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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Supervisory Memorandum

NDA number: 22-571
Sequence number/date/type of submission: 1 / September 28, 2009/ New NDA
Applicant: Shionogi Pharma, Inc.
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Date: May 20, 2010
Drug: Glycopyrrolate oral solution
Drug class: Nonselective antagonist of muscarinic cholinergic receptors
Indication: Treatment of drooling secondary to cerebral palsy and other neurodevelopmental deficits

General comments:

- I concur with the conclusions contained in Dr. Norman See's Pharmacology/Toxicology review for this drug product.
- I concur that there are no nonclinical approval issues for this drug product.
- I concur with the suggested nonclinical labeling changes proposed by Dr. See for this drug product contained in section 1.1.3 of his review including that the appropriate Pregnancy Category is C.
- I concur that it is appropriate to conduct the six nonclinical studies detailed in Section 1.1.2 of Dr. See's review as Post-Marketing Requirements (PMRs).
- Detailed information concerning the agreed upon timelines for conduct of the six nonclinical PMRs is contained in a separate document entered into DARRTS that contains individual PMR templates written by Dr. See for each nonclinical PMR. Also, additional information to be included in the approval letter for the six nonclinical PMRs is contained in this separate document.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

ORIG-1

SHIONOGI
PHARMA INC

GLYCOPYRROLATE ORAL
SOLUTION

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/s/

BARBARA A HILL
05/24/2010

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 22-571
Supporting document/s: DSN 1
Applicant's letter date: 26-SEP-2009
CDER stamp date: 28-SEP-2009
Product: Glycopyrrolate Oral Solution
Indication: Treatment of drooling secondary to cerebral palsy and other neurodevelopmental deficits
Applicant: Shionogi Pharma, Inc.
Review Division: Division of Dermatology and Dental Products
Reviewer: Norman A. See, Ph.D.
Supervisor/Team Leader: Barbara Hill, Ph.D.
Division Director: Susan Walker, M.D.
Project Manager: Dawn Williams, R.N., B.S.N.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-571 are owned by Shionogi Pharma, Inc., or are data for which Shionogi Pharma, Inc., has obtained a written right of reference. Any data or information described or referenced below from a previously approved application that Shionogi Pharma, Inc. does not own (or from FDA reviews or summaries of a previously approved application), or from published literature, is for descriptive purposes only, and is not relied upon for approval of NDA 22-571.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

The product is approvable with respect to nonclinical concerns.

1.1.2 Additional Nonclinical Recommendations

The sponsor has committed to conduct the following nonclinical studies post-approval of NDA 22-571; these matters are regarded as being post-marketing requirements (PMRs):

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

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

1.1.3 Labeling

It is recommended that section 8.1 (Pregnancy), 12.1 (Mechanism of Action), and section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the label be modified to the statements indicated below. (b) (4)

(b) (4)

8.1 Pregnancy

(b) (4) *Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have not been conducted with glycopyrrolate. It is also not known whether glycopyrrolate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Glycopyrrolate should be given to a pregnant woman only if clearly needed.

12.1 Mechanism of Action

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Glycopyrrolate has not been evaluated for potential to impair fertility.

1.2 Brief Discussion of Nonclinical Findings

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

Glycopyrrolate was reasonably well tolerated when orally administered for 13 weeks to mice at a dosage of 30 mg/kg/day (which equates to a human-equivalent dose (HED) approximately 8 times the maximum clinical dose proposed under NDA 22-571), and to rats at a dosage of 40 mg/kg/day (which equates to a HED approximately 20 times the maximum clinical dose proposed under NDA 22-571). Pupil dilation was noted in all test article-treated groups. There were no remarkable effects on hematology, clinical chemistry, mean organ weights, or gross pathology. Histopathological changes were of minor severity, and did not appear to be clinically meaningful.

Data which concern effects of glycopyrrolate on fertility of rodents, development toxicity (teratology) of rodents and nonrodents, prenatal and postnatal development of rodents, and carcinogenesis of mice and rats, will be regarded as being PMRs.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

596-51-0

2.1.2 Generic Name

Glycopyrrolate, USP

2.1.3 Code Name

AHR-504

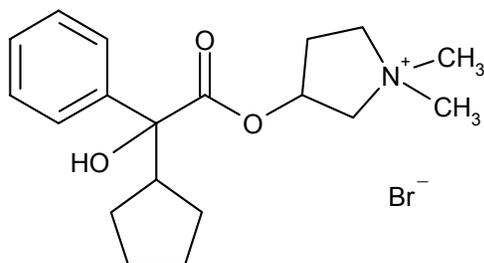
2.1.4 Chemical Name

Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-,bromide; 3-Hydroxy-1,1-dimethylpyrrolidinium bromide α -cyclopentylmandelate; Pyrrolidinium, 1,1-dimethyl-3-hydroxy, bromide α -cyclopentylmandelate; 1,1-Dimethyl-3-hydroxypyrrolidinium bromide α -cyclopentylmandelate; β -1-Methyl-3-pyrrolidyl- α -cyclopentylmandelate methobromide; Glycopyrrolate bromide

2.1.5 Molecular Formula/Molecular Weight

C₁₉H₂₈BrNO₃/398.33

2.1.6 Structure



2.1.7 Pharmacologic class

Anti-cholinergic (non-selective quaternary ammonium muscarinic receptor antagonist)

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 61,716; NDA 12-827; DMF (b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Ingredient	Amount per mL
Glycopyrrolate, USP	(b) (4)
Sorbitol Solution, NF	(b) (4)
Glycerin, USP	(b) (4)
Propylene glycol, USP	(b) (4)
Methylparaben, NF	(b) (4)
Propylparaben, NF	(b) (4)
Citric acid, USP	(b) (4)
Sodium citrate, USP	(b) (4)
Sodium saccharin, USP	(b) (4)
Natural and artificial cherry flavor (b) (4)	(b) (4)
Purified water, USP	(b) (4)

2.3.2 Comments on Novel Excipients

All the excipients are listed in the CDER Inactive Ingredients Guide in regard to oral use, at levels comparable to the levels proposed under NDA 22-571, with the exception of “cherry flavor (b) (4)”. The cherry flavoring (b) (4) “natural and artificial flavors” (b) (4). It is further stated that “all raw materials from which this flavor concentrate is produced are of food grade and comply with the specifications set forth by the Federal Food and Drug Administration”.

2.3.3 Comments on Impurities/Degradants of Concern

All impurities are qualified under the applicable ICH guidances.

2.4 Proposed Clinical Population and Dosing Regimen

The draft label submitted in DSN 1 to NDA 22-571 states that the maximum dose would be 0.1 mg/kg, three times daily, which would equate to individual doses in excess of 3 mg for patients that weighed more than 30 kg. However, clinical studies associated with NDA 22-571 limited individual doses to a maximum of 3

mg. The clinical reviewer has stated that, if approved, the label of the product under NDA 22-571 will be limited to a maximum dosage of 3 mg three times daily, or 9 mg per day. The product would be indicated for treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients aged 3 and older with cerebral palsy, mental retardation, or any other neurologic condition associated with problem drooling". This would involve chronic exposure of the subjects to glycopyrrolate.

2.5 Regulatory Background

Products containing glycopyrrolate have been approved for the treatment of peptic ulcer disease (Robinul tablets, NDA 12-827, approved in 1961) and as a preoperative medication to reduce salivation while under anesthesia (NDA 17-558, approved in 1975). The sponsor has purchased NDA 12-827, and therefore owns the data contained therein. Robinul tablets are currently marketed (under NDA 12-827) in formulations that contain either 1 mg or 2 mg glycopyrrolate per tablet. Robinul tablets are indicated for adjunctive therapy in the treatment of peptic ulcers, up to a recommended maximum daily dosage of 8 mg per day. Robinul tablets are not recommended for use in patients less than 12 years old on the basis of a lack of data concerning use in pediatric subjects.

When IND 61,716 was opened, the Division evaluated the nonclinical database associated with NDA 12-827 (Robinul tablets, which the sponsor owns) and found it to be deficient by current standards. The Division requested a battery of nonclinical studies to support development of the IND and NDA, including genotox, teratology, fertility, perinatal development, chronic toxicology, and carcinogenicity assessment. (b) (4)

(b) (4) the Division decided that it would be appropriate for some of these data (i.e., fertility, perinatal development, and carcinogenesis) to be accepted as post-approval requirements. It was requested that acceptable chronic toxicology and teratology data (from both rodent and nonrodent species) be submitted prior to initiation of Phase 3 studies.

(b) (4)

The Division decided that, since the product was currently being extemporaneously compounded and used off-label, and in view of the history of clinical use of glycopyrrolate, all the nonclinical requirements would be waived or deferred to PMR status. Specifically, it was stated during a guidance meeting on August 8, 2001, that "the requested toxicology data may be submitted post-approval, and that the need for chronic toxicology data will be waived." It was agreed that a NDA for the product would include protocols for suitable nonclinical

studies, and a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final study reports.

The Division engaged in an additional guidance meeting with the sponsor of IND 61,716 on March 20, 2007. Based upon the prior agreements, the Division reiterated that chronic toxicology studies would be waived. It was further stated that it appeared that the nonclinical database would be deficient with respect to teratology, genetic toxicology, fertility, perinatal development, and potential to induce carcinogenesis, and that these matters would need to be adequately addressed. It was reiterated that these data could be submitted post-approval of a NDA, provided the NDA contained a commitment on the part of the sponsor to obtain and submit data which are acceptable to the division, with a specific time frame for submitting final reports of the studies. It was also stated that the proposed dosages in these studies should be supported by suitable data from dose-range finding studies.

During another guidance meeting, that occurred on December 15, 2008, the sponsor was informed that:

“A NDA that is not acceptably based upon an appropriate prior finding of the Agency must be supported by complete information to which the sponsor has the right to reference. Complete information would include (without limitation) fully adequate data that concerned repeat-dose toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, from studies in appropriate species.”

NDA 22-571 was ultimately filed as a 505(b)(1) application. NDA 22-571 includes a letter of authorization permitting reference to NDA 12-827. As noted above, a NDA that is not acceptably based upon an appropriate prior finding of the Agency (i.e., in the absence of an acceptable bridge to a listed drug that is labeled for chronic oral administration under conditions relevant to the proposed new use) would require support from complete nonclinical information. Complete information would include fully adequate data that concerned repeat-dose toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, from studies in appropriate species. The Division has agreed that certain nonclinical issues may be addressed as PMRs, provided certain conditions were met. Specifically, it was agreed that data which concern teratology (in rodent and nonrodent species), fertility, perinatal development, and carcinogenicity (two rodent species) could be submitted post-approval, provided the initial submission to the NDA included: a) protocols for suitable nonclinical studies that would acceptably address the PMRs; b) acceptable data which support the dosages proposed in those protocols; and c) a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final reports of studies. It was further noted that the proposed dosages for use in these studies should be supported by suitable data from dose-range finding studies, and that the repeat-dose toxicology studies that are used to support

dosage selection should include complete clinical pathology, histopathology, and toxicokinetic evaluation, and be conducted in compliance with Good Laboratory Practice Regulations (21CFR 58).

3 Studies Submitted

3.1 Studies Reviewed

1. A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in CD-1 mice, study No. (b) (4)-714003.
2. A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in the Sprague-Dawley rat, study No. (b) (4)-714004.
3. Mutagenicity evaluation of AHR-504, (b) (4), in the Ames Salmonella/microsome plate assay, study no. 85-0326.
4. In vitro mammalian chromosome aberration test, study No. AC07BN.341.BTL.
5. Rat bone marrow erythrocyte micronucleus test following a single oral administration of glycopyrrolate, study No. AC07BN.125.BTL.
6. Oral (gavage) fertility and general reproduction toxicity study of glycopyrrolate in rats, study No. to be determined (draft protocol only).
7. Oral (gavage) dosage-range developmental toxicity study of glycopyrrolate in rats, study No. to be determined (draft protocol only).
8. Oral (gavage) developmental toxicity study of glycopyrrolate in rats, study No. to be determined (draft protocol only).
9. Oral (stomach tube) dosage-range developmental toxicity study of glycopyrrolate in rabbits, study No. to be determined (draft protocol only).
10. Oral (stomach tube) developmental toxicity study of glycopyrrolate in rabbits, study No. to be determined (draft protocol only).
11. Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of glycopyrrolate in rats, including a postnatal behavioral/function evaluation, study No. to be determined (draft protocol only).
12. A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in mice, study No. to be determined (draft protocol only).

13. A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in rats, study No. to be determined (draft protocol only).

3.2 Studies Not Reviewed

[REDACTED] (b) (4)

[REDACTED] (b) (4)

3.3 Previous Reviews Referenced

Nonclinical reviews of NDA 12-827 and IND 61,716.

