CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022571Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	22-571 / N-000
Drug Name:	Glycopyrrolate Oral Solution 1 mg/5 mL
Indication(s):	(b) (4) drooling
Applicant:	Shionogi
Dates:	Submitted: 9/28/2009 PDUFA: 7/28/2010
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Kathleen Fritsch, PhD
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Keywords: orphan drug, missing data, single study

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1 Executive Summary

1.1 Conclusions and Recommendations

Glycopyrrolate oral solution had demonstrated efficacy versus placebo in the treatment of pathologic drooling in patients with cerebral palsy or other neurologic conditions in one study. Glycopyrrolate was awarded orphan drug designation for the "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients" in 2006. The applicant conducted a placebo-controlled study in 38 subjects and a single-arm, open-label study in 137 subjects.

Study FH-00-01 treated 38 subjects age 3 to 23 with either glycopyrrolate or placebo for 8 weeks. Doses of glycopyrrolate were titrated over a 4-week period from a starting dose of 0.02 mg/kg three times per day to a maximum dose of the lesser of 0.1 mg/kg or 3 mg three times per day. Parents or caregivers assessed drooling levels using the 9-point Modified Teacher's Drooling Scale (mTDS) where scores ranged from 1 = 'Dry: never drools' to 9 = 'Profuse: clothing, hands, tray and objects become wet; frequently'. On designated assessment days, the parents and caregivers recorded mTDS scores 4 times per day (before the morning dose and then 2 hours after each dose. Daily mTDS scores were summarized with the mean of the three post-dose assessments (mid-morning, afternoon, evening). Treatment response was defined as at least a 3-point improvement from baseline to Week 8 in daily mean mTDS scores. The reviewer's analyses for the number of responders as well as the mean change from baseline are presented in Table 1.

Table 1 – Reviewer's Efficacy Analyses (FH-00-01)

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

The protocol and statistical analysis plan did not provide adequate detail about how to calculate the baseline mean mTDS score for each subject (data were collected on two baseline assessment days) and was not sufficiently clear about how to handle missing data. Due to the lack of detail in the protocol, the original study report and the integrated summary of effectiveness (ISE) present the results in two different ways. In addition, this reviewer's analyses differ from both of the applicant's analysis. The issues leading to the variations in the analyses result from:

- the choice of which observations to include in a subject's baseline mean calculation
- the handling of missing data
- the handling of subjects over age 16

The applicant's results are restricted to subjects age 3 to 16 and to subjects with at least one pre-baseline and one post-baseline assessment. As can be seen in Table 2, the applicant's responder rate estimates for glycopyrrolate range from 47% to 78% and thus the analysis issues regarding the baseline mean calculation and handling of missing data do have an impact on the estimates. However, all of the analyses lead to statistically significant results and the conclusion that glycopyrrolate is superior to placebo in the treatment of pathologic drooling.

Table 2 – Applicant's Responder Analyses for Ages 3 – 16 (FH-00-01)

	Glycopyrrolate	Placebo	p-value
Study Report	9/19 (47%)	1/17 (6%)	0.004
ISE	14/18 (78%)	3/16 (19%)	0.0016

The applicant also conducted an open-label, single-arm, 24-week study (SC-Glyco-06-01) in 137 subjects. Approximately half of the subjects met the responder definition at Week 24 in this uncontrolled study.

1.2 Brief Overview of Clinical Studies

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

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

1.3 Statistical Issues and Findings

The applicant has conducted a single placebo-controlled clinical study with support from an open-label single-arm study. The Agency agreed at the Pre-IND meeting for this product that a single controlled study with additional supportive information may be acceptable for filing. Although the study findings are highly statistically significant, the study does have a number of issues which make the interpretation of the findings challenging. These issues include changes to the study population and endpoints during the study and lack of detail in the protocol leading to a variety of

ways to classify subjects as responders or non-responders. The protocol underwent a fairly substantial revision after approximately half of the subjects were enrolled. The protocol revision modified the inclusion criteria and the list of secondary endpoints. Two of the key changes to the inclusion criteria were

- to change the age range (b) (4) to 3 – 16 years
- to expand the underlying diagnosis (b) (4) to cerebral palsy, (b) (4) or any other neurologic impairment or condition

The amendment also proposed restricting the analysis to subjects age 3 – 16 years. Prior to the amendment, two subjects >16 years of age had already completed the study. This review provides results from both the pediatric subset and the full enrolled population; there were no substantial differences between the two analyses.

The protocol specified that the primary efficacy endpoint was the change from baseline to Week 8 evaluations of the mTDS administered by parents/caregivers. An analysis of the proportion of responders (subjects with at least a 3-point improvement from baseline in mTDS) at Week 8 was listed in the protocol as a secondary endpoint. At the guidance meeting held with the Agency on 3/20/2007, the Agency recommended using the mTDS responder analysis at Week 8 as the primary efficacy endpoint.

Another issue which impacted the analysis was the handling of missing data—both single missing observations within an assessment day and completely missing assessment days due to dropout. The protocol and SAP provided inconsistent directions for handling missing assessment days. In addition, the neither the protocol nor the SAP provided any information about how to handle missing observations within an assessment day. Different interpretations of the way to handle missing data as well as different ways to compute the baseline means led to different analyses in the study report, ISE and reviewer's analysis. However, all of the various analyses led to statistically significant results.

Although the inclusion criteria stated that subjects were to have 'profuse, severe drooling in the absence of treatment so that clothing becomes damp on most days (5-7 days per week),' mTDS scores were not actually used to determine eligibility. With a responder defined as subjects whose mean daily score reduced by at least 3 units, baseline scores have an impact as to whether a subject is classified as a responder. The three subjects with the lowest baseline mTDS mean scores in Study FH-00-01 were all non-responders (there were a total of 5 non-responders on the glycopyrrolate arm).

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

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

2 Introduction

2.1 Overview

Glycopyrrolate is an anticholinergic agent. Robinul (glycopyrrolate) tablets were first approved by FDA in 1961 for the adjunctive treatment of peptic ulcer disease in adults. Robinul injection was approved in 1975 as a preoperative or intraoperative medication in adults and children 2 years of age and older to reduce salivary, tracheobronchial, and pharyngeal secretions. Glycopyrrolate tablets have been used off-label to manage drooling associated with neurodevelopmental conditions. The applicant has developed a glycopyrrolate oral solution specifically to address dosing for pediatric subjects in this population. On June 9, 2006 FDA granted glycopyrrolate orphan drug designation for the "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients." NDA 22-2571 / N-000 is a 505(b)(1) application.

The Agency held four meetings with the sponsor during product development for glycopyrrolate solution. Since the Pre-IND meeting in 2000, the Agency has agreed that a single well-designed and conducted, persuasive study plus additional supporting information may be sufficient for filing an application to support an indication for control of drooling. The applicant has conducted one placebo-controlled efficacy study in 38 subjects (Study FH-00-01) and one open-label 24-week study in 137 subjects (Study Sc-GLYCO-06-01). The clinical development milestones and key issues most relevant to overall study design are listed in Table 3. The amendments to Protocol FH-00-01 are discussed in Section 3.1.1.1.

Table 3 – Clinical Development Milestones for Glycopyrrolate Oral Solution

Date	Milestone	Key Issues
9/6/2000	Pre-IND Meeting	Conducting one well-designed and conducted, persuasive efficacy study, with additional supportive information may be acceptable.
12/29/2000	IND Submission	
8/8/2001	Guidance Meeting	Agency discouraged use of a randomized withdrawal design
5/24/2002	FH-00-01 Protocol Finalized	Amend. 1: 6/18/2002 First subject enrolled: 11/7/2002. Amend. 2: 5/13/2004 Amend. 3 (changes to incl/excl criteria): 6/28/2006 SAP: 1/25/2007 Last subject completed: 4/3/2007
6/9/2006	Orphan Drug Designation Granted	
3/20/2007	Guidance Meeting	Agency recommended using responder analysis as primary endpoint
2/1/2007	Sc-GLYCO-06-01 Protocol Finalized	First subject enrolled: 4/3/2007 Amend. 1: 4/20/2007 (add PK) SAP: 5/12/2008 Last subject completed: 5/30/2008
12/15/2008	Pre-NDA Meeting	

The applicant conducted both the randomized, placebo-controlled study and the open-label long-term safety study in the United States. Details of the study designs and enrollments are presented in Table 4. Twelve subjects participated in both Studies FH-00-01 and Sc-GLYCO-06-01.

Table 4 – Clinical Studies Overview

Study	**FH-00-01**	**Sc-GLYCO-06-01**
Type of study	Randomized, double-blind, placebo-controlled	Open-label
Treatment period	8 weeks	24 weeks
Number of subjects*	38	137
Treatment groups	Glycopyrrolate liquid TID (N=20) and placebo TID (N=18)	Glycopyrrolate liquid TID (N=137)
Dose levels (titrated)	0.02 mg/kg - 0.1 mg/kg	0.02 mg/kg - 0.1 mg/kg
Sites	10 sites in US	29 sites in US
Study Period	11/7/2002 to 4/3/2007	4/3/2007 to 5/30/2008

*Note: 12 subjects participated in both studies.

