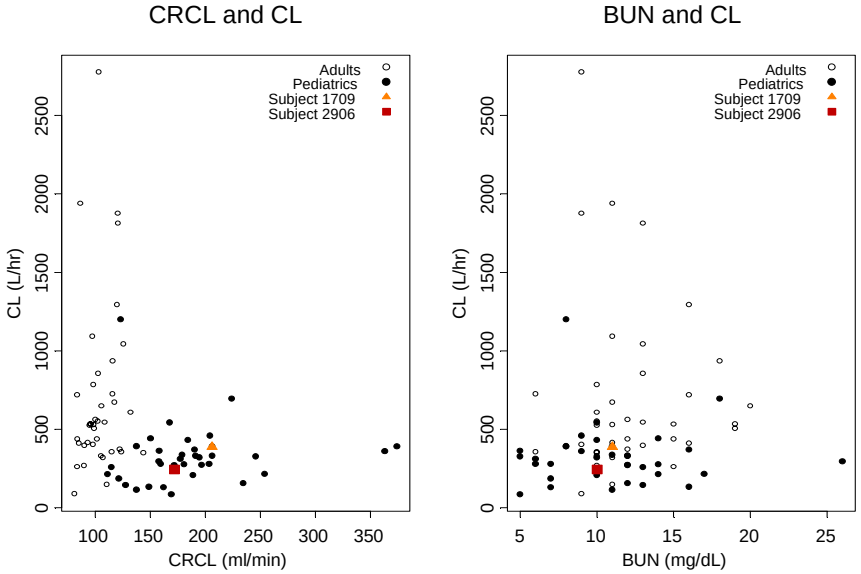


Figure 7. Concentration versus weight profile featuring the concentrations of the two pediatric patients who died after the clinical trial



(a) Hepatic function and clearance



(b) Renal function and clearance

Figure 8. Physiological conditions versus clearance

Analytical Summary
FH-002

Overview

A liquid chromatograph tandem mass spectrometry (LC/MS/MS) method for the determination of glycopyrrolate in heparinized human plasma was validated using (b) (4) as the internal standard. Sample preparation consisted of liquid-liquid extraction of glycopyrrolate and the internal standard from heparinized human plasma with an organic solvent system. Analysis was by liquid chromatography with tandem mass spectrometry using a reversed phase analytical column with a mobile phase consisting of methanol and ammonium acetate buffer. Identification of Glycopyrrolate and the internal standard was achieved through multiple reaction monitoring.

The relationship between concentration and peak area ratio was found to be acceptable within the range of 0.01 ng/ml to 10.0 ng/ml for Glycopyrrolate in heparinized human plasma. The lower limit of quantification from 0.150 ml of heparinized human plasma is 0.01 nglmL The between-run precision of the method ranged from 4.06% to 10.63% and the between run bias ranged from -4.50% to 4.82% of Glycopyrrolate.

Between-Run Precision and Bias Data for a Liquid Chromatography-Tandem Mass Spectrometry Method for the Quantification of Glycopyrrolate in Heparinized Human Plasma. Three-Run Validation.

Run Date	Curve Number	Low (0.0100 ng/mL)	Mid (0.0200 ng/mL)	Mid (0.850 ng/mL)	High (8.50 ng/mL)
28-Feb-2002	1	0.0104	0.0223	0.918	9.33
		0.00872	*0.0244	0.830	9.16
		~0.00835	0.0189	0.822	8.81
		0.00953	~0.0168	0.821	8.41
		0.00914	0.0190	0.825	8.45
		0.0102	0.0201	0.757	8.50
03-Mar-2002	2	0.0105	0.0202	0.886	9.17
		0.0105	*0.0269	0.821	9.50
		0.0111	0.0189	0.825	8.47
		0.00998	0.0199	0.835	8.96
		0.00921	0.0201	0.792	*6.36
		0.0105	0.0184	0.843	9.34
15-Mar-2002	3	~0.0121	0.0206	0.804	9.30
		0.00878	0.0179	0.846	8.72
		~0.0119	0.0206	0.847	8.53
		0.00970	0.0183	0.815	9.10
		0.00878	~0.0168	0.802	8.69
		0.0100	0.0172	0.826	8.99
Mean		0.00997	0.0191	0.829	8.91
S.D.		0.00106	0.00154	0.0346	0.362
%CV		10.63	8.06	4.17	4.06
%Theoretical		99.70	95.50	97.53	104.82
%Bias		-0.30	-4.50	-2.47	4.82
n		18	16	18	17
Overall %CV		6.73			
* Sample Deactivated					
~> 15%Theoretical					