4 Pharmacology

4.1 Primary Pharmacology

Glycopyrrolate is considered to be a nonselective antagonist of muscarinic cholinergic receptors. The binding activity of glycopyrrolate at specific receptor subtypes has apparently not been well characterized. Glycopyrrolate has been demonstrated to inhibit the actions of cholinergic agonists in both in vivo and in vitro models (e.g., inhibition of acetylcholine-induced contractions of isolated guinea pig ileum; inhibition of methacholine-stimulated salivary secretion in anesthetized dogs). The primary pharmacological effect of glycopyrrolate, with respect to NDA 22-571, is inhibition of peripheral muscarinic cholinergic receptors that are associated with salivary glands, resulting in reduced salivation. See reviews of NDA 12-827 for additional information concerning the pharmacology of glycopyrrolate.

4.2 Secondary Pharmacology

Glycopyrrolate is known to antagonize peripheral muscarinic cholinergic receptors, and therefore has indirect effects on a variety of tissues and organs that are innervated by postganglionic cholinergic nerves, as well as smooth muscle that responds to acetylcholine. These effects include actions on the cardiovascular system, respiratory tract, GI tract, eyes, and glandular tissues, among others. Cholinergic stimulation (i.e., increased "vagal tone") of cardiac tissue typically results in a decrease in cardiac rate (a negative chronotropic effect), a decrease in the rate of conduction within the sinoatrial and atrioventricular nodes (a negative dromotropic effect), and a decrease in the force of contraction (a negative inotropic effect). In general, cholinergic stimulation of smooth muscle of the respiratory system, GI tract, and urinary

bladder increases “tone” (contractile activity) of smooth muscle associated with these organs. Such stimulation can result in bronchoconstriction, altered motility, and decreased bladder capacity. Cholinergic stimulation of the eye induces contraction of the iris sphincter muscle (inducing miosis) and contraction of the ciliary muscle (accommodation for near vision). Cholinergic stimulation of exocrine glands, including the lacrimal, salivary, digestive, tracheobronchial, and sweat glands, results in increased secretory function. Glycopyrrolate, through antagonism of muscarinic cholinergic stimulation, may predispose toward reduction of these effects, including altered cardiac function (increased heart rate, conduction, and force of contraction), altered function of bronchiolar smooth muscle, urinary retention, reduced exocrine gland activity, blurred vision, and glaucoma.

4.3 Safety Pharmacology

Glycopyrrolate has not been evaluated in a standard battery of safety pharmacology studies, as described in ICH guidances. As noted above, glycopyrrolate, through inhibition of autonomic (cholinergic) innervation of peripheral tissues, may alter cardiac function (predispose toward an increased rate of contraction, increased rate of conduction through the AV node, and increased force of contraction), alter the contractile state of smooth muscle (e.g., muscle associated with bronchioles, the GI tract, or urinary bladder), and reduce secretory activity of glandular tissue (e.g., reduced secretory activity of the salivary glands and lacrimal glands; reduced acid secretion of parietal cells). Glycopyrrolate may be contraindicated in individuals with cardiovascular conditions (e.g., cardiac arrhythmias, hyper or hypotension), asthma, difficulty in voiding of the bladder, reduced glandular function (e.g., dry eyes), glaucoma, or obstructive or motility disorders of the GI tract.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Nonclinical data which describe the pharmacokinetics of glycopyrrolate are limited.

Absorption: Useful nonclinical data which describe the bioavailability of glycopyrrolate (i.e., the fraction of an oral dose absorbed) are not available. When orally administered to rats, glycopyrrolate exhibited a T_{max} of approximately 1.0-1.5 hours.

Distribution: Useful nonclinical data which describe the systemic distribution of glycopyrrolate are limited. Data from a published report were consistent with a hypothesis that glycopyrrolate, apparently on account of being a quaternary amine (charged ion), crosses the blood-brain barrier to a lesser extent than does

atropine (Proakis, AG. and Harris, GB. Comparative penetration of glycopyrrolate and atropine across the blood–brain and placental barriers in anesthetized dogs. *Anesthesiology* 48: 339–344, 1978).

Metabolism: Useful nonclinical data which describe the systemic distribution of glycopyrrolate are limited. When ¹⁴C-labeled glycopyrrolate was orally administered to mongrel dogs at a dosage of 50 mg/kg, activity was detected in both the urine and feces. It was unclear what fraction of the dose was systemically absorbed, or whether activity in the feces represented unabsorbed material, or material secreted in bile. Activity was associated with unchanged drug, as well as two metabolites, 3-[(α -(hydroxycyclopentyl)- α -hydroxy- α -phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, and N,N-dimethyl-3-hydroxypyrrrolidinium bromide.

Elimination: Useful nonclinical data which describe the elimination of glycopyrrolate are not available.

5.2 Toxicokinetics

Available toxicokinetic data are described with the applicable toxicology studies, in section 6 of this review.

6 General Toxicology

6.1 Single-Dose Toxicity

No useful single-dose toxicity data were submitted.

6.2 Repeat-Dose Toxicity

6.2.1 13-week mouse study:

Study title: A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in CD-1 mice

Study no.:	(b) (4)-714003
Study report location:	NDA 22-571, DSN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19-FEB-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrrolate, Lot No. 2007708, 99.4% pure.

Key Study Findings

This study involved oral dosing of male and female mice with glycopyrrolate for 13 weeks at dosages of 0, 30, 100, and 300 mg/kg/day. Survival was reduced in both genders at 100 and 300 mg/kg/day; survival at scheduled sacrifice in main-study groups was 10/10, 10/10, 7/10, and 3/10 for males and 9/10, 9/10, 8/10, and 1/10 for females in the control, 30, 100, and 300 mg/kg/day groups, respectively. In addition, 0/3, 0/24, 4/24, and 13/24 TK males and 0/3, 1/24, 3/24, and 16/24 TK females were found dead or euthanized *in extremis* in the control, 30, 100, and 300 mg/kg/day groups, respectively. Pupil dilation and piloerection were noted in all test article-treated groups. This was presumably a pharmacological response to the test article, and was observed in a dose-related manner. Mean weight gain over days 0-91 was reduced by more than 10% in both genders in all treatment groups, although mean body weight per se was reduced by less than 10% in the LD and MD groups. The cause(s) of the treatment-related mortality and reduced body weight gain were unclear. There were no remarkable effects on hematology or clinical chemistry, although the numbers of samples per group were limited (due to the limited volume of blood that can be obtained from a mouse), and the statistical analyses for clinical pathology parameters had limited power. There were no effects on mean organ weights or gross pathology. Treatment-related microscopic changes included acute inflammation of nasal tissues, acinar cell hypertrophy of the salivary glands, inflammation of the gingiva, and increased porphyrin pigment in the Harderian gland. These histopathological effects were of minimal to mild severity, and did not appear to reflect dose-limiting toxicity. It appears that all dosages evaluated in this study may have exceeded the MTD for a two-year study, based on the fact that the mean weight gain over days 0-91 was reduced by more than 10% in both genders in all treatment groups. However, given that mean body weight was reduced by less than 10% at both 30 and 100 mg/kg/day, and that glycopyrrolate appeared to be otherwise (with the exception of the effects on body weight gain) well tolerated at 30 mg/kg/day, these data suggest that 30 mg/kg/day may have only slightly exceeded the MTD.

Methods

Doses:	0, 30, 100, 300 mg/kg/day
Frequency of dosing:	Once daily for approximately 91 consecutive days (TK animals dosed either 1 day or 85 days)
Route of administration:	Oral (gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Glycopyrrolate was dissolved in water
Species/Strain:	Mouse/Crl:CD-1
Number/Sex/Group:	10/sex/group, +48/sex/group used for TK analysis (group 1 only 6 TK animals)
Age:	Seven weeks at start of treatment
Weight:	At start of dosing: males, approx. 29 g; females, approx. 23 g
Satellite groups:	Yes, for TK purposes; half the TK animals were

sacrificed on dosing day 1; surviving TK animals sacrificed on day 85

Unique study design: NA
Deviation from study protocol: NA

Observations and Results

Mortality

Animals observed twice daily.

Mortality: Deaths that were clearly treatment-related were observed in the HD (300 mg/kg/day) group in both genders, and probably in the MD (100 mg/kg/day) group in both genders. In the main-study, unscheduled deaths occurred in 7/10 males and 9/10 females in the HD group, and in 3/10 males and 2/10 females in the MD group. Among animals intended for TK sampling on day 85, unscheduled deaths occurred in 13/24 males and 16/24 females in the HD group and in 4/24 males and 3/24 females in the MD group. In addition, two females dosed at 30 mg/kg/day died on study (1/10 LD main-study females and 1/24 LD TK females). One control female died during week 6. Some of the deaths were confirmed to be secondary to trauma or gavage injury. It seems probable that the deaths of the LD females (2/34) were not related to treatment, in view of the seemingly limited toxicity observed in other animals at that dosage, and the seemingly similar death of a control female, although it is assumed by the sponsor that the death of the LD female was related to treatment.

Survival at scheduled sacrifice in main-study groups was 10/10, 10/10, 7/10, and 3/10 for males and 9/10, 9/10, 8/10, and 1/10 for females in the control, 30, 100, and 300 mg/kg/day groups, respectively. In addition, 0/3, 0/24, 4/24, and 13/24 TK males and 0/3, 1/24, 3/24, and 16/24 TK females were found dead or euthanized *in extremis* in the control, 30, 100, and 300 mg/kg/day groups, respectively. Unscheduled deaths of main-study and toxicokinetic group animals occurred between study days 3 and 75, inclusive; however, most of those animals died or were euthanized *in extremis* during study days 0-21. Survival statistics are summarized below:

Survival Summary, Males:

GROUP :		1				2				3				4			
MALES																	
WEEK	LIVE	FD	EE	SE													
0	10	0	0	0	10	0	0	0	10	0	0	0	9	1	0	0	
1	10	0	0	0	10	0	0	0	9	0	1	0	9	0	0	0	
2	10	0	0	0	10	0	0	0	9	0	0	0	5	4	0	0	
3	10	0	0	0	10	0	0	0	8	0	1	0	4	1	0	0	
4	10	0	0	0	10	0	0	0	8	0	0	0	4	0	0	0	
5	10	0	0	0	10	0	0	0	8	0	0	0	4	0	0	0	
6	10	0	0	0	10	0	0	0	8	0	0	0	4	0	0	0	
7	10	0	0	0	10	0	0	0	8	0	0	0	3	1	0	0	
8	10	0	0	0	10	0	0	0	8	0	0	0	3	0	0	0	
9	10	0	0	0	10	0	0	0	7	1	0	0	3	0	0	0	
10	10	0	0	0	10	0	0	0	7	0	0	0	3	0	0	0	
11	10	0	0	0	10	0	0	0	7	0	0	0	3	0	0	0	
12	10	0	0	0	10	0	0	0	7	0	0	0	3	0	0	0	
13	0	0	0	10	0	0	0	10	0	0	0	7	0	0	0	3	

WEEK = WEEK OF STUDY FD = FOUND DEAD EE = EUTHANIZED IN EXTREMIS SE = SCHEDULED EUTHANASIA

1- 0 MG/KG/DAY 2- 30 MG/KG/DAY 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY

Survival Summary, Females:

GROUP :		1				2				3				4			
FEMALES																	
WEEK	LIVE	FD	EE	SE													
0	10	0	0	0	10	0	0	0	10	0	0	0	4	5	1	0	
1	10	0	0	0	10	0	0	0	10	0	0	0	4	0	0	0	
2	10	0	0	0	10	0	0	0	9	0	1	0	4	0	0	0	
3	10	0	0	0	9	1	0	0	9	0	0	0	3	0	1	0	
4	10	0	0	0	9	0	0	0	9	0	0	0	3	0	0	0	
5	10	0	0	0	9	0	0	0	9	0	0	0	3	0	0	0	
6	9	0	1	0	9	0	0	0	8	0	1	0	3	0	0	0	
7	9	0	0	0	9	0	0	0	8	0	0	0	2	1	0	0	
8	9	0	0	0	9	0	0	0	8	0	0	0	2	0	0	0	
9	9	0	0	0	9	0	0	0	8	0	0	0	2	0	0	0	
10	9	0	0	0	9	0	0	0	8	0	0	0	1	1	0	0	
11	9	0	0	0	9	0	0	0	8	0	0	0	1	0	0	0	
12	9	0	0	0	9	0	0	0	8	0	0	0	1	0	0	0	
13	0	0	0	9	0	0	0	9	0	0	0	8	0	0	0	1	

WEEK = WEEK OF STUDY FD = FOUND DEAD EE = EUTHANIZED IN EXTREMIS SE = SCHEDULED EUTHANASIA

1- 0 MG/KG/DAY 2- 30 MG/KG/DAY 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY

The table below summarizes the speculated causes of death:

Text Table 1. Cause of Death/Debilitation, Unscheduled Necropsies

Dosage (mg/kg/day)	Males				Females			
	0	30	100	300	0	30	100	300
No. animals/group	10	10	10	10	10	10	10	10
No. early death animals	0	0	3	7	1	1	2	9
Cause of Death								
-Trauma	-	-	1	0	1	0	0	0
-Gavage injury	-	-	0	1	0	0	1	3
-Undetermined (microscopic evidence of laryngeal and/or pharyngeal irritation)	-	-	1	3	0	0	1	2
-Undetermined	-	-	1	3	0	1	0	4

Clinical Signs

Main study animals observed twice daily (time of dosing and 1.25 hr later) for general health and for clinical signs of toxicity, plus a detailed physical exam at least once weekly.