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets used in this review are archived at \\Cdsesub1\evsprod\NDA022571\0000\m5\datasets.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study FH-00-01

3.1.1.1 Study Design

Study FH-00-01 is a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of glycopyrrolate solution in the management of problem drooling. The study population included subjects age 3 and older with cerebral palsy. During the second half of the recruitment, the upper age limit was reduced to 16 years and the requirement that subjects have cerebral palsy was broadened to include other neurological conditions associated with drooling.

Subjects were treated with study medication three times a day (TID) for 8 weeks. The dosage levels of study treatment were titrated. Subjects began at the dose of 0.02 mg/kg TID. Every 5-7 days subjects could increase or decrease a dose level based on a discussion between the investigator and parent/caregiver based on response or adverse events. The possible dose levels were 0.02, 0.04, 0.06, 0.08, and 0.1 mg/kg TID. The maximum allowed dose was 3 mg TID. The optimal dose for a subject was to be identified by Week 4 and maintained through Week 8.

The protocol was amended twice during subject enrollment (Amendments 2 and 3—Amendment 1 was finalized before the first subject was enrolled). Amendment 2 was relatively minor and clarified the description of the drooling severity needed for enrollment. Originally eligible subjects were described as having 'drooling to the extent that clothing commonly becomes damp or wet.' In Amendment 2, eligibility was clarified as 'profuse, severe drooling in the absence of treatment so that clothing becomes damp on most days (5-7 days per week).' Amendment 3, however, involved broader changes to the inclusion/exclusion criteria and study endpoints. Amendment 3 went into effect after approximately half of the subjects were enrolled. The key changes to the inclusion and exclusion criteria were as follows.

- Age range changed from ≥3 (with no upper limit) to 3 – 16
- Underlying diagnosis expanded from cerebral palsy to cerebral palsy, mental retardation, or any other neurologic impairment or condition
- Restriction on prior glycopyrrolate use was changed from 'none within 16 days of randomization' to 'none within 24 hours prior to Day -8'
- Five additional exclusion criteria were added (restrictions on certain anticholinergics, no botulinum toxin within 10 months, no prior salivary gland

irradiation, no use of intra-oral devices within 1 week, and no acupuncture within 3 months)

The decision to limit the age range to pediatric subjects only was driven by the designation of glycopyrrolate as an orphan drug for 'the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients.' Orphan designation was granted by the Agency on June 9, 2006. At the time Amendment 3 went into effect, two subjects > 16 years of age had already completed the study. Amendment 3 stated that these two subjects would be excluded from all efficacy analyses.

Reviewer Comment
It is not clear that there is a regulatory requirement for an orphan indication defined for pediatric subjects that would require that all subjects evaluated in the clinical studies for that indication must be pediatric. Excluding subjects who were validly randomized into the study at the time of their enrollment violates the intent-to-treat principle. A more statistically sound approach to assessing the effect of glycopyrrolate on pediatric subjects would be to include all randomized subjects in the ITT population and to conduct subgroup analyses for pediatric subjects to support efficacy and safety claims for the pediatric population.

Protocol FH-00-01 was variously described during its development as a Phase 2 and Phase 3 study. When the protocol for Study FH-00-01 was originally submitted to the Agency, the cover letter (IND 61,716/ SDN 11, stamp date April 3, 2002) stated that this "proposed phase 3 trial has been shifted to phase 2," and the review reflected the designation as a Phase 2 protocol. Thus, the Agency did not provide detailed comments on the protocol when it was first submitted. When the sponsor came in for a guidance meeting in March 2007 to discuss Amendment 3, they were describing the study as a Phase 3 study.

3.1.1.2 Efficacy Endpoints

Efficacy endpoints and analysis methods were modified through the various protocol amendments and the statistical analysis plan (SAP). The Agency also made recommendations at a guidance meeting about the primary efficacy endpoint after all protocol amendments and the SAP had been finalized. The differences among the various documents with regard to the efficacy endpoints are discussed in this section.

Efficacy was assessed using the Modified Teacher's Drooling Scale (mTDS). The mTDS is defined as follows. Each mTDS assessment was to cover a 30-60 minute time period.

1 = Dry: **never drools**
2 = Mild: only the lips are wet; **occasionally**
3 = Mild: only the lips are wet; **frequently**
4 = Moderate: wet on the lips and chin; **occasionally**
5 = Moderate: wet on the lips and chin; **frequently**
6 = Severe: drools to the extent that clothing becomes damp; **occasionally**

7 = Severe: drools to the extent that clothing becomes damp; **frequently**
8 = Profuse: clothing, hands, tray and objects become wet; **occasionally**
9 = Profuse: clothing, hands, tray and objects become wet; **frequently**

Drooling severity was assessed by the parent/caregiver prior to randomization (on two separate days of the parent/caregiver's choice within a 9-day period prior to randomization). Drooling severity was assessed four times per day (7-8 am, 9-10 am, 3-4 pm, and at bedtime, approximately 9-10 pm). Although subjects were to have 'severe or profuse' drooling to be eligible for the study, there were no specific requirements on the mTDS scores collected in the baseline period. After randomization, subjects were to take study treatment three times per day (7-8 am, 1-2 pm, and 7-8 pm). The mTDS scores were to be assessed before the early morning dose and then two hours after each of the three daily doses. After randomization, the parent/caregiver also used the mTDS to assess drooling on this schedule on Days 14, 28, 42, and 56.

Prior to Amendment 3, the subjects' teachers, if applicable, were also to assess drooling with the mTDS on two baseline school days and on school days closest to Days 14, 28, 42, and 56. The teacher assessments were collected two times per day (10-11 am and 3-4 pm). All teacher assessments were eliminated after Amendment 3. Thus only a subset of subjects have teacher mTDS assessments and they are not analyzed in this review.

An additional evaluation asked parents/caregivers and physicians to make a global assessment of the treatment at Week 8. Parents/caregivers and physicians reported their level of agreement at Week 8 with the statement 'this is a worthwhile treatment,' using the categories strongly agree, agree, neutral, disagree, or strongly disagree.

The protocol specified the primary efficacy endpoint as the change from baseline to Week 8 evaluations of the mTDS administered by parents/caregivers. As supportive analyses of the primary efficacy analysis, each mTDS assessment (i.e. mid-morning, afternoon, and evening) at Week 8 was to be analyzed individually.

The list of secondary endpoints was modified in Amendment 3. Prior to Amendment 3, the list of secondary efficacy measures was

- analyze teacher mTDS evaluations
- conduct an area-under-the-curve (AUC) analysis of parent/caregiver mTDS assessments from baseline to Week 8
- analyze the proportion of subjects who drop out due to lack of efficacy
- descriptively analyze data obtained at individual timepoints for parent/caregiver and teacher assessments
- analyze the caregiver's and physician's global assessments
- analyze the proportion of responders, where a responder is defined as a subject with at least a 3-point improvement from baseline in mTDS (Weeks 2, 4, 6, and 8)

In Amendment 3, the teacher evaluations were discontinued and AUC analysis was dropped, reducing the list of secondary efficacy measures as follows

- analyze the proportion of subjects who drop out due to lack of efficacy
- descriptively analyze data obtained at individual timepoints for parent/caregiver assessments
- analyze the caregiver's and physician's global assessments
- analyze the proportion of responders, where a responder is defined as a subject with at least a 3-point improvement from baseline in mTDS (Weeks 2, 4, 6, and 8)

The statistical analysis plan (SAP) included all secondary efficacy measures from Amendment 3, plus also included the AUC analysis that was dropped from the protocol in Amendment 3.

At the guidance meeting held with the Agency on 3/20/2007, the Agency recommended using the responder analysis (at least a 3-point improvement from baseline) in mTDS at Week 8 as the primary efficacy endpoint. This recommendation was made after the SAP was finalized and thus the protocol and SAP list change from baseline as the primary efficacy endpoint. The study report used the responder analysis recommended by the Agency as the primary endpoint.

3.1.1.3 Missing Data and Statistical Analysis Details

Some key details about how to implement the proposed efficacy analyses in the protocol and statistical analysis plan were either vague or contradictory. Particularly problematic were the plans for summarizing multiple mTDS observations within a day and for handling missing data. Because the study documents left room for interpretation, the applicant has presented results differently in the study report for Study FH-00-01 and in the integrated summary of effectiveness (ISE).

One issue that was not completely clear in the protocol and statistical analysis plan is how to deal with the fact that each assessment day had four mTDS observations. The protocol did state that the 'primary analysis will use the mean of each daily post-dose evaluation; i.e., the mean of three post-dose evaluations for each day' (page 271-272)[1]. On the other hand, the statistical analysis plan used the phrasing 'primary analysis will use the daily mean week-8 evaluation' (page 16)[2]. In the study report, the applicant used all four observations for calculating the baseline means, but post-baseline only the three-post-dose observations were used. According to notes in the applicant's statistical program, the rationale for using all four baseline scores was that 'no dosing data was collected[3]' at baseline. Thus the assumption was the in the absence of treatment, the early morning observations were from the same distribution as the

[1] \\CDSESUB1\EVSPROD\NDA022571\\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\protocol.pdf
[2] \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\fh-00-01\statistical-methods.pdf
[3] \\ CDSESUB1\EVSPROD \NDA022571\0007\m5\datasets\74-day\analysis\program\ tabresponderjan10.txt

observations later in the day. However, as discussed in the Section 3.1.1.4, drooling scores vary with the time of day, and that baseline drooling scores at the early morning timepoint tended to be lower than at timepoints later in the day. Therefore including the early morning observations at baseline, but not post-baseline, computations biases the baseline estimates downward relative to the later estimates. For the integrated summary of effectiveness, however, the applicant used the three post-dose evaluations to calculate means for both the baseline and post-baseline assessment days.