The mean recovery was 57.01% for Glycopyrrolate. The recovery of the internal standard was 59.68%. During the validation process the stability of the drug in the matrix after three freeze thaw cycles and after 23 hours storage at room temperature was established. In addition the stability of frozen glycopyrrolate after 164 days was also demonstrated.

Glycopyrrolate Frozen Storage Stabilities

Concentration (ng/mL)	Date Tested	Mean Peak Area Ratio -70°C	Mean Peak Area Ratio -140°C	Relative % Difference (-70°C vs -140°C)
0.0200	03-19-02 04-08-02	0.171 0.154	0.152 0.142	11.59 8.09
0.100	03-19-02 04-08-02	0.938 0.784	0.827 0.781	12.59 0.34

Conclusions

Although problems were noted in the data evaluation portion of this study report, it is unclear if the differences noted were poor analytical technique or poor sample recordkeeping. Given the many hands this data has passed through since 2002 it is unlikely that a conclusive answer could be developed. The general conclusion that can be drawn from the submitted analytical report is that it appears that the proper validation procedures were in place and that mislabeling of samples is the most probable cause of the noted differences. The analytical report is acceptable for this study.

Sc-GLYCO-06-01

Overview

The analysis of glycopyrrolate by (b) (4) was performed on an API 4000 LC/MS/MS system using propranolol hydrochloride as an internal standard (IS). The interface used with the API 4000 LC/MS/MS was a Turbo Ionspray®. The positive ions were measured in MRM mode.

Sample Accountability

The study involved the analysis of one hundred and sixty-nine (169) samples (38 subjects with 5 time points) over one hundred and eight-eight (188) days by two (2) analysts. Eight samples from two subjects (1406 and 1407) were received in a thawed condition and were not analyzed. Furthermore an additional six samples from four subjects (1709, 2803, 2903, and 2911) were not received. Five samples from three additional subjects (1707, 1712, and 1713) although received at the analytical site were "misplaced". Thus, 19 samples or 11% of the total samples taken were unavailable for analysis

General Analytical Acceptance Procedures (Standard and QC Samples)

For the run to be accepted, the back calculated individual standards and QC samples should be within ±15% of the nominal value, except for the LLOQ for which the back calculated value should be within ±20% of the nominal value. In addition, 2/3 of the total QC samples and at least 50% of the QC samples from each concentration level must be within ±15% of the nominal value for the run to be accepted. For the standard curve to be accepted, 75%, but not less than six (6) non-zero standards, of all the standards must be within the stated acceptance range. Where the "r2" value of the calibration curve is calculated, it must be 0.98 or better for the run to be acceptable.

The study samples were assayed (b) (4) Of some concern was the daily generation of a standard curve using only SINGLE sample concentrations for each standard. While QC samples were run in duplicate and dispersed throughout the run, the lack of replication at each standard concentration is not proper analytical technique. The fact that the standards are so reproducible across the runs is less impressive given this procedure.