Pupil dilation and piloerection were noted in all test article-treated groups. This was presumably a pharmacological response to the test article, and was observed in a dose-related manner. Adverse signs observed in animals that were found dead or were euthanized included impaired equilibrium, intermittent tremors, hypoactivity, prostration, thinness, dermal atonia, body pale, extremities pale, hypothermia (body cool to the touch, extremities cool to the touch), ptosis (partial closure of the eyes), abnormal respiration (rales, gasping, labored respiration, decreased respiration rate), swollen abdominal area, soft feces, decreased defecation, and/or yellow material on various body surfaces (anogenital and/or or urogenital areas, ventral trunk).

Body Weights

Measured at least weekly.

Mean weight gain over days 0-91 was reduced by more than 10% in both genders in all treatment groups, although reduction in mean body weight per se was reduced by less than 10% in the LD and MD groups.

Mean body weights at day 91, Males:

Group	Mean BW (g)	% of Control Value	No. Animals at Day 91 (n)
1 (Vehicle)	37.5±2.15	NA	10
2 (30 mg/kg/day)	36.1±2.05	96%	10
3 (100 mg/kg/day)	35.8±3.27	96%	7
4 (300 mg/kg/day)	34.8±0.95	93%	3

None significant.

Mean body weights at day 91, Females:

Group	Mean BW (g)	% of Control Value	No. Animals at Day 91 (n)
1 (Vehicle)	30.2±2.23	NA	9
2 (30 mg/kg/day)	28.4±1.71	94%	9
3 (100 mg/kg/day)	28.3±1.71	94%	8
4 (300 mg/kg/day)	24.0	80%	1

None significant.

Mean body weight gains over days 0-91, Males:

Group	Mean BW Gain (g)	% of Control Value	No. Animals at Day 91 (n)
1 (Vehicle)	8.5±1.44	NA	10
2 (30 mg/kg/day)	7.6±1.46	89%	10
3 (100 mg/kg/day)	7.5±2.39	88%	7
4 (300 mg/kg/day)	5.8±0.91	68%	3

None significant.

Mean body weight gains over days 0-91, Females:

Group	Mean BW Gain (g)	% of Control Value	No. Animals at Day 91 (n)
1 (Vehicle)	6.5±1.35	NA	9
2 (30 mg/kg/day)	4.8±2.05	74%	9
3 (100 mg/kg/day)	4.8±1.55	74%	8
4 (300 mg/kg/day)	-0.6	NA	1

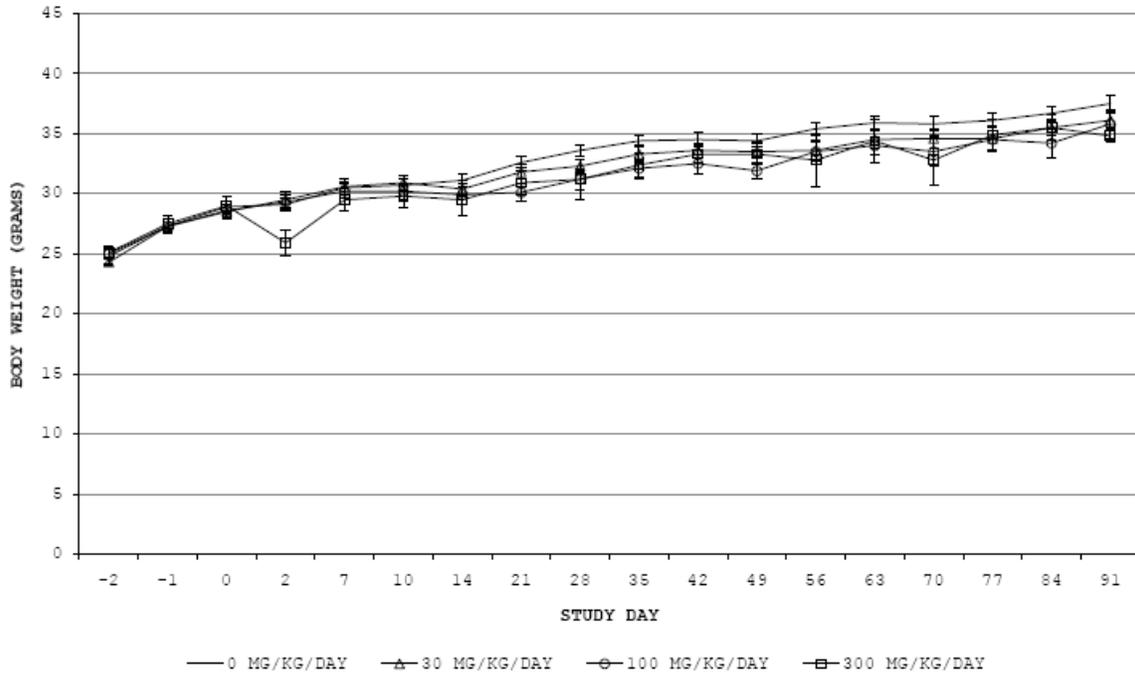
None significant.

Body weight curves are presented below:

Males:

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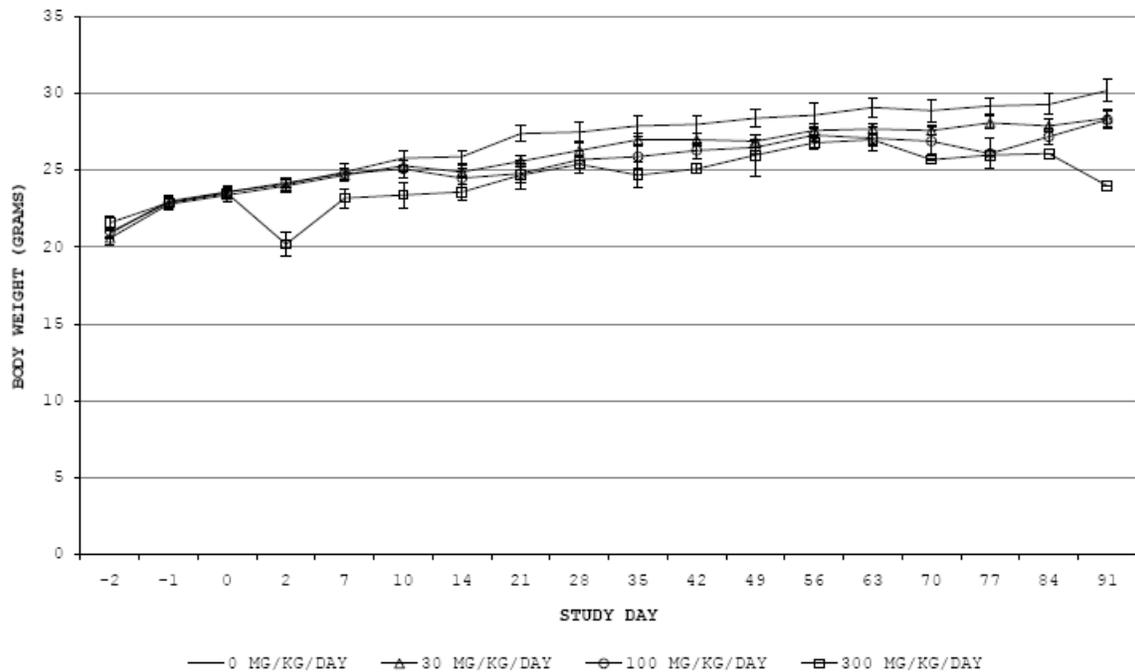
FIGURE 1
SUMMARY OF BODY WEIGHTS (G) - MALES
DATA PRESENTED AS MEAN ± SE



Females:

PROJECT NO. (b) 714003
SPONSOR: SCIELE PHARMA, INC.

FIGURE 2
SUMMARY OF BODY WEIGHTS (G) - FEMALES
DATA PRESENTED AS MEAN ± SE



Feed Consumption

Measured weekly.

Food consumption tended to be slightly reduced in treated animals of both genders. The differences were small, but achieved statistical significance over some time intervals.

Ophthalmoscopy

Assessed at baseline and during week 12.

No remarkable observations.

ECG

Not assessed.

Hematology

Assessed in all main-study groups at termination (approximately half of surviving animals used for hematology, remainder for clinical chemistry, resulting in n's of 4 or less per group).

The data appeared unremarkable, including no statistically significant differences, although the statistical power of the analysis was low (n of 4, 4, 3, and 1 in males, and 4, 2, 4, and 0 in females, at 0, 30, 100, and 300 mg/kg/day, respectively).

Clinical Chemistry

Assessed in all main-study groups at termination (approximately half of surviving animals used for hematology, remainder for clinical chemistry, resulting in n's of 4 or less per group).

No remarkable observations. Although some statistically significant differences were observed, these did not appear to reflect genuine or dose-limiting toxicity. It should be noted that the statistical power of the analysis was rather low (n of 5, 5, 2, and 1 in males, and 4, 4, 4, and 0 in females at 0, 30, 100, and 300 mg/kg/day, respectively).

Urinalysis

No

Gross Pathology

All main-study animals were grossly examined.

No remarkable observations.

Organ Weights

Adrenals, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, spleen, testes, thymus, thyroid/parathyroid, uterus.

No remarkable observations.

Histopathology

Adequate Battery

Yes. A standard list of tissues (including gross lesions) from all main-study animals was examined.

Peer Review

No

Histological Findings

Treatment-related microscopic lesions in both premature decedents and animals killed at scheduled sacrifice were limited to the salivary glands (acinar cell hypertrophy), nasal tissue (inflammation, degeneration of the epithelium, and luminal exudate), gingiva (inflammation and ulceration), and Harderian gland (increased porphyrin pigment). These effects were largely of minimal to mild severity, would presumably have been fully reversible, and did not appear to reflect dose-limiting toxicity.

1. **Unscheduled deaths:** Among animals found dead or sacrificed in extremis, test article-related microscopic changes were observed in the mandibular and sublingual salivary glands, nasal tissue, and gingiva of the 100 and 300 mg/kg/day early death males and females, the mandibular salivary gland of the 30 mg/kg/day early death females, and the Harderian glands of the 30 and 300 mg/kg/day female groups. The incidences and severities of these changes are presented in the following table:

Text Table 2. Incidences of Selected Histopathologic Findings, Unscheduled Deaths

Dosage (mg/kg/day):	Males				Females			
	0	30	100	300	0	30	100	300
Mandibular Salivary Gland ^a	0	0	3	7	1	1	2	9
Hypertrophy, acinar cell	0	0	2	6	0	1	1	9
Minimal	-	-	1	4	-	0	1	2
Mild	-	-	1	2	-	1	0	4
Moderate	-	-	0	0	-	0	0	3
Sublingual Salivary Gland ^a	0	0	3	7	1	1	2	9
Hypertrophy, acinar cell	0	0	2	3	0	0	2	7
Minimal	-	-	2	3	-	-	1	3
Mild	-	-	0	0	-	-	1	4
Nasal Tissue ^a	0	0	3	7	1	1	2	9
Inflammation, subacute	-	-	2	6	0	0	2	2
Minimal	-	-	2	4	-	-	2	2
Mild	-	-	0	2	-	-	0	0
Degeneration, nasal epithelium	0	0	2	5	0	0	2	2
Minimal	-	-	0	2	-	-	2	1
Mild	-	-	2	3	-	-	0	1
Exudate, luminal	0	0	2	6	0	0	2	4
Minimal	-	-	0	0	-	-	1	2
Mild	-	-	2	4	-	-	1	1
Moderate	-	-	0	2	-	-	0	1
Harderian Gland ^a	0	0	3	7	1	1	2	9
Pigment, porphyrin, increased	0	0	0	1	1	1	0	3
Minimal	-	-	-	1	1	0	-	2
Mild	-	-	-	0	0	1	-	1
Gingiva ^a	0	0	3	7	1	1	2	9
Inflammation, subacute	0	0	1	1	0	0	0	4
Minimal	-	-	1	1	-	-	-	4
Ulceration	0	0	0	1	0	0	1	0
Minimal	-	-	-	0	-	-	1	-
Mild	-	-	-	1	-	-	0	-

^a = Number of tissues examined from each group.