Related to this issue is how to handle the fact that there were baseline mTDS assessments collected on two separate days. The protocol does not state anything about how to handle the information from the two baseline days. While not specifically addressing the issue of two baseline days, the SAP does provide information on how to handle 'repeated samples.' In terms of handling 'repeated samples' the SAP states that the 'latter sample will be used' (page 13). It is not clear whether the applicant intended this to apply to the baseline samples or whether is was only to apply in the relatively rare cases where a subject would have repeated visits at another timepoint. However, in the study report, the applicant calculated baseline means by using all eight baseline observations from both baseline days (and thus did not consider the two planned baseline assessment days as repeated samples). In the integrated summary of effectiveness, the applicant used only the observations from the second baseline day (the one closest to randomization).

Another unsettled issue in the protocol and SAP is how to handle missing data: either due to dropout (an entire day's assessment missing) or individual missing observations within an assessment day. Throughout the submission, the applicant has simply 'ignored' individual missing observations within an assessment day. That is, if on an assessment day the evening observation is missing, the mean for that day would be calculated as the mean of the mid-morning and afternoon observations only. Because of the within-day variability of the observations, simply ignoring the missing observations within a day can impact the interpretation of the results, and this is more fully discussed in Section 3.1.1.4.

With regard to subjects completely missing the Week 8 observations, the protocol stated that subjects who drop out due to lack of efficacy will have the worst score carried forward (WOCF) and subjects who drop out for other reasons will have their last observation carried forward (LOCF). The SAP states that subjects will be treated as a 'treatment failure' if they discontinue early for the primary efficacy endpoint (page 13). In the study report, the applicant imputed treatment failure in the responder analysis for subjects with missing Week 8 assessments (in line with the SAP). In the integrated summary of effectiveness, the applicant used LOCF (or WOCF if dropout was due to lack of efficacy) to impute response or non-response in the responder analysis (in line with the protocol).

Both the protocol and the statistical analysis plan stated that the primary analysis for the change from baseline in mTDS scores was to be analyzed with a non-parametric analysis of covariance adjusted for mean baseline mTDS from the same evaluator and

other 'known important cofactors.' The cofactors were listed as including, but not limited to: age, severity of neurological defects, presence of tracheostomy, and underlying pattern of cerebral palsy. Both the protocol and the SAP agreed on the analyses for the secondary endpoints. Subjects who dropped out due to lack of efficacy were to be analyzed with Fisher's exact test. The Caregiver's and Physician's Global Assessments were to be analyzed using binomial proportions test. However, neither the protocol nor the SAP specifically stated how the 5-point global assessment was to be dichotomized for analysis. The proportion of responders (at least a 3-point improvement) was to be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted by the 'important cofactors' previously identified. In the study report the proportion of responders was analyzed with the CMH test. No stratification factors were used in the analysis. The p-value for the applicant's analysis for the change from baseline could not be replicated by this reviewer, but according to the study report it was analyzed with the CMH test. In the integrated summary of effectiveness, the applicant used Fisher's exact test to analyze the proportion of responders and ANCOVA with baseline mTDS as a covariate for the change from baseline analysis. Although it had not been clearly specified in the protocol or SAP how to dichotomize the Caregiver's and Physician's Global Assessment for analysis, the applicant dichotomized the assessment into whether the assessor agreed ('strongly agree' or 'agree') that the treatment was worthwhile or did not agree ('neutral', 'disagree', or 'strongly disagree').

3.1.1.4 Reviewer's Handling of Missing Data and Baseline Observations

Because the applicant used different interpretations throughout the application package about how to handle missing data and multiple baseline observation days, this review will be explicit about which assumptions were used for various presentations of results. If not otherwise stated, results in this review will attempt to follow the conventions as they were stated in the earliest document when two documents are in conflict. If a convention was not clearly specified in any of the applicant's documents, this review will present the reasons behind the reviewer's choice. Unless otherwise stated, mTDS result presentations will use the following conventions.

- subject means will use the three post-dose observations (mid-morning, afternoon, evening) [specified in protocol]
- baseline means will use the three observations from the assessment day closest to randomization [specified in SAP]
- if at least one of the three utilized observations from the baseline assessment day closest to randomization is missing, but all three observations from the earlier baseline assessment day are available, then the data from the earlier assessment day will be used instead [reviewer's choice-see discussion below]
- if at least one of the three utilized observations from both baseline assessment days are missing, the data from the most complete assessment will be used, ignoring the missing observations; if neither baseline day has a complete assessment available, then only observations from the matching timepoints will be used at later visits when computing mean change (e.g. if the most complete baseline assessment has only the afternoon and evening observations, then only

the afternoon and evening observations from the Week 8 assessment will be used) [reviewer's choice-see discussion below]

- if at least one of the three utilized observations from the Week 8 (or final) assessment day are missing, then the individual missing value(s) will be imputed from the most recent available assessment day [reviewer's choice]
- if a full day's assessment is missing LOCF will be used, unless the subject discontinued due to lack of efficacy in which case worst observation carried forward will be used [specified in protocol]

This reviewer needed to specify how to handle subjects with individual missing observations within an assessment day because this was not specified in any of the applicant's documents. The applicant handled this problem by ignoring the missing observations. However, ignoring the missing observations is not a benign issue and can have a significant impact on the evaluation for a subject. Note that ignoring an observation actually is the same as imputing the mean of the observed values for the missing value. However for most subjects, the observations at different times of day are not all from the same distribution—drooling levels vary for most subjects according to the time of day. For example, consider the baseline and Week 8 data for Subject 1006 who was treated with placebo (Table 5). Subject 1006 had complete data on the first baseline day and on the Week 8 assessment day, but was missing the mid-morning assessment on the second baseline day. On the baseline day where full assessments were made, the observed mid-morning value was 3 and the overall mean for the three later observations is 6.33. But for the second baseline visit, if the missing observation is ignored, the mean calculation essentially imputes a value of 8.5 for the missing value [(8 + 9)/2 = (8.5 + 8 + 9)/3 = 8.5]. The 'imputed' value of 8.5 from the second visit is much different from the observed value from the first visit of 3. Throughout the rest of the study, Subject 1006 had a mid-morning mTDS observed values of either 1 or 2. Thus an imputed value of 8.5 for the baseline assessment day is an unlikely value for this subject. This imputation also makes a big difference in the baseline mean (6.33 vs. 8.5) for the two assessment days, even though the values that were observed on these two days were similar. Also, as the subject's Week 8 mean was 5, using 8.5 as the baseline mean causes the subject to be classified as a success (> 3-point reduction from baseline), while using 6.33 causes the subject to be classified as a failure. Ignoring the missing baseline mid-morning value artificially raises the baseline mean for this subject, by having the effect of imputing an unlikely value of the missing observation. Note that Subject 1006 is counted as a success in the applicant's ISE analysis and counted as a failure in the reviewer's analysis.

Table 5 – mTDS Data for Subject 1006 (Placebo)

Visit	Early Morning	Mid Morning	Afternoon	Evening	Mean*
BL1	2	3	7	9	6.33
BL2	4	NA	8	9	8.5
WK2	2	2	7	8	5.67
WK4	2	1	5	5	3.67
WK6	2	2	6	5	4.33
WK8	2	2	7	6	5

*Mean of mid-morning, afternoon, and evening observed values.

In this review, all subjects with missing observations will be considered carefully in the discussion of the results. Because of the problem with missing observations, this review uses the baseline assessment day with the most complete data whenever possible rather than make imputation assumptions about the missing observations. In a few cases neither of the baseline days had complete assessments at all timepoints. To avoid introducing bias from mismatched sets of timepoints when computing change from baseline, in such cases the means calculated from the Week 8 assessment were based on the same observation timepoints as available from the most complete baseline assessment day (e.g. if the most complete baseline assessment has only the afternoon and evening observations, then only the afternoon and evening observations from the Week 8 assessment will be used).

3.1.1.5 Subject Disposition

Five subjects discontinued Study FH-00-01 early, 2 on glycopyrrolate and 3 on placebo. The reasons for discontinuation were similar in the two treatment groups and are presented in Table 6. Table 6 also presents the amount of efficacy information available on the subjects who discontinued the study early. The two subjects who discontinued due to adverse events had efficacy assessments only through baseline or Week 2, while the other discontinuing subjects had efficacy assessments through Week 4 or 6.