Summary of Back Calculated Calibration Standard Concentration Data for Glycopyrrolate in Human Plasma

(b) (4)

Batch Run ID	Assay Date	STD 1 0.02000 ng/mL	STD 2 0.04000 ng/mL	STD 3 0.1000 ng/mL	STD 4 0.2000 ng/mL	STD 5 0.4000 ng/mL	STD 6 1.000 ng/mL	STD 7 2.500 ng/mL	STD 8 3.000 ng/mL
1	12-Sep-2007	0.02059	0.03760	0.09997	0.1983	0.4064	1.024	2.485	3.017
3	25-Oct-2007	0.01993	0.04038	0.1021	0.1912	0.3940	0.9685	2.537	3.148
4	26-Feb-2008	0.01999	0.04146	0.09240	0.1977	0.3913	0.9488	2.676	3.164
5	27-Feb-2008	0.02019	0.03910	0.1012	0.1974	0.4034	1.003	2.645	2.835
6	18-Mar-2008	0.02083	0.03793	0.09566	0.1869	0.3905	0.9712	2.757	3.206
	Mean	0.02031	0.03929	0.09827	0.1943	0.3971	0.9831	2.620	3.074
	S.D.	0.0003905	0.001631	0.004105	0.005038	0.007297	0.03000	0.1091	0.1511
	%CV	1.9	4.2	4.2	2.6	1.8	3.1	4.2	4.9
	%Bias	1.6	-1.8	-1.7	-2.9	-0.7	-1.7	4.8	2.5
	n	5	5	5	5	5	5	5	5

Summary of Calibration Parameters for Glycopyrrolate in Human Plasma

(b) (4) Batch Run ID	Assay Date	Slope	Intercept	R^2
1	12-Sep-2007	0.786421	-0.00274967	0.998967
3	25-Oct-2007	0.788193	-0.00385550	0.998799
4	26-Feb-2008	1.84169	-0.00128617	0.996546
5	27-Feb-2008	1.72419	-0.000356135	0.998603
6	18-Mar-2008	0.944642	-0.00303627	0.994858
	Mean	1.21703	-0.00225675	0.997555
	n	5	5	5

It is unclear if this procedure affected the results of the study. As it has been shown in the previously there is considerable variability in the pk data for glycopyrrolate. Whether or not some of this attendant variability seen in the data analysis for this study is due to analytical reasons is unknowable. The sponsor will be advised about this for future studies as this technique (relying on a single standard concentration) is wholly unacceptable and could undo an entire NDA.

The QC samples were prepared, in bulk, prior to the first run on September 11, 2007 and kept frozen at -20°C ±10°C with the study samples. For QC samples, the inter-day precision (CV) was 14.4% or better and the accuracy (Bias) ranged from –2.7 to 6.2%. The precision and accuracy for the diluted high QC samples was 3.8% and 6.5%, respectively.

Summary of QC Sample Concentration Data for Glycopyrrolate in Human Plasma

(b) (4) Batch Run ID	Assay Date	LQC 0.05000 ng/mL	MQC 0.3000 ng/mL	DQC 2.400 ng/mL	HQC 2.400 ng/mL
1	12-Sep-2007	0.04724	0.2961		2.332
		0.04312	0.2791		2.228
3	25-Oct-2007	0.05228	0.3315		2.586
		0.04612	0.3416		2.612
4	26-Feb-2008	0.04422	0.2984		~1.693
		0.05256	0.3323		2.625
5	27-Feb-2008	0.05116	0.3174		2.540
		0.05682	0.3287		~2.938
6	18-Mar-2008	0.04409	0.3131	2.486	2.682
		0.04873	~0.3486	2.516	~2.916
				2.669	
	Mean	0.04863	0.3187	2.557	2.515
	S.D.	0.004483	0.02209	0.09815	0.3631
	%CV	9.2	6.9	3.8	14.4
	%Bias	-2.7	6.2	6.5	4.8
	n	10	10	3	10
	Overall %CV	8.6			

~ > 15%Accuracy

The long term freezer stability has been established for one hundred and thirty-nine (139) days at -20ºC ±10ºC in the Addendum to the Method Validation. The study sample collection started on July 09, 2007 and the sample analysis was completed on March 18, 2008. To cover the required two hundred and fifty-three (253) days freezer storage

period, extended long term freezer stability will be performed at -20ºC ±10ºC. None of this information has been submitted as of April 20, 2010.

Conclusions

The analytical method appears to be acceptable, the lack of long term frozen stability is less important here as the sponsor has shown in the validation of study FH-02 that the samples there were stable when held under similar conditions for 164 days.

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

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

/s/

EDWARD D BASHAW
06/23/2010