2. Scheduled deaths: Test article-related microscopic changes were observed in the mandibular salivary glands of the 300 mg/kg/day group females, nasal tissue of the 100 and 300 mg/kg/day group males and all test article-treated female groups, gingiva of the 100 mg/kg/day group males and 30 mg/kg/day group females, and the Harderian glands of all test article-treated female groups. The incidences and severities of these changes are presented in the following table:

Text Table 3. Incidences of Selected Histopathologic Findings, Study Week 13 Scheduled Necropsy

Dosage (mg/kg/day):	Males				Females			
	0	30	100	300	0	30	100	300
Mandibular Salivary Gland^a	10	10	7	3	9	9	8	1
Hypertrophy, acinar cell	0	0	0	0	0	0	0	1
Minimal	-	-	-	-	-	-	-	1
Nasal Tissue^a	10	10	7	3	9	9	8	1
Inflammation, subacute	0	0	4	1	0	4	5	1
Minimal	-	-	4	1	-	4	4	-
Mild	-	-	-	-	-	-	1	1
Degeneration, nasal epithelium	0	0	4	1	0	1	6	1
Minimal	-	-	3	-	-	1	4	-
Mild	-	-	1	1	-	-	2	1
Exudate, luminal	0	0	1	1	0	1	3	1
Minimal	-	-	-	-	-	1	3	-
Mild	-	-	1	1	-	-	-	1
Harderian Gland^a	10	10	7	3	9	9	8	1
Pigment, porphyrin, increased	2	5	1	1	0	4	4	1
Minimal	2	4	1	1	-	2	-	-
Mild	-	1	-	-	-	2	4	1
Gingiva^a	10	10	7	3	9	9	8	1
Inflammation, subacute	0	0	1	0	0	1	0	0
Minimal	-	-	1	-	-	1	-	-

^a = Number of tissues examined from each group.

Quoting the submission:

Salivary glands: “Minimal acinar cell hypertrophy of the mandibular salivary gland was observed in the single 300 mg/kg/day group female that survived to the scheduled necropsy. Acinar cell hypertrophy was not observed in the sublingual salivary glands of either sex at the scheduled necropsy. The incidence and severity of salivary gland hypertrophy were much less at the scheduled necropsy compared to the incidence and severity in the unscheduled death animals, and this finding was not considered adverse.”

Nasal Tissue: “Minimal to mild subacute inflammation, epithelial degeneration, and luminal exudate were observed in the nasal tissues of the 100 and 300 mg/kg/day group males and in all test article-treated female groups. Luminal exudate was of slightly lesser severity in males and females at the scheduled necropsy compared to that observed in the unscheduled death animals. These findings were not considered adverse at the severities noted in animals at the terminal necropsy.”

Gingiva: “Minimal inflammation of the gingiva was observed in one 100 mg/kg/day group male and one 30 mg/kg/day group female at the scheduled necropsy. It was considered test article-related because it occurred only in test article-treated animals but was not considered adverse because of the minimal nature of the change.”

Harderian Gland: “A dose-related higher incidence of increased porphyrin pigment in the Harderian gland was noted in all groups of test article-treated females and was considered test article-related. In males, the incidences of increased porphyrin pigment in the Harderian gland of the scheduled death animals did not show a dose response in incidence or severity, and the relationship of the increased pigment in males to test article administration is uncertain. Increased porphyrin was not considered an adverse effect.”

Special Evaluation

NA

Toxicokinetics

Blood samples were collected from approximately 3 TK animals per gender per group (as permitted by survival) for toxicokinetic analysis prior to dosing and at 1, 1.5, 3, 6, 8, 12, and 24 hours post-dosing on days 0 (first day of dosing) and 85. Group 1 (control) animals were bled at 1 hour post-dosing only, on days 0 and 85. The lower limit of quantitation was 1 ng/mL.

In general, exposures seemed to increase with increasing dosage, although there was no clear mathematical relationship between dosage administered and C_{max} or AUC. Many of the data points vary widely for a given dosage, gender, and time point post-dosing (e.g., on day 85, males dosed at 100 mg/kg/day, at 1.5 hours post-dosing, reported plasma concentrations include 205, 2.59, and 69.4 ng/mL). For the sake of completeness I will capture the reported values for C_{max} and AUC_{last} in the table below, but these data should be regarded as being suspect, possibly due to methodological problems. Some samples from control animals were above the level of quantitation (1 ng/mL); the report considered these data to reflect contamination of the samples.

Toxicokinetic Parameters Calculated from Data Obtained On Study Day 85:

Gender/Dose Group (mg/kg/day)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	T_{max} (hr)
Males/30	13.62	2.51±2.18	9.77	1.5

Males/100	122.49	92.33±103.13	2.01	1.5
Males/300	NA			
Females/30	37.11	25.57±37.53	2.50	1.0
Females/100	41.02	8.33±5.55	5.14	1.0
Females/300	NA			

Group sizes of 3 animals per time point, except at 300 mg/kg/day, where n's were reduced due to reduced survival (see table of plasma concentrations, below). NA indicates "data not shown" due to low survival.

Plasma concentration data obtained on day 85 are presented below:

Table 2: Plasma Concentrations of Glycopyrrolate in Mice Study Day 85

Sex	Dose mg/kg	Plasma Concentration (ng/mL)							
		Time (hr)							
		0	1	1.5	3	6	8	12	24
M	30	BLQ	BLQ	3.94	BLQ	BLQ	BLQ	1.66	1.51
		BLQ	BLQ	3.59	BLQ	BLQ	BLQ	1.19	BLQ
		BLQ	1.97	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	Average	0.00	0.66	2.51	0.00	0.00	0.00	0.95	0.50
StDev	0.00	1.14	2.18	0.00	0.00	0.00	0.86	0.87	
Count	3	3	3	3	3	3	3	3	
M	100	34.6	3.65	205	2.16	BLQ	1.2	BLQ	
		29.4	16.2	2.59	1.13	BLQ	2.44	1.64	
		1.85	12.6	69.4	3.15	1.15	BLQ		
	Average	21.95	10.82	92.33	2.15	0.38	1.21	0.82	
StDev	17.60	6.46	103.13	1.01	0.66	1.22	1.16		
Count	3	3	3	3	3	3	2		
M	300	47.2	23.1	25.6	16.1	15.5	2.1		
		277	259	162	210			679	
		162.10	141.05	93.80	113.05	15.50	2.10	679	
	Average	162.49	166.81	96.45	137.11	N/A	N/A	N/A	
StDev									
Count	2	2	2	2	1	1	1		
F	30	BLQ	4.69	9.38	4.7	9.76	BLQ	BLQ	BLQ
		BLQ	68.9	4.46	1.43	1.79	BLQ	BLQ	BLQ
		1.65	3.12	4.29	1.66	BLQ	BLQ	BLQ	
	Average	0.55	25.57	6.04	2.60	3.85	0.00	0.00	0.00
StDev	0.95	37.53	2.89	1.83	5.20	0.00	0.00	0.00	
Count	3	3	3	3	3	3	3	2	
F	100	BLQ	9.35	6.09	10.7	1.31	BLQ	BLQ	
		BLQ	13.3	5.98	5.71	1.36	12.3	BLQ	
		BLQ	2.34	10.7	6.44	3.7	1.9	BLQ	
	Average	0.00	8.33	7.59	7.62	2.12	4.73	0.00	
StDev	0.00	5.55	2.69	2.70	1.37	6.62	0.00		
Count	3	3	3	3	3	3	3		
F	300	1.62	118	24.1	51.1	4.31	13.1		
		1.55						18.5	
	Average	1.59	118.00	24.10	51.10	4.31	13.10	18.50	
StDev	0.05	N/A	N/A	N/A	N/A	N/A	N/A		
Count	2	1	1	1	1	1	1		

N/A = not available

Stability and Homogeneity

Adequate.

6.2.2 13-week rat study:

Study title: A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in the Sprague-Dawley rat

Study no.:	(b) (4) -714004
Study report location:	NDA 22-571, DSN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19-FEB-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrrolate, Lot No. 2007708, 99.4% pure

Key Study Findings

This study involved oral dosing of male and female rats with glycopyrrolate for 13 weeks at dosages of 0, 40, 120, and 360 mg/kg/day. There were no effects on survival. The only relevant “clinical sign” was pupil dilation, which was noted in all test article-treated groups in relation to dosage. Reduced mean body weight and weight gain were observed in all treatment groups, in relation to dosage; the mean weight gain differed significantly from controls for all treatment groups except low-dose males. There were no remarkable effects on hematology or clinical chemistry. Mean urine volume was increased in both genders in proportion to dosage (ranging over approximately 2 to 3 times the control value), and achieved statistical significance at 360 mg/kg/day in both genders. There were no effects on mean organ weights or gross pathology. Treatment-related microscopic changes included acute inflammation of nasal tissues, the larynx, pharynx, and prostate gland, acinar cell hypertrophy of the submandibular salivary gland, and increased porphyrin pigment in the Harderian gland. These histopathological effects were of minimal to mild severity, and did not appear to reflect dose-limiting toxicity. A dosage of 40 mg/kg/day appears to have been reasonably well tolerated by both genders under the conditions of the 13-week study, although evidence of stress was apparent, as indicated by trends toward increased urine volume and reduced mean body weight and weight gain (body weight gain was statistically significantly reduced in females at 40 mg/kg/day, but not males). The mean absolute body weights of males and females at 40 mg/kg/day, while 4%-6% lower than the control values, did not differ statistically significantly from the control value.

Methods

Doses:	0, 40, 120, 360
Frequency of dosing:	Once daily for approximately 91 consecutive days (TK animals dosed 85 days)
Route of administration:	Oral (gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Dissolved in water
Species/Strain:	Rat/ Crl:CD (SD)
Number/Sex/Group:	10/sex/group, +12/sex/group used for TK analysis (group 1 only 3 TK animals)
Age:	Seven weeks at start of treatment
Weight:	At start of dosing: males, approx. 240 g; females, approx. 175 g
Satellite groups:	Yes, for TK analysis
Unique study design:	NA
Deviation from study protocol:	NA

Observations and Results

Mortality

Observed twice daily.

No treatment-related deaths. One male in the mid-dose group (120 mg/kg/day) was found dead on day 7; this death was considered incidental. All other animals survived to scheduled sacrifice.

Clinical Signs

Main study animals observed twice daily (time of dosing and 1.25 hr later) for general health and for clinical signs of toxicity, plus a detailed physical exam at least once weekly.

Pupil dilation was noted in all test article-treated groups. This was presumably a pharmacological response to the test article, and was observed in a dose-related manner. Quoting the report:

“Generally beginning at 1.25 hours post-dosing on study day 0, pupil dilation was noted post-dose in the 120 and 360 mg/kg/day groups throughout the study; pupil dilation occurred less frequently in the 40 mg/kg/day group. This finding often resolved by the time of dosing on the following day in the 40 and 120 mg/kg/day group males and females but was frequently present at the time of dosing in the 360 mg/kg/day group males and females. Pupil dilation was not observed in the control group animals.”

Body Weights

Measured Weekly.