Table 6 – Subject Disposition

	Glycopyrrolate		Placebo	
Subjects Randomized	20		18	
Discontinued	2 (10%)		3 (17%)	
Discontinuation Reason	*Subj. ID*	*Last Visit*	*Subj. ID*	*Last Visit*
Adverse Event	6009[a]	Baseline	1002[b]	Week 2
Lack of Efficacy	--	--	6003	Week 4
Patient/Parent Decision	4004	Week 6	8001	Week 4

[a] Abdominal distension

[b] constipation, dry mouth, flushing, aggression, attention disturbance, somnolence

3.1.1.6 Baseline and Demographic Data

The average age of subjects in Study FH-00-01 was approximately 10 years with a range of 3 to 23 years. Slightly more than half of the subjects were male. The racial

balance among the treatment arms varied slightly with most subjects on the glycopyrrolate arm being White/Non-Hispanic, while the subjects on the placebo arm were more evenly split among White/Non-Hispanic, Hispanic, and African-American. See Table 7.

Table 7 – Demographic Data (FH-00-01)

	Glycopyrrolate N=20	Placebo N=18
Age (years)		
Mean	10.8	9.3
Range	4-23	3-20
3 – 9	8 (40%)	9 (50%)
10 – 16	11 (55%)	8 (44%)
> 16	1 (5%)	1 (6%)
Gender		
Male	13 (65%)	9 (50%)
Female	7 (35%)	9 (50%)
Race		
White (Non-Hispanic)	14 (70%)	5 (28%)
White (Hispanic)	3 (15%)	6 (33%)
African-American	2 (10%)	7 (39%)
Asian	1 (5%)	--
Weight (kg)		
Mean (sd)	31.3 (15.0)	25.4 (9.5)
Range	13 – 63.7	14.5 – 47.7

The majority of subjects (84%) had cerebral palsy and most of these subjects were classified as spastic and quadriplegic. All enrolled subjects had mental retardation and speech impairment. About half of the subjects had oral feeding problems. Most subjects lived with their parents, though a few lived with foster parents or guardians. See Table 8.

Table 8 – Neurological and Other Characteristics (FH-00-01)

	Glycopyrrolate N=20	Placebo N=18
Neurological Condition		
Cerebral Palsy	17 (85%)	15 (83%)
Rett's Syndrome	2 (10%)	--
Other (Epilepsy, seizures, development and motor disorders)	1 (5%)	3 (17%)
Cerebral Palsy Category 1	N=17	N=15
Spastic	15 (88%)	13 (87%)
Hypotonic	1 (6%)	1 (7%)
Athetoid	--	1 (7%)
Mixed	1 (6%)	--
Cerebral Palsy Category 2	N=17	N=15
Quadriplegic	14 (82%)	13 (87%)
Hemiplegic	3 (18%)	1 (7%)
Diplegic	--	1 (7%)
Other Characteristics		
Mental retardation	20 (100%)	18 (100%)
Speech impairment	20 (100%)	18 (100%)
Oral feeding problems	10 (50%)	8 (44%)
Uses tube for feeding	7 (35%)	5 (28%)
Undernourished	1 (5%)	2 (11%)
Residence of subject		
Home with parent	17 (85%)	17 (94%)
Foster parent/ guardian	3 (15%)	1 (6%)

Prior to randomization, parents/caregivers collected four mTDS scores per day on two separate days. The average baseline scores by assessment time are presented in Table 9. On average, the morning assessments had lower scores than the afternoon and evening assessments. Overall, the placebo arm had lower mean mTDS scores than the glycopyrrolate arm, particularly at the two morning observations and the evening observation. As described in Section 3.1.1.4, the baseline assessment date closest to randomization is used for establishing baseline drooling levels, unless the earlier day has more complete data. Some subjects did not have complete assessment on either day, so the sample size is reduced.

Table 9 – Baseline Mean mTDS Scores (FH-00-01)

	Glycopyrrolate N=20	Placebo N=18
Early Morning (N=20/N=16)	5.25	3.69
Mid Morning (N=20/N=16)	6.55	4.13
Afternoon (N=20/N=17)	6.90	6.94
Evening (N=19/N=17)	6.95	5.65
Mean of Mid Morning, Afternoon, and Evening Assessments	6.79	5.63

3.1.1.7 Efficacy on the Modified Teacher's Drooling Scale

Efficacy on the mTDS will be evaluated both by way of the primary analysis specified in the protocol (the mean change from baseline to Week 8) and the primary analysis recommended by the Agency (the proportion of responders at Week 8, where a responder is defined as at least 3 grades reduction from baseline in mean mTDS). Unless otherwise specified, the analyses presented use the reviewer's data handling rules specified in Section 3.1.1.4. All analyses will be presented for the full randomized population (all ages) and for the subgroups based on age. The analyses for the responders and the mean change from baseline are statistically significant, both for the ITT population and the pediatric subgroup.

Table 10 – Reviewer's Efficacy Analyses Based on mTDS (FH-00-01)

Responders			
	Glycopyrrolate	Placebo	p-value
All ages	15/20 (75%)	2/18 (11%)	<0.0001[a]
3 – 16	14/19 (74%)	2/17 (12%)	0.0002[a]
> 16	1/1	0/1	
***Mean Change* (sd)**			
	Glycopyrrolate	Placebo	p-value
All ages	N=20	N=18	
Baseline	6.79	5.59	
Week 8	3.08	5.06	
Change	3.71 (2.18)	0.54 (1.93)	0.0002[b]
3 – 16	N=19	N=17	
Baseline	6.85	5.73	
Week 8	3.18	5.12	
Change	3.68 (2.23)	0.61 (1.97)	0.0005[b]

[a] Fisher's exact test
[b] ANCOVA (baseline as covariate)

The complete set of mTDS scores for each subject, along with the baseline and final mean scores are presented in Figure 1 (glycopyrrolate) and Figure 2 (placebo). Means for the baseline and final assessment days are based on the mid-morning, afternoon, and evening observations using the reviewer's missing data handling rules. The observed change from baseline value is displayed for each subject.

Figure 1 – Modified Teacher's Drooling Scale Scores and Mean Change from Baseline to the End of the Study by Subject (Glycopyrrolate) – FH-00-01

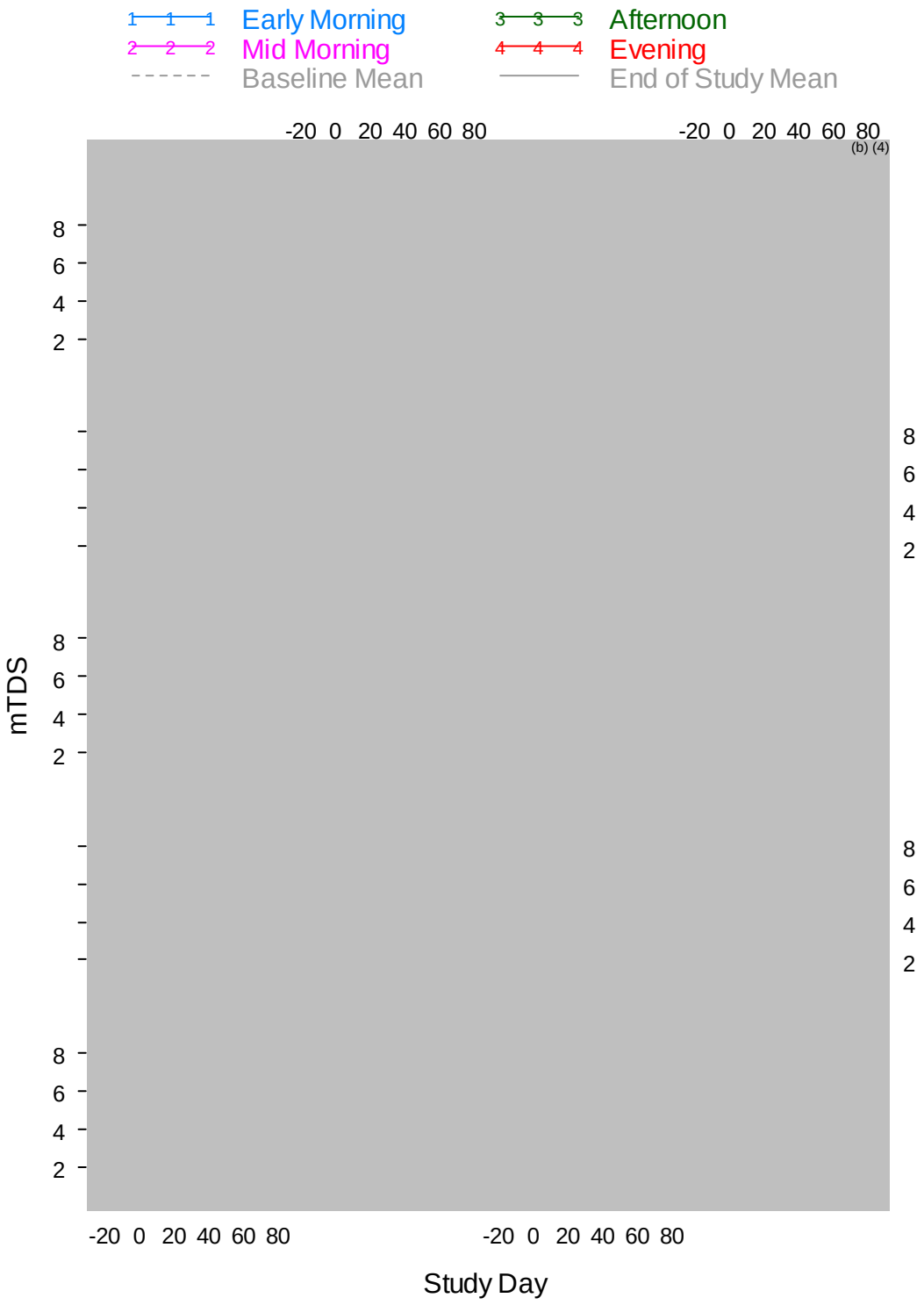
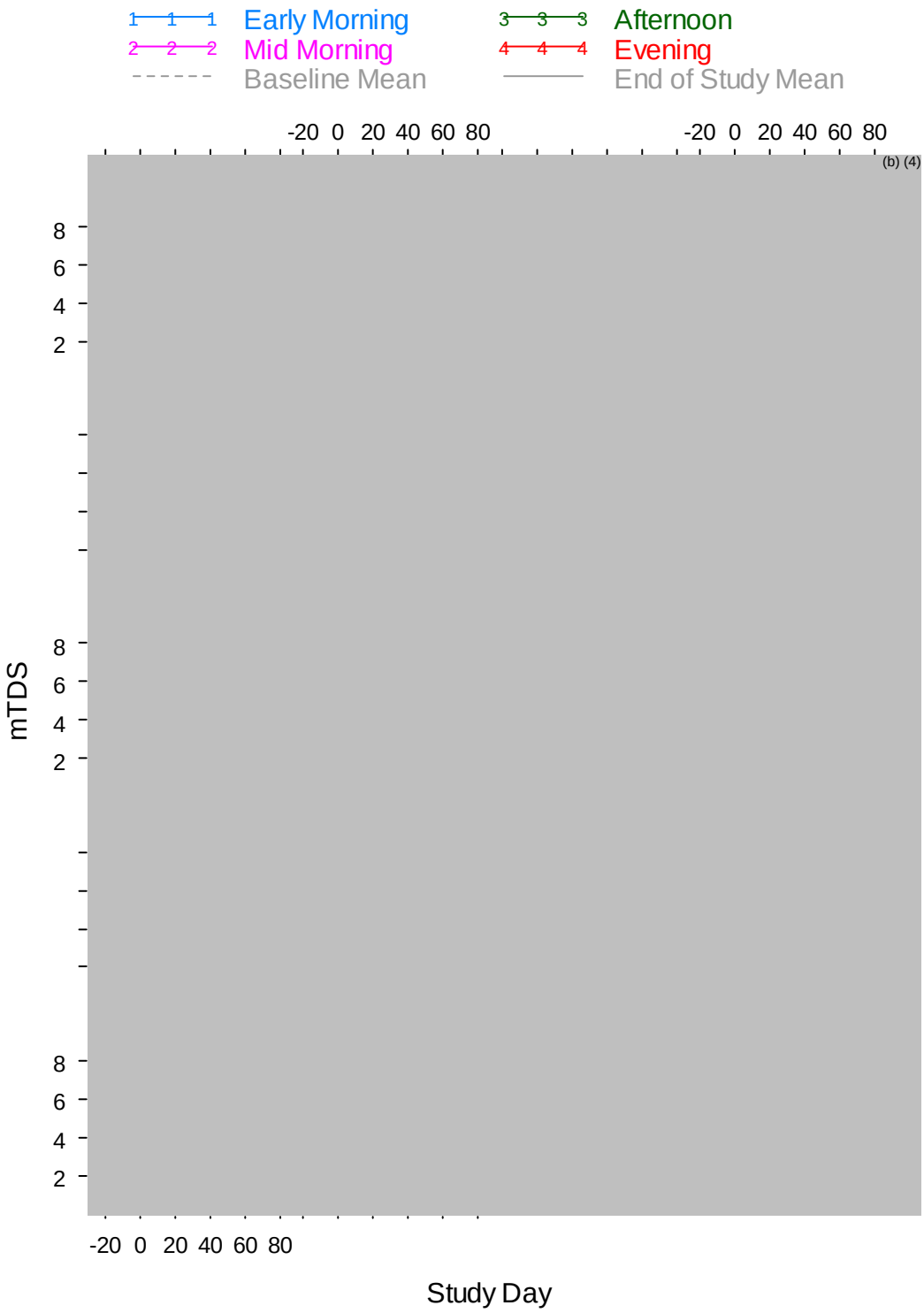


Figure 2 Modified Teacher's Drooling Scale Scores and Mean Change from Baseline to the End of the Study by Subject (Placebo) – FH-00-01



Note that the inclusion criteria for the drooling level stated either 'drooling to the extent that clothing commonly becomes damp or wet.' (Amendment 1) or 'profuse,

severe drooling in the absence of treatment so that clothing becomes damp on most days (5-7 days per week)' (Amendments 2 and 3). However, the determination as to whether a subject met this inclusion criterion was made at the screening visit before any mTDS scores were collected for the study. Therefore the study had no controls to exclude subjects who had lower mTDS scores collected during the screening period. The three glycopyrrolate subjects with the lowest baseline mean scores (and therefore had less room to improve) were all classified as non-responders (Subjects 1003, 6011, 7001). The baseline means for these three subjects were 2, 4, and 5.33 (the lowest baseline mean of a subject classified as a responder was 5.67). Since the minimum mTDS score is 1, the subject with a baseline mean of 2 had no chance of getting a 3-point improvement, and the subject with a baseline mean of 4 would have needed to have had no drooling at all (score of 1 for each observation) on the final assessment day to have been classified as a responder. One of the other non-responding subjects dropped out of the study early and had no post-baseline mTDS assessments.

The applicant presented different results in the study report and integrated summary of efficacy (ISE). All of the applicant's analyses were limited to subjects ≤ 16 years of age. The applicant did not present any efficacy results which included the subjects > 16 years of age. The applicant's two sets of results differed because they used different ways of calculating the baseline means and different ways of handling missing observations. These differences led to quite different point estimates in the 3-16 age group for the glycopyrrolate responder rate (47% [study report], 74% [reviewer], and 78% [ISE]) and placebo responder rate (6% [study report], 12% [reviewer], and 19% [ISE]). The applicant's results are presented in Table 11 and the differences between the analyses will be described below. Note that the applicant's analyses are based on fewer subjects than the reviewer's analyses, which use all 36 randomized subjects age 3-16. For the analysis of the mean change the study report uses only the 30 subjects with baseline and Week 8 data and uses no imputation. The analyses from the ISE are based on 34 subjects. Two subjects were excluded from the ISE analyses for either not having baseline mTDS assessments or not having any post-baseline mTDS assessments. The remaining subjects with missing Week 8 data were handled with LOCF/WOCF for the mean change analysis.

Table 11 – Applicant's mTDS Efficacy Analyses (Age 3 – 16) (Study Report and ISE) - FH-00-01

Responders			
	Glycopyrrolate	Placebo	p-value
Study Report	9/19 (47%)	1/17 (6%)	0.004[a]
ISE	14/18 (78%)	3/16 (19%)	0.0016[b]
***Mean Change* (sd)**			
	Glycopyrrolate	Placebo	p-value
Study Report	N=16	N=14	
Baseline	7.0	5.8	
Week 8	3.7	5.3	
Change	3.5 (1.9)	0.1 (1.8)	0.019[a]
ISE	N=18	N=16	
Baseline	6.86	5.89	
Week 8	2.92	5.18	
Change	3.94 (1.95)	0.71 (2.14)	<0.0001[c]

[a] CMH
[b] Fisher's exact test
[c] ANCOVA (baseline as covariate)
Source: pg. 48,123, and 125 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\fh-00-01\report-body.pdf; pg. 38 and 173 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\fh-00-01\report-body.pdf.

The nine glycopyrrolate subjects and one placebo subject (age 3-16) identified as responders in the study report were all identified as responders in all analyses (both the ISE and reviewer's analyses, see Table 12 and Table 13). Both the reviewer's analysis and the ISE identify an additional five glycopyrrolate subjects and one placebo subject as responders. Further, the ISE identifies one additional placebo responder that is not included in the reviewer's analysis. The reviewer's analyses that include subjects of all ages also include Subject 5002 (glycopyrrolate) as a responder. Based on the applicant's algorithms, Subject 5002 would have been considered a responder in both the study report and ISE analyses if the analyses had included subjects older than 16 years. The seven subjects who were classified as responders in some analyses and non-responders in other analyses will be further discussed below.