Reduced mean body weight and weight gain were observed in all treatment groups, in relation to dosage; the mean weight gain differed significantly from controls for all treatment groups except low-dose males:

Mean body weights at week 13, Males:

Group	Mean BW (g)	% of Control Value
1 (Vehicle)	537±40.4	NA
2 (40 mg/kg/day)	517±52.4	96%
3 (120 mg/kg/day)	485±41.7*	90%
4 (360 mg/kg/day)	473±36.4**	88%

*p<0.05; **p<0.01

Mean body weights at week 13, Females:

Group	Mean BW (g)	% of Control Value
1 (Vehicle)	327±27.7	NA
2 (40 mg/kg/day)	306±26.0	94%
3 (120 mg/kg/day)	295±16.5*	90%
4 (360 mg/kg/day)	279±24.1**	85%

*p<0.05; **p<0.01

Mean body weight gains over weeks 0-13, Males:

Group	Mean BW Gain (g)	% of Control Value
1 (Vehicle)	299±40.8	NA
2 (40 mg/kg/day)	277±40.3	93%
3 (120 mg/kg/day)	250±37.0*	84%
4 (360 mg/kg/day)	236±28.3**	79%

*p<0.05; **p<0.01

Mean body weight gains over weeks 0-13, Females:

Group	Mean BW Gain (g)	% of Control Value
1 (Vehicle)	154±20.7	NA

2 (40 mg/kg/day)	130±23.4*	84%
3 (120 mg/kg/day)	122±13.7**	79%
4 (360 mg/kg/day)	102±21.1**	66%

*p<0.05; **p<0.01

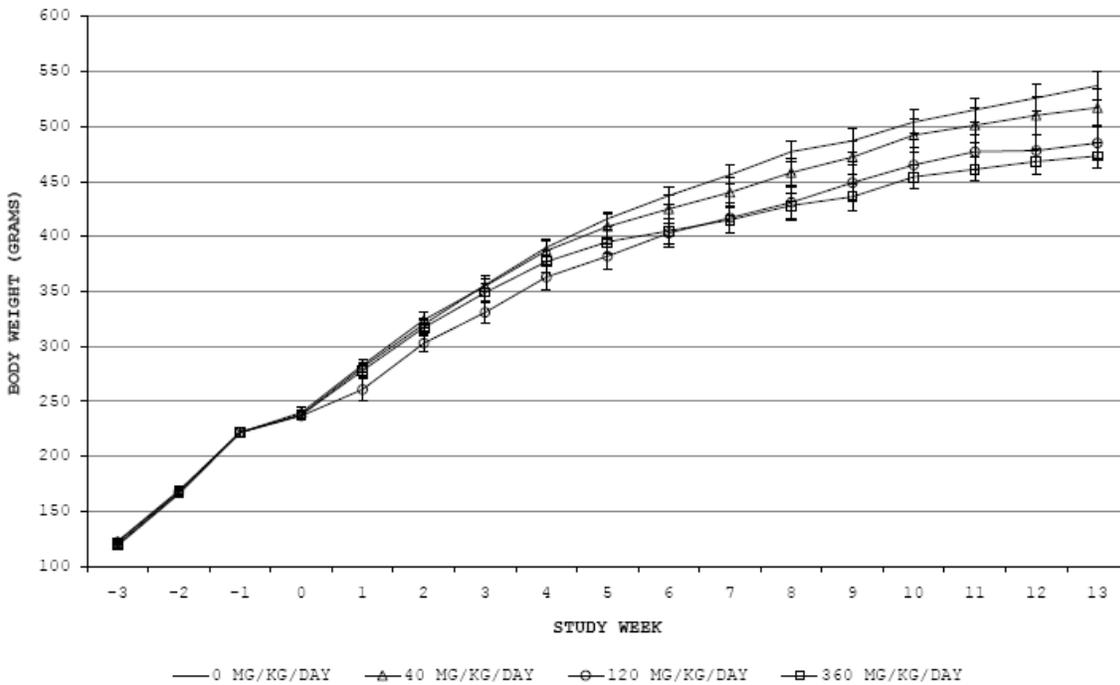
Note: Animals were fasted overnight prior to final weighing, but were unfasted in week 0.

Body weight curves are presented below:

Males:

PROJECT NO. (b) 714004
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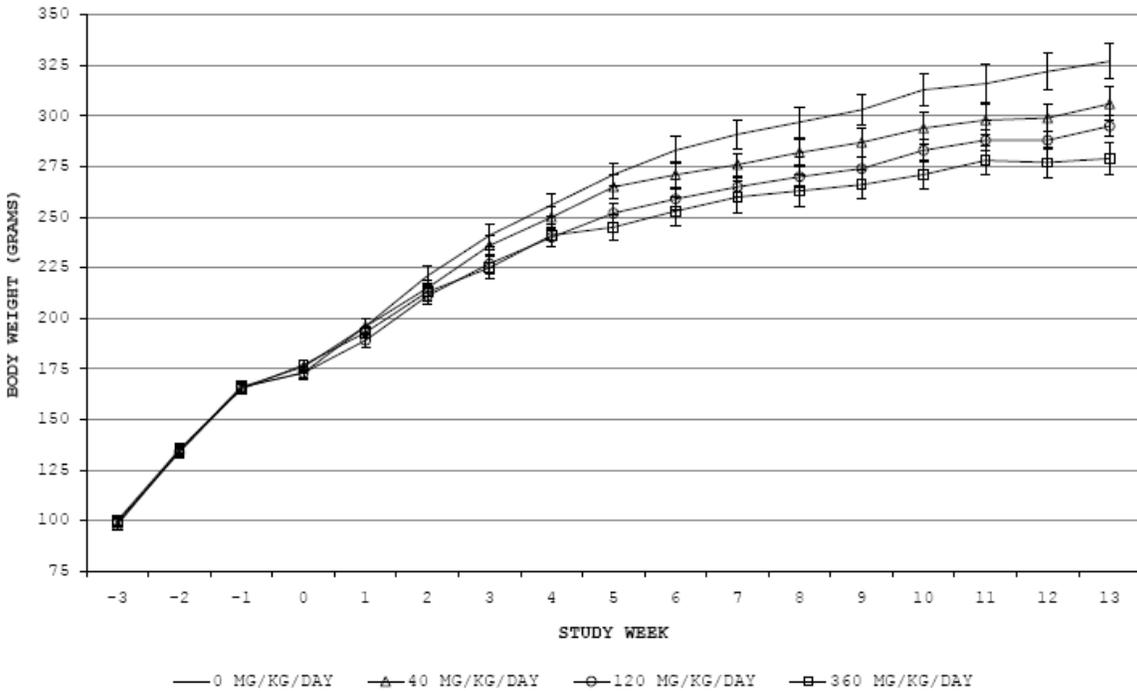
FIGURE 1
 SUMMARY OF BODY WEIGHTS (G) - MALES



Females:

PROJECT NO. (b) (4)-714004
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FIGURE 2
 SUMMARY OF BODY WEIGHTS (G) - FEMALES



Feed Consumption

Measured weekly.

Food consumption tended to be slightly reduced in males at 120 mg/kg/day and above; there were no apparent effects in females. In males, the differences from control values achieved statistical significance over some time intervals.

Ophthalmoscopy

Assessed at baseline and during week 12.

No remarkable observations.

ECG

Not assessed.

Hematology

Assessed in all main-study animals at termination following overnight fasting.

No remarkable observations. Statistically significantly elevated levels of monocytes were observed in both genders at 360 mg/kg/day only, and the mean reticulocyte count was significantly reduced in males at all treatment levels. These effects did not appear to reflect dose-limiting toxicity. No other remarkable differences in hematology values were observed, including no effects on coagulation.

Clinical Chemistry

Assessed in all main-study animals at termination following overnight fasting.

No remarkable observations. Although some statistically significant differences were observed, these did not appear to reflect genuine or dose-limiting toxicity.

Urinalysis

Assessed in all main-study animals at termination.

Mean urine volume was increased in both genders in proportion to dosage (ranging over approximately 2 to 3 times the control value), and achieved statistical significance at 360 mg/kg/day in both genders. Related parameters (reduced osmolality and specific gravity) were also observed.

Gross Pathology

All main-study animals.

No remarkable observations.

Organ Weights

Adrenals, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, spleen, testes, thymus, thyroid/parathyroid, uterus.

No remarkable observations.

Histopathology

Adequate Battery

Yes, a standard list of tissues (including gross lesions) from main-study animals in the control and HD groups was examined (groups 1 and 4), plus all specified tissues from the group 3 animal that was found dead, plus gross lesions from all other main-study animals, plus the nasal cavity, mandibular salivary glands,

Hardarian glands, prostate, larynx, and pharynx (identified as potential target tissues) were examined from all main-study animals.

Peer Review

No.

Histological Findings

Treatment-related microscopic changes were considered to include acute inflammation of nasal tissues, the larynx, pharynx, and prostate gland, acinar cell hypertrophy of the submandibular salivary gland, and increased porphyrin pigment in the Harderian gland. These effects were of minimal to mild severity, and did not appear to reflect dose-limiting toxicity. Quoting the submission:

“Nasal Tissue. Acute inflammation occurred in the nasal cavity tissues of 4/9 males in the 120 mg/kg/day group and 5/10 males and 5/10 females in the 360 mg/kg/day group. This finding was graded from minimal to mild and was characterized microscopically as an infiltrate of neutrophils within focal or multifocal segments of nasal epithelium and/or a neutrophilic exudate into the nasal cavities. Respiratory epithelium was predominantly affected but some segments of olfactory epithelium were also involved. The epithelium of affected areas was usually flattened and devoid of apical cilia, if respiratory epithelium. These changes were not observed in the control or 40 mg/kg/day groups.

Prostate Gland. Acute inflammation was diagnosed in the prostate glands of 3/9 males in the 120 mg/kg/day group and 6/10 males in the 360 mg/kg/day group. This finding was graded as minimal for 3 males and mild for 3 males in the high-dose group and as minimal for 3 males in the mid-dose group. It was characterized microscopically as single or several glands containing a neutrophilic exudate and a slight neutrophilic infiltrate in the prostatic epithelium. Randomly, both dorsolateral and ventral prostatic glands were affected. One control group male and 2 males in the 40 mg/kg/day group also had minimal acute inflammation of the prostate gland.

Larynx and Pharynx. Acute inflammation was present in the larynx 2/10 males administered 360 mg/kg/day Glycopyrrolate. In the pharynx, acute inflammation was present in 1 male in the 120 mg/kg/day group and 1 male and 3 females in the 360 mg/kg/day groups. The acute inflammation was minimal characterized microscopically as focal or multifocal infiltrates or exudates of neutrophils. The presence of acute inflammation in the pharynx and/or larynx did not appear to simply be an extension of nasal tissue inflammation, at least in the sections examined, as only 1 male and 2 females administered 360 mg/kg/day with nasal tissue inflammation also had inflammation of the pharynx, larynx, or both. Additionally, only 1 primary necropsy animal (No. 4252) had concomitant laryngeal and pharyngeal inflammation.

Mandibular Salivary Gland. In the mandibular salivary gland, acinar cell hypertrophy was diagnosed in 6/10 males and 6/10 females administered 360 mg/kg/day and in 3/9 males and 5/10 females administered 120 mg/kg/day. The acinar cell hypertrophy was minimal and characterized microscopically as somewhat more lightly staining cells with expanded cytoplasm containing plump secretory granules. These changes were not observed in the control or 40 mg/kg/day groups.

Harderian Gland. The incidence of increased porphyrin pigment in the Harderian gland was higher for the 120 and 360 mg/kg/day group males and 40, 120 and 360 mg/kg/day group females. Five of 9 males at 120 mg/kg/day and 10/10 males at 360 mg/kg/day exhibited the finding, whereas only 2 males in the group control group and 1 male in the 40 mg/kg/day group had increased porphyrin pigment. For Glycopyrrolate-treated females, the incidences were 4/10, 6/10, and 9/10 for those administered 40, 120, and 360 mg/kg/day, respectively. Only 1 control group female had minimal increased porphyrin pigment. Microscopically, this finding was characterized as glandular lumina containing the yellow-brown amorphous secretory material.”

These observations are summarized below:

**Text Table 1. Incidence Of Selected Histopathologic Findings,
Study Week 13 Scheduled Necropsy**

Dosage (mg/kg/day):	Males				Females			
	0	40	120	360	0	40	120	360
Nasal Tissue ^a	10	10	9	10	10	10	10	10
Acute inflammation	0	0	4	5	0	0	0	5
Minimal	0	0	4	1	0	0	0	2
Mild	0	0	0	4	0	0	0	3
Prostate Gland ^a	10	10	9	10	0	0	0	0
Acute inflammation	1	2	3	6	-	-	-	-
Minimal	1	2	3	3	-	-	-	-
Mild	0	0	0	3	-	-	-	-
Larynx ^a	10	10	9	10	10	10	10	10
Acute inflammation	0	0	0	2	0	0	0	0
Minimal	0	0	0	2	0	0	0	0
Pharynx ^a	10	10	9	10	10	9	10	10
Acute inflammation	0	0	1	1	1	0	0	3
Minimal	0	0	1	1	1	0	0	3
Mandibular Salivary Gland ^a	10	10	9	10	10	10	10	10
Hypertrophy, acinar cell	0	0	3	6	0	0	5	6
Minimal	0	0	3	6	0	0	5	6
Harderian Gland ^a	10	10	9	10	10	10	10	10
Pigment, porphyrin, increased	2	1	5	10	1	4	6	9
Minimal	2	1	5	1	1	4	5	3
Mild	0	0	0	9	0	0	1	5
Moderate	0	0	0	0	0	0	0	1

^a = Number of tissues examined from each group.

Special Evaluation

NA

Toxicokinetics

Blood samples were collected from approximately 3 TK animals per gender per group for toxicokinetic analysis prior to dosing and at 1, 1.5, 3, 6, 8, 12, and 24 hours post-dosing on days 0 (first day of dosing) and 84. Group 1 (control) animals were bled at 1 hour post-dosing only. The lower limit of quantitation was 1 ng/mL.

Toxicokinetic Parameters Calculated from Data Obtained On Study Day 84:

Gender/Dose Group (mg/kg/day)	AUC _{last} (ng·hr/mL)	C _{max} (ng/mL)	T _{1/2} (hr)	T _{max} (hr)
Males/40	25.06	8.67±10.68	9.18	1.5
Males/120	37.75	8.72±1.58	33.98	3.0

Males/360	641.24	549.67±458.71	3.53	1.0
Females/40	9.18	2.96±2.80	28.79	0.0
Females/120	96.08	13.59±5.16	9.40	1.5
Females/360	2013.73	1152.67±494.38	2.97	1.0

Group sizes of 3 animals per time point.

Plasma concentration data obtained on day 84 are presented below:

Table 2: Plasma Concentrations of Glycopyrrolate in Rats Study Day 84

Sex	Dose mg/kg	Plasma Concentration ng/mL							
		Time (hr)							
		0	1	1.5	3	6	8	12	24
M	40	BLQ	3.56	BLQ	2.71	7.73	4.08	BLQ	BLQ
		3.08	1.7	5.42	BLQ	1.31	BLQ	BLQ	BLQ
		BLQ	9.85	20.6	BLQ	BLQ	3.5	BLQ	BLQ
	Average	1.03	5.04	8.67	0.90	3.01	2.53	0.00	0.00
	StDev	1.78	4.27	10.68	1.56	4.14	2.21	0.00	0.00
	Count	3	3	3	3	3	3	3	3
M	120	1.25	2.08	1.51	9.42	BLQ	BLQ	BLQ	1.53
		BLQ	5.63	4.31	9.84	2.06	1.15	BLQ	1.4
		1.42	2.09	2.29	6.91	BLQ	BLQ	BLQ	1.9
	Average	0.89	3.27	2.70	8.72	0.69	0.38	0.00	1.61
	StDev	0.78	2.05	1.45	1.58	1.19	0.66	0.00	0.26
	Count	3	3	3	3	3	3	3	3
M	360	7.42	813	19.7	57.9	11.3	3.51	1.94	3.06
		7.9	816	33.7	90.3	8.59	3.89	1.48	1.41
		7.52	20.0	56.3	28.5	2.93	6.91	BLQ	2.35
	Average	7.61	549.67	36.57	58.90	7.61	4.77	1.14	2.27
	StDev	0.25	458.71	18.47	30.91	4.27	1.86	1.01	0.83
	Count	3	3	3	3	3	3	3	3
F	40	3.31	BLQ	BLQ	BLQ	1.58	BLQ	BLQ	BLQ
		5.56	BLQ	1.09	1.53	BLQ	BLQ	BLQ	1.43
		BLQ	1.97	1.2	1.5	BLQ	BLQ	BLQ	BLQ
	Average	2.96	0.66	0.76	1.01	0.53	0.00	0.00	0.48
	StDev	2.80	1.14	0.66	0.87	0.91	0.00	0.00	0.83
	Count	3	3	3	3	3	3	3	3
F	120	2.47	2.98	11.8	5.05	3.43	1.42	BLQ	BLQ
		3.58	28.1	9.56	4.1	3.05	23	BLQ	2.38
		25.5	1.48	19.4	11.1	11.3	3.03	BLQ	3.44
	Average	10.52	10.85	13.59	6.75	5.93	9.15	0.00	1.94
	StDev	12.99	14.95	5.16	3.80	4.66	12.02	0.00	1.76
	Count	3	3	3	3	3	3	3	3
F	360	26.2	981	350	49.4	27.5	11.3	5.06	4.19
		5.94	767	611	73	15.1	7.57	3.03	1.98
		2.47	1710	98.2	768	5.57	7.56	3.74	6.07
	Average	11.54	1152.67	353.07	296.80	16.06	8.81	3.94	4.08
	StDev	12.82	494.38	256.41	408.24	11.00	2.16	1.03	2.05
	Count	3	3	3	3	3	3	3	3

Stability and Homogeneity

Adequate.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Mutagenicity evaluation of AHR-504, (b) (4), in the Ames Salmonella/microsome plate assay

Study no.:	85-0326
Study report location:	NDA 22-571, DSN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11-JUN-1985
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AHR-504 (glycopyrrolate), lot No. 41561

Key Study Findings

Glycopyrrolate was not mutagenic in an Ames assay.

Methods

Strains: Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537, and TA1538.
Note: As mentioned in ICH documents, an Ames assay should ideally include S. typhimurium strain TA102 or E. coli strain WP2_{uvrA}, which will detect point mutations at A-T sites. However, this assay pre-dated that guidance, and the absence of those strains is not deemed to invalidate the assay.

Concentrations in definitive study: 0 to 10,000 µg/plate

Basis of concentration selection: Cytotoxicity

Negative control: Vehicle (water)

Positive control: 2-Nitrofluorene (TA98, TA1538), sodium azide (TA100, TA1535), 9-aminoacridine (TA1537), in absence of S9; 2-aminoanthracene in presence of S9

Formulation/Vehicle: Dissolved in water

Incubation & sampling time: 48 hours

Study Validity

Minimally acceptable, although the assay was not entirely consistent with current standards, in regard to the strains used (see note, above), and the fact that a confirmatory assay was not performed.

Results

No cytotoxicity was observed in the definitive assay. The high-dose (10,000 µg/plate) was adequately high (based upon ICH guidelines). Glycopyrrolate did not increase the incidence of revertants either in the presence or absence of S9. Appropriate results were obtained with the controls.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title: In vitro mammalian chromosome aberration test

Study no.:	AC07BN.341.BTL
Study report location:	NDA 22-571, DSN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	31-OCT-2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrrolate, lot No. 1001832, 99.8%

Key Study Findings

Glycopyrrolate was not clastogenic in an in vitro assay with human peripheral blood lymphocytes.

Methods

Cell line:	Peripheral blood lymphocytes obtained from one healthy, nonsmoking adult (31 years old) female were used.
Concentrations in definitive study:	995, 1990, and 3980 µg/mL at both incubation times (see below) and conditions of activation.
Basis of concentration selection:	Cytotoxicity
Negative control:	Vehicle (water)
Positive control:	Mitomycin C in absence of S9; cyclophosphamide in presence of S9
Formulation/Vehicle:	Dissolved in water
Incubation & sampling time:	Exposure for 4 hours with or without S9 followed by 16 hour resting period, or exposure for 20 hours without S9; in each case colcemid was added for final two hours prior to harvest. The cells were processed, fixed, placed on slides, stained, and microscopically examined.

Study Validity

Acceptable.

Results

Glycopyrrolate did not increase the number of structural or numerical chromosome aberrations either in the presence or absence of S9. Substantial cytotoxicity (50% reduction in mitotic index) was not observed in cultures incubated with glycopyrrolate for 4 hours, but was observed at the highest

concentration of glycopyrrolate in cultures incubated for 20 hours. Appropriate results were obtained with the controls.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Rat bone marrow erythrocyte micronucleus test following a single oral administration of glycopyrrolate

Study no.:	AC07BN.125.BTL
Study report location:	NDA 22-571, DSN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	06-NOV-2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrrolate, lot No. 1001832, 99.8%

Key Study Findings

Glycopyrrolate was not clastogenic in an *in vivo* micronucleus assay.

Methods

Doses in definitive study:	425, 850, and 1700 mg/kg, administered once via oral gavage (10 mL/kg dose volume).
Frequency of dosing:	Acute
Route of administration:	Oral (gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Dissolved in water
Species/Strain:	Rat/SD
Number/Sex/Group:	5 LD and 5 MD rats per sex sacrificed 24 hours post-dosing. 5 HD and 5 vehicle control rats per sex sacrificed at both 24 and 48 hours post-dosing. 5 positive control rats per sex sacrificed at 24 hours post-dosing. Animals in satellite groups used for obtaining blood samples for toxicokinetic purposes. Immediately following sacrifice marrow from femurs was aspirated, centrifuged, smears produced, fixed, and stained. The slides were examined and 2000 polychromatic erythrocytes per rat were scored for the presence of micronuclei (round, darkly staining nuclear fragments).
Satellite groups:	No
Basis of dose selection:	Tolerability in preliminary studies
Negative control:	Vehicle (water)
Positive control:	Cyclophosphamide (40 mg/kg)

Study Validity

Acceptable.

Results

In preliminary toxicity studies involving dosages from 400 mg/kg to 2000 mg/kg, mortality was observed at 2000 mg/kg, and piloerection was observed at all dosages. In the definitive assay, no mortality was observed, but piloerection and lethargy were observed at 1700 mg/kg. TK data from satellite animals confirmed that C_{max} and AUC values in both genders increased with increasing dosage. Glycopyrrolate did not increase the incidence of polychromatic erythrocytes with micronuclei. Appropriate results were obtained with the controls.

7.4 Other Genetic Toxicity Studies

None.

8 Carcinogenicity

The Division has agreed that the need to submit data which describe the carcinogenicity of glycopyrrolate may be submitted post-approval, provided certain conditions were met (see section 2.5, "Regulatory Background", above). Specifically, it was agreed that data which concern carcinogenicity (from studies with two rodent species) would be regarded as PMRs, provided the initial submission to the NDA included: a) protocols for suitable nonclinical studies that would acceptably address the PMRs; b) acceptable data which support the dosages proposed in those protocols; and c) a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final reports of studies. It was further noted that the protocols for the carcinogenicity studies would only be acceptable to support a NDA if they were deemed adequate by the executive-carcinogenicity assessment committee of CDER (exec-CAC).

It is considered acceptable for nonclinical data which describe the carcinogenicity of glycopyrrolate to be submitted post-approval. This conclusion is based upon the history of use associated with Robinul tablets (NDA 12-827), which has provided no known signals suggestive of carcinogenic potential, the fact that glycopyrrolate is apparently not genotoxic, and consideration of the limited nature of the proposed patient population (pediatric subjects with pathologic drooling). It is noted that the clinical team leader (Dr. John Kelsey) has stated that the product appears to offer substantial potential benefit to the proposed patient population, for which few treatment options are currently available (memorandum to IND 61,716, dated 12-DEC-2008; see attachments).

DSN 1 to NDA 22-571 contained protocols for two-year carcinogenicity studies in mice and rats, as well as data from 90-day studies conducted with those species to support dosage selection in the two-year studies. Those protocols were discussed by the exec-CAC on 26-JAN-2010. The supporting data and carcinogenicity protocols, if modified as recommended by the exec-CAC, were found to be acceptable. The acceptability of the final carcinogenicity data will be a review issue. The following is an excerpt from the minutes of the exec-CAC discussion:

“Protocols for proposed carcinogenicity studies to be conducted with glycopyrrolate in mice and in rats were discussed.

104 week oral Mouse Carcinogenicity Study Protocol and Dosage Selection:

The sponsor agreed to conduct a 104-week carcinogenicity study in CD-1 mice post-approval to support, in part, marketing of an oral product that contains glycopyrrolate. A 13-week dose-range finding study was conducted in which dosages of 30 mg/kg/day and above impaired body weight gain by more than 10%. The study, as proposed by the sponsor, would involve oral (gavage) administration of glycopyrrolate to (b) (4) mice (b) (4)

104 week oral Rat Carcinogenicity Study Protocol and Dosage Selection:

The sponsor agreed to conduct a 104-week carcinogenicity study in Sprague-Dawley rats post-approval to support, in part, marketing of an oral product that contains glycopyrrolate. In a 13-week dose-range finding study, dosages greater than 40 mg/kg/day resulted in significantly reduced values for both mean body weight and mean body weight gain. The dosage of 40 mg/kg/day appeared to have been reasonably well tolerated by both genders under the conditions of the 13-week study. The study, as proposed by the sponsor, would involve oral (gavage) administration of glycopyrrolate to rats (b) (4)

Executive CAC Recommendations and Conclusions

Mice:

1. The Committee did not concur with the dosages proposed by the sponsor. The Committee recommended dosages of 0, 0, 2.5, 7, and 20 mg/kg/day, based on body weight effects.
2. The Committee noted that toxicokinetic data obtained in the 13-week study (“A 13-week oral gavage dose range-finding toxicity study of

glycopyrrolate in CD-1 mice”, study No. (b) (4)-714003) did not appear to document a clear dose-related increase in systemic exposure to glycopyrrolate. The Committee recommended that the sponsor further investigate this issue prior to analysis of toxicokinetic samples collected in the two-year study.