Table 12 – Glycopyrrolate Subjects (Age 3 – 16) Classified as Responders in Various Analyses

Subject ID	Study Report	ISE	Reviewer	Subject ID	Study Report	ISE	Reviewer
1008	Y	Y	Y	8003	Y	Y	Y
3001	Y	Y	Y	9002	Y	Y	Y
4001	Y	Y	Y	1005[a]	N	Y	Y
6002	Y	Y	Y	4004[a,b]	N	Y	Y
6004	Y	Y	Y	5003[a]	N	Y	Y
6005	Y	Y	Y	7007[b]	N	Y	Y
7003	Y	Y	Y	8002[a]	N	Y	Y

Table 13 – Placebo Subjects (Age 3 – 16) Classified as Responders in Various Analyses

Subject ID	Study Report	ISE	Reviewer
9001	Y	Y	Y
8001[b]	N	Y	Y
1006[c]	N	Y	N

[a] Non-responder when early morning observation is included in baseline mean/Responder when early morning observation is not included in baseline mean
[b] Dropout prior to Week 8 (responder under LOCF)
[c] Responder only when missing mid-morning observation at baseline is ignored in ISE analysis, yielding unexpectedly high baseline estimate

Nearly all of the discrepancies between the analyses resulted from two issues, (1) the inclusion/exclusion of the early morning assessment in the baseline mean computation, or (2) handling of dropouts (imputing non-response vs. LOCF). As discussed in Section 3.1.1.3, in the study report analysis the applicant calculated the baseline mean using 8 values (early morning, mid-morning, afternoon, and evening on two assessment days) and the Week 8 mean using 3 values (mid-morning, afternoon, and evening). Many subjects exhibit their lowest levels of drooling in the early morning (both on and off active treatment—see Figure 1 and Figure 2). Thus, including the early morning assessments into the baseline calculation tends to bias the baseline mean downward, but because the Week 8 calculation does not include the early morning assessment, it is not similarly affected. Subjects 1005, 4004, 5003, and 8002 all had levels of improvement that were < 3 units when the early morning assessments were included in the baseline mean, but ≥ 3 units when the early morning assessments were not included in the baseline mean. Because drooling levels can vary with the time of day, all daily mean summaries should use the same set of timepoints for both baseline and post-baseline assessment days. Subjects 7007 and 8001 were missing Week 8 assessments, but were classified as responders at their last available assessment day. (Subject 4004 also dropped out from the study early, in addition to being impacted by the way baseline means were calculated.) The baseline mTDS scores, baseline means and final visit means for these 7 subjects are presented in Table 14.

Table 14 –mTDS Scores and Means for Subjects Classified Differently in Different Analyses

	Baseline 1				Baseline 2				Baseline Means			Final Visit	
Subj.	EM	MM	AF	EV	EM	MM	AF	EV	Study Rep.[a]	ISE[b]	Rev.[b]	Mean[c]	Week
Glycopyrrolate													
1005	4	7	7	4	4	7	7	4	5.5	6	6	3	8
4004	3	6	8	6	3	6	7	7	5.75	6.67	6.67	3.33	6
5003	5	7	7	-	4	6	7	-	6	6.5	6.5	3.5	8
7007	9	9	9	9	9	9	9	9	9	9	9	2	6
8002	5	8	8	8	5	8	8	9	7.38	8.33	8.33	5	8
Placebo													
8001	-	6	6	7	-	5	7	7	6.33	6.33	6.33	2	4
1006	2	3	7	9	4	-	8	9	6.13	8.5	6.33	5	8

Note: EM – early morning, MM - mid-morning, AF – afternoon, EV- evening

[a] Study Report mean = [mean(EM1, MM1, AF1, EV1) + mean(EM2, MM2, AF2, EV2)]/2

[b] ISE and Reviewer mean = mean(MM2, AF2, EV2), except Reviewer analysis uses MM1, AF1, and EV1 if the baseline 1 data is more complete than the baseline 2 data.

[c] All analyses use the same computations for post-baseline means (mean of mid-morning, afternoon, and evening observations).

Subject 1006 was the only subject not classified the same way in the ISE and reviewer's analyses. This subject is discussed in Section 3.1.1.4 (see Table 5). Subject 1006 is missing the mid-morning observation from the second assessment day. This missing observation leads to a wide variation of baseline mean estimates. In the study report analysis, the baseline mean used is 6.125, in the ISE analysis the baseline mean used is 8.5, and in the reviewer analysis the baseline mean used is 6.33[4]. All three analyses use a Week 8 mean of 5, so only the ISE analyses leads to this subject being classified as a responder. Ignoring the missing mid-morning observation inflates the estimate baseline mean by around 2 units for the second baseline day relative to the first baseline day (8.5 vs. 6.33). Ignoring the missing value assumes that the missing mid-morning observation behaves like the observed outcomes for later that day (in the range of 8-9) rather than the midmorning values observed on other days (in the range of 1-3). Even though the study report analysis also ignores the missing mid-morning observation, because the study report baseline mean calculation is based on 7 observed values from the two assessment days rather than only 2 observed values from the second assessment day, the impact of the missing value is much less. This reviewer used the baseline assessment day with complete observations to avoid making assumptions about the missing observation.

An additional discrepancy between the reviewer's and the applicant's analyses was the handling of one subject who did not have any baseline mTDS scores recorded by the parent/caregiver (one pre-dose observation was collected on the randomization day at the center), and the handling of one subject who did not have any post-baseline mTDS

[4] Study report: $\frac{1}{2}\left(\frac{2+3+7+9}{4}+\frac{4+8+9}{3}\right)$=6.125; ISE: $\frac{8+9}{2}$ = 8.5; Reviewer: $\frac{3+7+9}{3}$ = 6.33

assessments. The subject without baseline assessments (5001) was randomized to placebo. Baseline assessments were not collected for Subject 5001 due to confusion by the parent/caregiver on how to collect and record the appropriate information. The subject without post-baseline assessments (6009) was randomized to glycopyrrolate. Subject 6009 stopped taking study treatment after approximately 1 week due to an adverse event (abdominal distension) and had no post-baseline mTDS assessments. Note that in the study report, the applicant appears to have confused subjects 5001 and 6009. Table 7 of the study report (pg 48) states that Subject 6009 was the subject without baseline assessments and classified as 'indeterminate' for the response analysis and not counted as either a responder or a non-responder, when in fact it was Subject 5001 without baseline assessments (Subject 5001 was recorded as a non-responder in the table). In the ISE (Table 8, pg 38), the applicant removed Subjects 5001 and 6009 from the analysis and did not record these subjects as either responders or non-responders. The analysis was based on 18 glycopyrrolate and 16 placebo subjects age 3-16. The ISE correctly identifies Subject 5001 as the subject excluded due to no baseline assessments. The reviewer included both subjects as non-responders in the analyses.

As noted above, the handling of missing data was one of the key factors leading to different results among different analysis, along with the formula used to calculate the baseline mean. The first sensitivity analysis will focus specifically on the handling of subjects who did not have an efficacy assessment at Week 8. The primary method of imputation was LOCF. If, as a sensitivity analysis, the subjects without Week 8 data are counted as failures regardless of their outcome at the time of dropout, then the glycopyrrolate responder counts are reduced by two subjects, and the placebo counts by one subject. The p-values under this analysis are similar. See Table 15. The second sensitivity analysis will focus on the computation of the baseline mean. Although the ISE and reviewer's analysis used only observations from one baseline assessment day, the study report analysis attempted to incorporate information from both assessment days. Although including the early morning observations into the baseline mean calculations, but not the post-baseline mean calculations may not have been a good choice (introducing bias), another reasonable choice might have been to calculate the baseline mean on the six observations from the mid-morning, afternoon, and evening assessments on the two baseline days. All of the subjects previously identified as responders in the reviewer's analysis maintain that status under this '6-observation baseline' analysis, and one additional vehicle subject is classified as a responder (Subject 7006, with a 3-observation baseline mean of 6.33, a 6-observation baseline mean of 7.33, and a Week 8 mean of 3.67). Thus the 6-observation baseline mean leads to a slightly more conservative analysis, and the results are also presented in Table 15. The analysis with the largest p-value was the analysis using the 6-observation baseline mean and treating missing subjects as failures, using only subjects 3 – 16 years old and it had a p-value of 0.0022, which is still statistically significant.