3. The Committee recommended that blood samples for toxicokinetic analysis be collected at 6 months, (b) (4)

4. The Committee recommended that the sponsor contact the division for guidance if the number of surviving animals of a given gender in any group should reach 25.

Rats:

1. The Committee did not concur with the dosages proposed by the sponsor. The Committee recommended dosages of 0, 0, 5, 15, and 40 mg/kg/day. The high dose was based on body weight effects.

2. The Committee noted that toxicokinetic data obtained in the 13-week study (“A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in the Sprague-Dawley rat,” study No. WIL-714004) did not appear to document a clear dose-related increase in systemic exposure to glycopyrrolate. The Committee recommended that the sponsor further investigate this issue prior to analysis of toxicokinetic samples collected in the two-year study.

3. The Committee recommended that blood samples for toxicokinetic analysis be collected at 6 months, (b) (4)

4. The Committee recommended that the sponsor contact the division for guidance if the number of surviving animals of a given gender in any group should reach 25.”

The draft carcinogenicity protocols, incorporating the recommendations of the exec-CAC, are summarized below.

8.1 Carcinogenicity assessment in mice:

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9 Reproductive and Developmental Toxicology

The Division has agreed that, under NDA 22-571, the need to submit data which describe the reproductive toxicology of glycopyrrolate may be addressed as a series of PMRs, provided certain conditions were met (see section 2.5, "Regulatory Background", above). Specifically, it was agreed that data which concern teratology (in rodent and nonrodent species), fertility, and perinatal development could be submitted post-approval, provided the initial submission to the NDA included: a) protocols for suitable nonclinical studies that would acceptably address the PMRs; b) acceptable data which support the dosages proposed in those protocols; and c) a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final reports of studies. It was further noted that the proposed dosages for use in these studies should be supported by suitable data from dose-range finding studies, and that the repeat-dose toxicology studies that are used to support dosage selection should include complete clinical pathology, histopathology, and toxicokinetic evaluation, and be conducted in compliance with Good Laboratory Practice Regulations (21CFR 58).

DSN 1 to NDA 22-571 contained draft protocols for a battery of nonclinical studies that would include studies to assess teratology (in rodent and nonrodent species), fertility, and perinatal development. The submission also contained the following statements:

"..the Sponsor commits to performing the following nonclinical toxicology studies, and to submit the final reports for these studies to the NDA by the approximate dates stated below, provided FDA approves the NDA by the end of June 2010:

Segment I rat study report, entitled "Oral (Gavage) Fertility and General Reproduction Toxicity Study of Glycopyrrolate in Rats": the projected final report submission date is 04 May 2012.

Segment II rabbit study report, entitled "Oral (Stomach Tube) Developmental Toxicity Study of Glycopyrrolate in Rabbits"; the projected final report submission date is 06 Sept 2013, recognizing a preliminary dose finding study must be first completed by the Sponsor.

Segment II rat study report, entitled "Oral (Gavage) Developmental Toxicity Study of Glycopyrrolate in Rats"; the projected final report submission date is 06 Dec 2013, recognizing a preliminary dose finding study must be first completed by the Sponsor.

Segment III rat study report, entitled "Oral (Gavage) Developmental and

Perinatal/Postnatal Reproduction Toxicity Study of Glycopyrrolate in Rats, Including a Postnatal Behavioral/Functional Evaluation"; the projected final report submission date is 30 Mar 2015, recognizing a preliminary dose finding study for Segment II must be first completed by the Sponsor."

Please see the PMR memorandum to NDA 22-571 for detailed information concerning the timelines associated with the PMRs.

It is considered acceptable for nonclinical data which describe the reproductive toxicology of glycopyrrolate to be submitted post-approval. This conclusion is based in part upon the history of use associated with Robinul tablets (NDA 12-827), which has provided no known signals suggestive of altered reproductive function, and in part upon consideration of the limited nature of the proposed patient population (pediatric subjects with (b) (4) drooling). It is noted that the clinical team leader (Dr. John Kelsey) has stated that the product appears to offer substantial potential benefit to the proposed patient population, for which few treatment options are currently available (memorandum to IND 61,716, dated 12-DEC-2008; see attachments). The submitted protocols for nonclinical reproductive toxicology studies are summarized below. Although the submission did not contain final protocols for all of the reproductive toxicology studies, or data which support dosages in those protocols, the sponsor has committed to conduct of dose-range finding studies post-approval, in association with the PMRs, and this is judged to be acceptable.

9.1 Fertility and Early Embryonic Development



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(b) (4)

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10 Special Toxicology Studies

No special toxicology data were submitted.

11 Integrated Summary and Safety Evaluation

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

Data which concern effects of glycopyrrolate on fertility of rodents, development toxicity (teratology) of rodents and nonrodents, prenatal and postnatal development of rodents, and carcinogenesis of mice and rats, will be regarded as being PMRs.

Glycopyrrolate was orally administered to mice for 13 weeks at dosages of 0, 30, 100, and 300 mg/kg/day. Survival was reduced in both genders at 100 and 300

mg/kg/day. Pupil dilation and piloerection were noted in all test article-treated groups. Mean weight gain was reduced by more than 10% in both genders in all treatment groups, although mean body weight per se was reduced by less than 10% at 30 and 100 mg/kg/day. The cause(s) of the treatment-related mortality and reduced body weight gain were unclear. There were no remarkable effects on hematology, clinical chemistry, mean organ weights, or gross pathology. Histopathological changes were of minor severity, and did not appear to be clinically meaningful. Glycopyrrolate appeared to be reasonably well tolerated at 30 mg/kg/day, although the effect on mean weight gain suggested that this dose may have slightly exceeded the maximum dosage that would be tolerated by mice over a lifetime exposure. A dosage of 30 mg/kg/day in mice equates to a human-equivalent dose (HED) of approximately 2.4 mg/kg/day, which is approximately 8 times the maximum clinical dose proposed under NDA 22-571 (0.3 mg/kg/day).

Glycopyrrolate was orally administered to rats for 13 weeks at dosages of 0, 40, 120, and 360 mg/kg/day. There were no effects on survival. The only relevant "clinical sign" was pupil dilation, which was noted in all test article-treated groups in relation to dosage. Reduced mean body weight and weight gain were observed in all treatment groups, in relation to dosage; the mean weight gain differed significantly from controls for all treatment groups except low-dose males. There were no remarkable effects on hematology or clinical chemistry. Mean urine volume was increased in both genders in proportion to dosage. There were no effects on mean organ weights or gross pathology. Histopathological effects were of minor severity, and did not appear to reflect dose-limiting toxicity. A dosage of 40 mg/kg/day was reasonably well tolerated by both genders; this dosage in rats equates to a HED of approximately 6.5 mg/kg/day, which is approximately 20 times the maximum clinical dose proposed under NDA 22-571 (0.3 mg/kg/day).

The submission referenced a study ("AHR 504 Effects in Rats and Dogs Following Repeated Oral Administration, no study No. indicated), originally submitted to NDA 12-827, in which dogs received glycopyrrolate at dosages of 0, 4, 16, or 64 mg/kg/day, six days per week, for 27 weeks (the animals were dosed once daily on the days of dosing, with the exception that the high-dose (64 mg/kg/day) was divided between two equal dosages, administered in the morning and afternoon). This study was conducted in 1960 (prior to the advent of GLP regulations), and involved only two animals per gender per dose group (with the exception of the 16 mg/kg/day group, which included three females and only one male). The small number of animals per group precluded statistical analysis between groups. The study was deficient in many respects by current standards. However, all animals survived to scheduled sacrifice, and apparently glycopyrrolate was considered to have been reasonably well tolerated.

Under NDA 12-827 (Robinul tablets), glycopyrrolate is associated with a substantial history of clinical use via oral administration at dosages similar to

those associated with NDA 22-571. The label of Robinul tablets (NDA 12-827) states that the “presently recommended maximum daily dosage of glycopyrrolate is 8 mg”. NDA 22-571 would be associated with a maximum daily dosage of 9 mg per day (3 mg three times daily)¹. Although the daily dosage of glycopyrrolate proposed under NDA 22-571 slightly exceeds that approved under NDA 12-827, it is noted that glycopyrrolate is apparently less bioavailable when administered in the formulation associated with NDA 22-571 (glycopyrrolate oral solution), in comparison to glycopyrrolate administered in the form of Robinul tablets. Following oral administration to fasted individuals, C_{max} and AUC_{0-inf} values associated with a given dose of glycopyrrolate in the form of the solution were approximately 25% lower than with the same dose in the form of tablets (see Clinical Pharmacology and Biopharmaceutics reviews of NDA 22-571 for details). This suggests that the maximum systemic exposure to glycopyrrolate proposed under NDA 22-571 is less than the maximum exposure that is associated with NDA 12-827. It is noted that glycopyrrolate, during approximately 50 years of marketing experience under NDA 12-827, has been associated with a positive safety record. Quoting the clinical review:

“Glycopyrrolate liquid will be a chronically used drug, which requires an evaluation of adequate demonstration of safe long-term use prior to approval. Towards that end, there is a long history of the safe use of glycopyrrolate in humans. During review of this NDA, it was revealed that Robinul tablets have been approved for use as a treatment of peptic ulcers since 1961, and there has been widespread use of it in children with similar medical background to the target population for the glycopyrrolate liquid. Drug utilization data has shown that approximately 20 million tablets of Robinul are sold every year, 4 million of which are prescribed annually to children under 18. An examination of all AERS reports and other related databases did not uncover any serious adverse events related to this extensive glycopyrrolate use. In addition, the three deaths that occurred during the open label study submitted to this NDA were not related to the drug use, and were within the normal background mortality rate for this population. In summary, there has been no signal to support a need for nonclinical chronic toxicology studies to be conducted as a part of the review process.”

This clinical safety record, in conjunction with data submitted to NDA 22-571, supports the safety of the proposed new use.

¹ The draft label submitted in DSN 1 to NDA 22-571 states that the maximum dose would be 0.1 mg/kg, three times daily, which would equate to individual doses in excess of 3 mg for patients that weighed more than 30 kg. However, clinical studies associated with NDA 22-571 limited individual doses to a maximum of 3 mg. The clinical reviewer has stated that, if approved, the label of the product under NDA 22-571 will be limited to a maximum dosage of 3 mg three times daily, or 9 mg per day.

12 Appendix/Attachments

Attachment 1 Clinical memorandum of medical necessity for Glycopyrrolate Oral Solution (memorandum to IND 61,716, dated 12-DEC-2008).

Dental Officer's Review of IND 61,716
Memo to the File

Drug: Glycopyrrolate Liquid, 1mg/5mL

Supp. Doc. Number: 070 & 071

Sponsor: Sciele Pharma, Inc.

CDER Date: September 29, 2008

DDDP Date: October 10, 2008

Proposed Indication: Treatment of
(b) (4) (chronic, (b) (4)
severe) drooling in pediatric patients

Review Date: December 12, 2008

Due Date: None

Pharmacologic Category: Muscarinic
antagonist

PM: Dawn Williams

DO: John V. Kelsey, DDS

Regulatory Intent:

The submissions cited above concern a request for a pre-NDA meeting and a follow-up submission from the sponsor. This memo to the file is to record internal discussions within DDDP concerning deferring some Pharm/Tox requirements until Phase 4, and to record the recommendation of the Clinical discipline.

Background:

The active ingredient, Glycopyrrolate, has been approved in tablet form in 1961 (Robinul and Robinul Forte for peptic ulcer disease in adults) and in injectable form in 1975 (Robinul Injection) as preoperative or intraoperative medication in adults and children 2 years of age and older. The sponsor of the current submission, Sciele Pharma, Inc. owns the tablet formulations and Robinul Injection is owned by Baxter Healthcare.

The IND for this product was submitted in January of 2001.

Per Dr. See, the Pharmacology/Toxicology reviewer on this IND,

“When the IND was opened in 2001, the Division evaluated the nonclinical database associated with NDA 12-827 (Robinul tablets, which the sponsor owns) and found it to be deficient by current standards. The Division requested a battery of nonclinical studies to support development of the IND and NDA, including genotox, teratology, fertility, perinatal development, chronic toxicology, and carcinogenicity assessment (b) (4)

(b) (4) it would be appropriate for some of these data (i.e., fertility, perinatal development, and carcinogenesis) to be accepted as post-approval commitments. It was requested that acceptable chronic toxicology and teratology data (from both rodent and nonrodent species) be submitted prior to initiation of Phase 3 studies.