Table 15 – Sensitivity Analyses for Responder Analysis

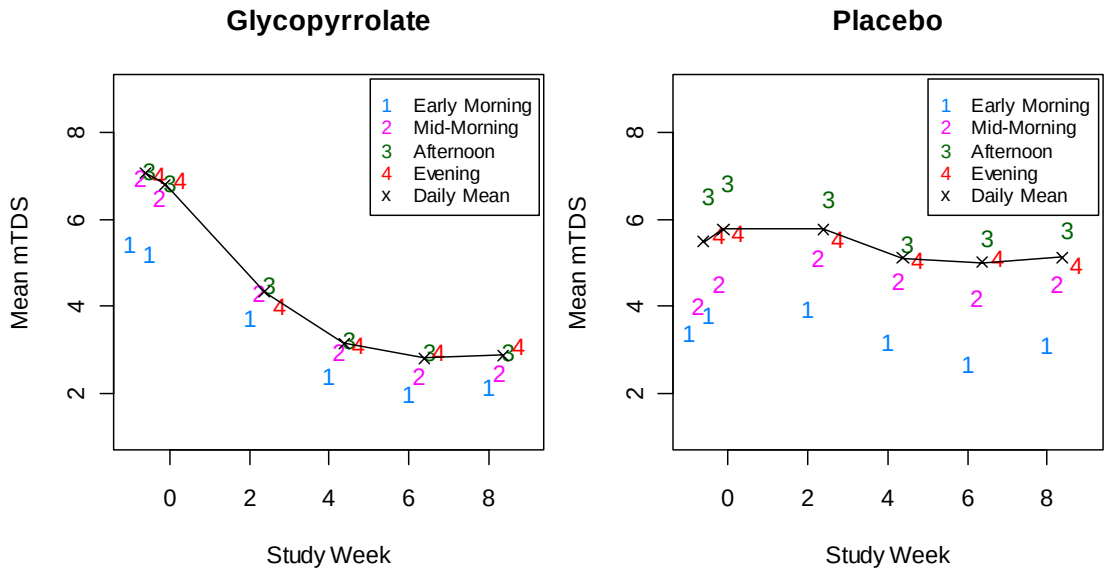
	Glycopyrrolate	Placebo	p-value[a]
All ages			
LOCF (3-obs BL)[b]	15/20 (75%)	2/18 (11%)	<0.0001
Missing as failure (3-obs BL)	13/20 (65%)	1/18 (6%)	0.0002
LOCF (6-obs BL)	15/20 (75%)	3/18 (17%)	0.0004
Missing as failure (6-obs BL)	13/20 (65%)	2/18 (11%)	0.0009
Age 3 – 16			
LOCF (3-obs BL)	14/19 (74%)	2/17 (12%)	0.0002
Missing as failure (3-obs BL)	12/19 (63%)	1/17 (6%)	0.0004
LOCF (6-obs BL)	14/19 (74%)	3/17 (18%)	0.0011
Missing as failure (6-obs BL)	12/19 (63%)	2/17 (12%)	0.0022

[a] Fisher's exact test
[b] Reviewer's primary analysis.

3.1.1.8 Efficacy by Study Week and Efficacy by Center

Over the 8 weeks of the study, the mTDS scores decreased over time on average for the glycopyrrolate subjects and remained fairly constant for the placebo subjects. The mean subject mTDS scores for each daily timepoint, as well as the mean of the three daily scores (mid-morning, afternoon, and evening) are presented in Figure 3.

Figure 3 – Mean mTDS Scores at each Assessment Timepoint and Daily Means over Time (FH-00-01)

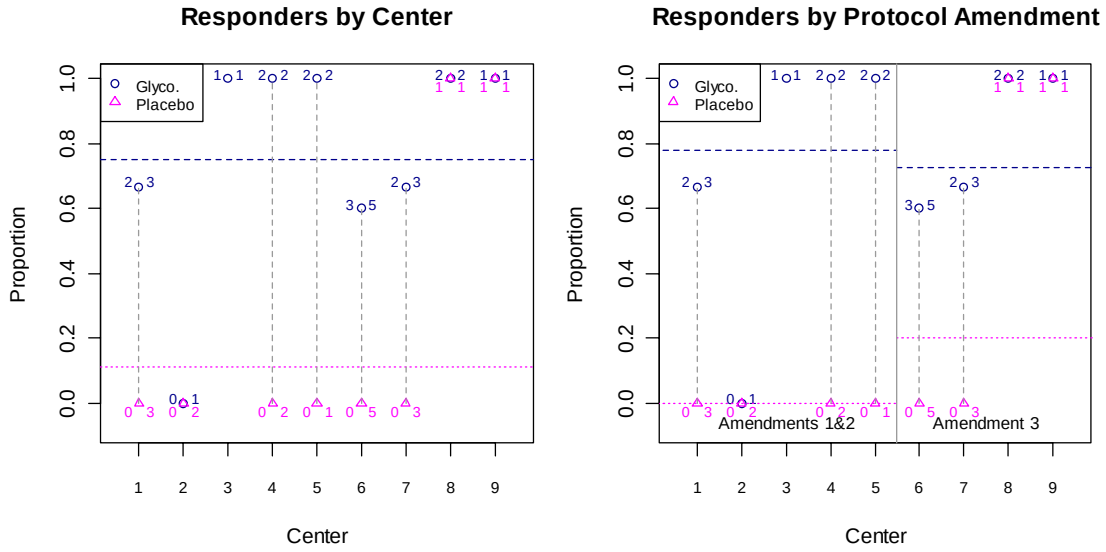


Note: Daily mean is the mean of the mid-morning, afternoon, and evening scores.

Study FH-00-01 used 9 centers; the largest center enrolled 11 subjects. As noted in Section 3.1.1.1, Amendment 3 of the protocol modified some of the inclusion and exclusion criteria (the age range was restricted, additional neurological conditions other than cerebral palsy were permitted, and restrictions on prior treatments were

modified). The recruitment period for the study extended from November 2002 to January 2007. Amendments 1 and 2 covered subjects who were recruited from November 2002 through July 2005 (32 months) and Amendment 3 covered subjects who were recruited from September 2006 through January 2007 (5 months). No subjects were recruited from August 2005 to August 2006. Approximately half of the subjects were enrolled in each part of the study (17 under Amendments 1 and 2, and 21 under Amendment 3). Five centers (Centers 1-5) participated in the first half of the study and 4 centers (Centers 6-9) participated in the second half of the study. None of the centers participated in both parts of the study. Responder rates by center are presented in Figure 4. The first graph in Figure 4 presents the overall responder rates for glycopyrrolate and placebo in the study, while the second graph presents the responder rates for the centers enrolling under Amendments 1 and 2 and for those enrolling under Amendment 3 separately. The response rates for glycopyrrolate subjects were similar in both halves of the study, though both placebo responders were in the second half of the study, causing the placebo rate to be higher in the second half (Amendment 3).

Figure 4 – Responders by Center (Whole Study and by Protocol Amendment)



Note: the numbers represent the number of responders and number of subjects per center; the horizontal lines represent the overall proportions (either whole study or by protocol amendment)

3.1.1.9 Global Assessment Endpoints

In addition to the analyses on the mTDS, the protocol also listed the caregiver/parent and investigator global assessments as secondary endpoints. Parents/caregivers and investigators reported their level of agreement at Week 8 with the statement 'this is a worthwhile treatment,' using the categories strongly agree, agree, neutral, disagree, or strongly disagree. The respondents were asked to consider their overall evaluation of the study medication in the treatment of drooling, including the benefits and side effects observed over the course of the study. The applicant collapsed 'agree' and

'strongly agree' together as the successful response. The global assessment results are presented in Table 16. Eight subjects had discordant parent/caregiver and investigator assessments (Agree/Disagree). The subject number, global assessment results, and brief summaries of efficacy and safety results for these 8 subjects are presented in Table 17. Note that both subjects who discontinued the study due to adverse events had a parent/caregiver who strongly agreed that that the study medication was a worthwhile treatment (the investigators disagreed). Also, several subjects whose mean mTDS scores worsened during the study had a parent/caregiver who strongly agreed that that the study medication was a worthwhile treatment. Overall, the global assessment may be difficult to interpret due to the discordance between the raters and the high assessment of the parent/caregivers on both glycopyrrolate and placebo that the treatment was worthwhile.

Table 16 – Parent/Caregiver and Investigator Global Assessments at Week 8

	Parent/Caregiver		Investigator	
	Glycopyrrolate N=20	Placebo N=18	Glycopyrrolate N=20	Placebo N=18
Strongly Agree	18 (90%)	7 (39%)	13 (65%)	5 (28%)
Agree	2 (10%)	3 (17%)	4 (20%)	2 (11%)
Neutral	--	1 (6%)	--	--
Disagree	--	2 (11%)	3 (15%)	4 (22%)
Strongly Disagree	--	4 (22%)	--	7 (39%)
Missing	--	1 (6%)	--	--
Strongly Agree/Agree	20 (100%)	10 (56%)	17 (85%)	7 (39%)
	p = 0.0009		p=0.0063	

P-values based on Fisher's exact test.

Table 17 – Subjects with Discordant Parent/Caregiver and Investigator Global Assessments

			Glycopyrrolate	
Subject	Parent	Investigator	Change in mTDS[a]	Adverse Event Information[b]
6009	Str. Agree	Disagree	No post-BL	Discontinued for AE (abdominal distension)
6011	Str. Agree	Disagree	1.33	no 'related' AEs
8002	Str. Agree	Disagree	3.33	'Possibly related' diarrhea
			Placebo	
Subject	Parent	Investigator	Change in mTDS[a]	Adverse Event Information[b]
1002	Str. Agree	Disagree	-0.67	Discontinued for AE (constipation, dry mouth, flushing, aggression, attention disturbance, somnolence)
5001	Str. Agree	Str. Disagree	no BL	no 'related' AEs
6007	Str. Agree	Disagree	-1.67	no 'related' AEs
6010	Agree	Disagree	-0.33	no 'related' AEs
7002	Disagree	Agree	1.33	no 'related' AEs

[a] Positive changes in mTDS represent improvement

[b] Adverse event information is limited to adverse events leading to discontinuation or those classified as 'possibly' or 'probably' related.