(b) (4)

Dr. Wilkin decided that, since the product was currently being extemporaneously compounded and used off-label, and in view of the history of clinical use of glycopyrrolate, all the nonclinical requirements would be waived or deferred to Phase 4. Specifically, it was stated during a guidance meeting on August 8, 2001, that "the requested toxicology data may be submitted post-approval, and that the need for chronic toxicology data will be waived." It was agreed that a NDA for the product would include protocols for suitable nonclinical studies, and a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final study reports.

The Division engaged in an additional guidance meeting with the sponsor of IND 61,716 on March 20, 2007. Based upon the prior agreements, the Division reiterated that chronic toxicology studies would be waived. It was further stated that it appeared that the nonclinical database would be deficient with respect to teratology, genetic toxicology, fertility, perinatal development, and potential to induce carcinogenesis, and that these matters would need to be adequately addressed. It was reiterated that these data could be submitted post-approval of a NDA, provided the NDA contained a commitment on the part of the sponsor to obtain and submit data which are acceptable to the division, with a specific time frame for submitting final reports of the studies. It was also stated that the proposed dosages in these studies should be supported by suitable data from dose-range finding studies.”

Discussion:

This memo is to confirm that this reviewer supports the proposed deferral of some of the Pharm/Tox requirements for approval of Glycopyrrolate Liquid, 1 mg/5mL (Sciele Pharma, Inc.) for the treatment of (b) (4) (chronic, (b) (4) severe) drooling in pediatric patients. I agree that the current Pharm/Tox database is inadequate, but recommend that the Division allow the sponsor to bring the Pharm/Tox database up to current standards as a Phase 4 commitment.

I support this path for a number of reasons as follows:

1. This path is consistent with previous agreements made to the sponsor by DDDP, and reiterated as recently as March 2007.
2. I believe that it would be very desirable to have this product available to the limited number of patients who suffer from (b) (4) (chronic, (b) (4) severe) drooling. Many of these patients suffer from cerebral palsy and other neurodevelopmental defects and most are children. Drooling may lead to aspiration, maceration of surrounding skin, and secondary fungal and bacterial infections. It can also interfere with education and can effect patient placement. To the extent that this product would improve patient care, it would be a benefit. I would add that this product has Orphan Designation for this indication.
3. We are aware that Glycopyrrolate is already commonly used off label to control pathological drooling in children. If a liquid formulation of Glycopyrrolate is required, a pharmacist must add crushed pills or I.V. solution to varying ingredients because none of the medications are commercially available in liquid formulations.
4. From a safety perspective, considerable information is already available. Glycopyrrolate is a muscarinic antagonist, and the mechanism of action is well understood. In addition to Glycopyrrolate, antimuscarinics in use include benztropine, scopolamine, and trihexyphenidyl. The drugs inhibit the action of acetylcholine on structures innervated by postganglionic muscarinic receptors and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the

autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia.

Because there are muscarinic receptors on end organs throughout the body, the effects of these medications are widespread. Small doses depress salivary and bronchial secretion and sweating, at larger doses the eyes dilate and accommodation is inhibited, the vagal tone on the heart is depressed, and the heart rate increases. Larger doses can lead to inhibition of urination and gut motility, and in some of the medications, neurologic effects such as headache, drowsiness, disorientation, nervousness and depression may be seen.

The FDA has approved the use of these drugs in adults for various indications (see table 2.1). None of the medications have been approved for the chronic control of drooling in children.

Table 2.1: Approved Indications for Antimuscarinics.

Medications	Approved Indications
Benztropine	Adjunct in the therapy of all forms of Parkinsonism Control of extrapyramidal disorders due to neuroleptic drugs
Glycopyrrolate	Peptic ulcer disease Premedication to reduce secretions for anesthesia
Scopolamine	Prevention of nausea and vomiting due to motion sickness and recovery from anesthesia and surgery
Trihexyphenidyl	Adjunct therapy of all forms of Parkinsonism

- The sponsor has conducted studies for this NDA in which approximately 160 patients have received at least one dose of Glycopyrrolate. The safety profile reported by the sponsor is as might be expected with a muscarinic antagonist. The most commonly reported drug related treatment-emergent adverse events were: constipation (18.2%), dry mouth (10.9%), flushing (10.2%), dysuria (4.4%), vomiting (3.6%), diarrhea (2.9%), dry lip (2.2%) and urinary retention (2.2%).

Though there were no deaths while on study drug, three patients died within 30 days of the last dose of study drug. Fourteen patients had 20 serious adverse events (SAE) during the study, 8 patients experienced at least one SAE while taking study drug and 6 patients had SAEs within 30 days of the last dose of study drug. Of the 20 SAEs reported during the study, four (nystagmus, esophageal candidiasis, dehydration and gastrointestinal motility disorder) were considered by the sponsor to be treatment related.

Though the safety database for this NDA will be reviewed as part of the NDA review, the clinical studies are complete, and while there were 20 SAEs and three deaths, this is not unexpected, given the fact that this is a seriously ill population.

Recommendation:

In conclusion, while I acknowledge that the Pharm/Tox database for this product is inadequate, I believe that it would be very desirable to have a liquid formulation of Glycopyrrolate available for this seriously ill and vulnerable patient population and I support deferring most Pharm/Tox requirements until Phase 4 in order to get this product on the market sooner. Glycopyrrolate in tablet and injectable formulations are already used off-label for this indication and the mechanism of action of the muscarinic antagonists is well known. The safety data available from sponsor conducted studies of their product are largely expected. Finally, the Division has previously made agreement with the sponsor that much of the Pharm/Tox could be submitted in Phase 4, and I don't feel that the data as described above warrant changing that agreement.

John V. Kelsey, DDS, MBA

cc: IND 61,716
DDDP/DTL/Kelsey
DDDP/DO/Hyman
DDDP/CPMS/Gould
DDDP/PMTL/Owens
DDDP/PTTL/Hill
DDDP/PT/See
DB3/STL/Alosh
DB3/Biostat./Soukup
DPAII/PAL/Ding
DPSIII/Clin. Pharm/Velazquez

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/

NORMAN A SEE
05/20/2010

BARBARA A HILL
05/20/2010
I concr

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-571 Applicant: Sciele Pharma, Inc. Stamp Date: 28-SEP-2009

**Drug Name: Glycopyrrolate NDA/BLA Type: 505(b)(2)
Oral Solution**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		See attachment 1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?		X	Repro. tox. and carc. issues to be handled as PMCs; label will be modified as necessary.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No known issues; will be considered a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	X		No abuse issues.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

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

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The pivotal reproductive toxicology data, when submitted, should be acceptably supported by toxicokinetic data. Note that this includes both rats and rabbits at the dosages used in the pivotal studies.
2. Submit detailed information concerning the impurity profiles of the lots of drug substance used in the nonclinical studies conducted by Sciele Pharma, Inc., including the 14-day and 90-day repeat-dose toxicology studies conducted with rats and mice and the genetic toxicology studies.
3. Submit detailed information concerning the impurity profiles of the lots of drug substance used in the pivotal clinical trials that are associated with NDA 22-571.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

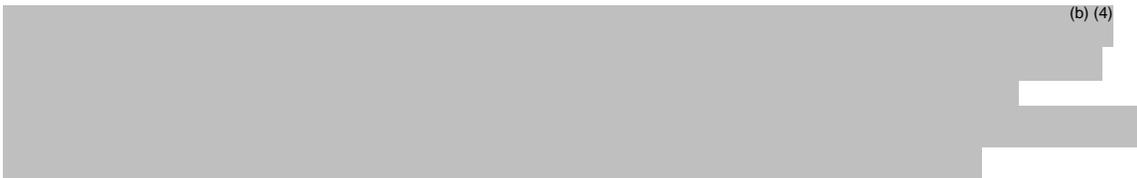
Date

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Attachment 1

The proposed clinical use would involve chronic exposure of incapacitated children to glycopyrrolate at dosages up to 9 mg per day¹. The submission does not appear to contain or reference a suitable nonclinical database, nor does it appear to establish an acceptable bridge to an appropriate prior finding of the Agency (listed drug). The sponsor was informed during a meeting on 15-DEC-2008 that:

“A NDA that is not acceptably based upon an appropriate prior finding of the Agency must be supported by complete information to which the sponsor has the right to reference. Complete information would include (without limitation) fully adequate data that concerned repeat-dose toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, from studies in appropriate species.”



As noted above, a NDA that is not acceptably based upon an appropriate prior finding of the Agency (i.e., in the absence of an acceptable bridge to a listed drug that is labeled for chronic oral administration under conditions relevant to the proposed new use) would require support from complete nonclinical information. Complete information would include fully adequate data that concerned repeat-dose toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, from studies in appropriate species. The Division has agreed that certain nonclinical issues may be addressed as PMCs, provided certain conditions were met. Specifically, it was agreed that data which concern teratology (in rodent and nonrodent species), fertility, perinatal development, and carcinogenicity (two rodent species) could be submitted post-approval, provided the initial submission to the NDA included: a) protocols for suitable nonclinical studies that would acceptably address the postmarketing commitments (PMCs); b) acceptable data which support the dosages proposed in those protocols; and c) a clear commitment to obtain and submit data acceptable to the division, with a specific time frame for submitting final reports of studies. It was further noted that the proposed dosages for use in these studies should be supported by suitable data from dose-range finding studies, and that the repeat-dose toxicology studies that are used to support dosage selection should include complete clinical pathology, histopathology, and toxicokinetic evaluation, and be conducted in compliance with Good Laboratory Practice Regulations (21CFR 58). It was also stated that as a filing issue, final reports of suitable dose-range finding studies must be included in the initial submission to the NDA.

The NDA includes draft protocols for two-year carcinogenicity studies to be conducted in rats and mice, and data from GLP-compliant dose-ranging (90-day repeat-dose toxicology) studies. The suitability of those carcinogenicity protocols will be a review issue.

¹ The draft label states that the maximum dose would be 0.1 mg/kg, three times daily, which would equate to individual doses in excess of 3 mg for patients that weighed more than 30 kg. However, clinical studies associated with NDA 22-571 limited individual doses to a maximum of 3 mg. Therefore, for the purposes of this filing review, I will consider the maximum dosage that would be considered for labeling purposes to be 3 mg three times daily, or 9 mg per day.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

As noted above, a NDA that is not acceptably based upon an appropriate prior finding of the Agency must be supported by complete information, which would include fully adequate data that concerned repeat-dose toxicology. Since the product is proposed for chronic administration, the NDA should acceptably address the chronic toxicology of glycopyrrolate. While the Division has stated that it may be possible to address this matter through reference to the prior finding of the Agency associated with the approval of Robinul Tablets (NDA 12-827), a suitable bridge to the NDA 12-827 has not been established. Therefore, the NDA appears to be deficient with respect to data which concern the chronic toxicology of glycopyrrolate (typically, repeat-dose toxicology studies involving six and nine months of administration to appropriate rodent and nonrodent species, respectively, would be expected). However, as some repeat-dose toxicology data are available, as well as some clinical safety data, this matter will be regarded as being a review issue, rather than a filing issue.

The NDA contains draft protocols for teratology studies with rats and rabbits, a fertility study to be conducted with rats, and a perinatal development study to be conducted with rats. These protocols are not supported by data from dose-range finding studies (the NDA proposed that dose-range finding studies for the reproductive toxicology studies would be conducted post-approval). No provision was made to obtain or submit toxicokinetic (TK) data that would necessarily be relevant to the dosages that may be used in the reproductive toxicology studies, and such TK data would be needed to support labeling of the product. While TK data were obtained in a 90-day repeat-dose toxicology study conducted with rats, it is unclear if those data would encompass the exposures that would be achieved in the reproductive toxicology studies. No TK data from studies conducted with rabbits are available, and the rabbit teratology studies proposed for conduct post-approval make no provision for obtaining TK data. Therefore, apparent deficiencies in the NDA include a lack of complete protocols for appropriate reproductive toxicology studies (including specific dosages to be evaluated, and data from dose-range finding studies that support those dosage proposals), and a failure to address the need for suitable TK data. However, since the Division has agreed that reproductive toxicology issues may be addressed as PMCs under certain conditions, the adequacy of the sponsor's proposals regarding reproductive toxicology issues will be regarded as being a review issue. A comment will be included in the 74-day letter which reminds the sponsor that the pivotal reproductive toxicology data, when submitted, should be acceptably supported by toxicokinetic data.

It is unclear whether the NDA contains data which adequately qualify the proposed exposures to excipients and impurities. This will be regarded as being a review issue. Comments will be included in the 74-day letter which request submission of detailed information concerning the impurity profiles of the lots of drug substance used in the pivotal nonclinical and clinical studies that are associated with NDA 22-571.

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

/s/

NORMAN A SEE
10/29/2009

BARBARA A HILL
10/29/2009
I concur