3.1.2 Study Sc-GLYCO-06-01

3.1.2.1 Study Design

Study Sc-GLYCO-06-01 is a single-arm, open-label study to assess the safety and efficacy of glycopyrrolate solution for the treatment of pathologic drooling. The study population included subjects age 3 to 18 with cerebral palsy or other neurologic conditions who weighed at least 13 kg. All subjects received glycopyrrolate in this study. Subjects were treated with study medication three times a day (TID) for 24 weeks. The dosage levels of study treatment were titrated. The dosing regimen and titration schedule were the same as in Study FH-00-01. Subjects began at the dose of 0.02 mg/kg TID. Every 5-7 days subjects could increase or decrease a dose level based on a discussion between the investigator and parent/caregiver based on response or adverse events. The possible dose levels were 0.02, 0.04, 0.06, 0.08, and 0.1 mg/kg TID. The maximum allowed dose was 3 mg TID. The optimal dose for a subject was to be identified by Week 4 and maintained through Week 24. To be enrolled in the study, subjects were to have chronic drooling in the absence of treatment to the extent that the chin or clothing becomes wet most days by confirming mTDS score ≥5. Subjects were classified as either naïve or non-naïve to glycopyrrolate at baseline.

Efficacy was assessed using the Modified Teacher's Drooling Scale (mTDS) by the parent/caregiver. The mTDS is defined in Section 3.1.1.2. The baseline observations were to be taken on the two days prior to the first day of treatment (Days -2 and -1).

Drooling severity was assessed four times per day (7-8 am, 9-10 am, 3-4 pm, and at bedtime, approximately 9-10 pm), approximately two hours after each of the three daily doses. The parent/caregiver also used the mTDS to assess drooling on this schedule on Days 1, 28, 56, 84, 112, 140, and 168.

3.1.2.2 Subject Disposition

The study screened 160 subjects and 137 subjects were treated with glycopyrrolate (ITT population). Subjects were classified as either naïve to glycopyrrolate or non-naïve at baseline. A higher proportion of dropouts occurred in the naïve group (33% vs. 11%). Much of this difference was due to dropouts due to adverse events (14% vs. 4%), though most other discontinuation reasons were also slightly higher for naïve vs. non-naïve subjects.

Table 18 – Subject Disposition (Sc-GLYCO-06-01)

	Naive	Non-Naive	Total
Subjects Screened	99	61	160
ITT (treated) Subjects	84	53	137
Subjects Completing Study	56 (67%)	47 (89%)	103 (75%)
Discontinuation Reason			
Adverse Event	12 (14%)	2 (4%)	14 (10%)
Patient/Parent Decision	4 (5%)	1 (2%)	5 (4%)
Lost to Follow-up	3 (4%)	--	3 (2%)
Death	2 (2%)	1 (2%)	3 (2%)
Lack of Efficacy	1 (1%)	1 (2%)	2 (1%)
Investigator Decision	2 (2%)	--	2 (1%)
Non-Compliance	2 (2%)	--	2 (1%)
Other (prohibited medication)	--	1 (2%)	1 (1%)

Source: pg 37 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5352-stud-rep-uncontr\sc-glyco-06-01\sc-glyco-06-01\report-body.pdf

Twelve subjects enrolled in Study Sc-GLYCO-06-01 who had previously been enrolled in Study FH-00-01. Six of these subjects received glycopyrrolate in Study FH-00-01 and six received placebo. The minimum amount of time between the date of the last dose in Study FH-00-01 and the date of the first dose in Study Sc-GLYCO-06-01 was 3 months and the maximum amount of time was about 4 years 7 months.

Table 19 – Subjects Enrolled in Both FH-00-01 and Sc-GLYCO-06-01

FH-00-01 ID	Trt[a]	Date of Last Dose in FH-00-01	06-01 ID	Date of First Dose in 06-01
02-004	G	5/11/2005	02-01	8/06/2007
04-003	P	4/28/2003	24-03	11/27/2007
05-001	P	6/14/2005	05-01	9/05/2007
05-003	G	9/21/2005	05-02	9/18/2007
06-001	P	11/20/2006	06-06	6/13/2007
06-002	G	11/21/2006	06-04	6/11/2007
06-003	P	11/08/2006	06-08	6/25/2007
06-004	G	12/11/2006	06-01	5/29/2007
06-005	G	11/29/2006	06-02	5/29/2007
06-007	P	1/31/2007	06-03	5/29/2007
06-010	P	3/03/2007	06-09	7/14/2007
08-003	G	2/23/2007	08-01	5/29/2007

[a] Treatment received in Study FH-00-01; G=glycopyrrolate, P=placebo

3.1.2.3 Baseline and Demographic Data

The average age of subjects in Study Sc-GLYCO-06-01 was approximately 10 years with a range of 3 to 18 years. Slightly more than half of the subjects were male. Most subjects were white (72%) or African-American (21%). See Table 20.

Table 20 – Demographic Data (Sc-GLYCO-06-01)

		Glycopyrrolate N=137
Age (years)	Mean	11
	Range	3 – 18
	3 – 9	54 (39%)
	10 – 16	66 (48%)
	> 16	17 (12%)
Gender	Male	77 (56%)
	Female	60 (44%)
Race	White	98 (72%)
	African-American	29 (21%)
	Am. Indian/AK Native	1 (1%)
	Asian	4 (3%)
	Other	5 (4%)
Ethnicity	Hispanic/Latino	15 (11%)
	Non-Hispanic/Latino	121 (89%)
	Missing	1 (1%)
Weight (kg)	Mean (sd)	31.0 (15.1)
	Range	12.6 – 104.0

Source: pg 39 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5352-stud-rep-uncontr\sc-glyco-06-01\sc-glyco-06-01\report-body.pdf

The majority of subjects (70%) had cerebral palsy and most of these subjects were classified as spastic and quadriplegic. Most subjects had mental retardation (91%) and speech impairment (98%). About two-thirds of the subjects had oral feeding problems. Most subjects lived with their parents (66%), though a few lived with foster parents or guardians (9%) and the rest lived in institutional settings (25%). See Table 21.

Table 21 – Neurological and Other Characteristics (Sc-GLYCO-06-01)

	Glycopyrrolate N=137
Neurological Condition	
Cerebral Palsy	96 (70%)
Rett's Syndrome	3 (2%)
Other	38 (28%)
Cerebral Palsy Category 1	N=96
Spastic	78 (81%)
Hypotonic	8 (8%)
Ataxic	2 (2%)
Athetoid	3 (3%)
Mixed	5 (5%)
Cerebral Palsy Category 2	N=96
Quadriplegic	79 (82%)
Hemiplegic	6 (6%)
Diplegic	7 (7%)
Triplegic	3 (3%)
Other Characteristics	
Mental retardation	124 (91%)
Speech impairment	134 (98%)
Oral feeding problems	91 (66%)
Uses tube for feeding	70 (51%)
Nutritional status	
Undernourished	14 (10%)
Overweight	3 (2%)
Residence of subject	
Home with parent	91 (66%)
Foster parent/ guardian	12 (9%)
Institutional setting	34 (25%)

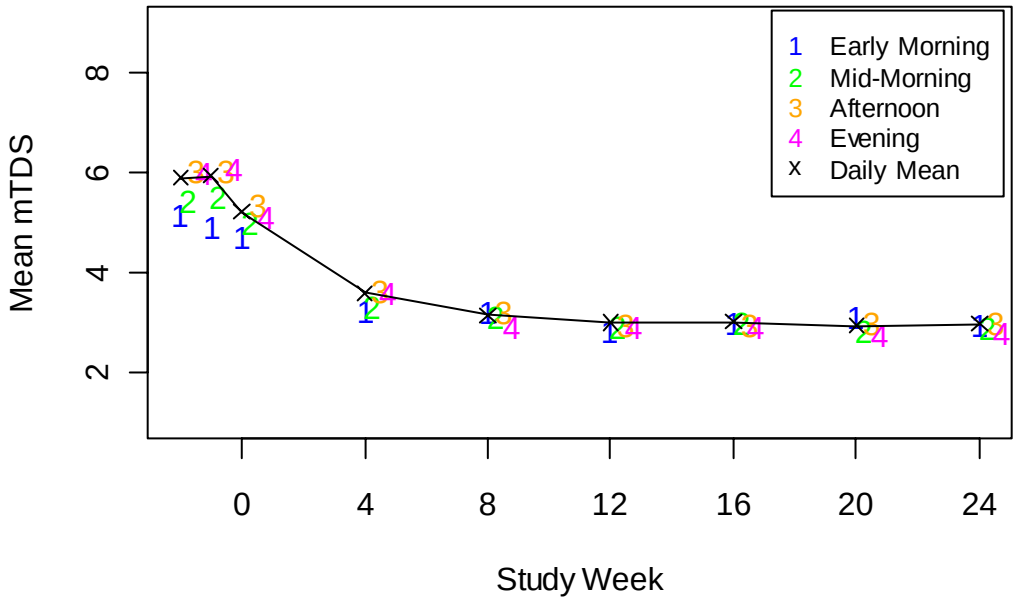
Source: pg 41 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5352-stud-rep-uncontr\sc-glyco-06-01\sc-glyco-06-01\report-body.pdf

3.1.2.4 Efficacy on the Modified Teacher's Drooling Scale

The parent/caregiver assessed drooling using the mTDS four times per day on Days -2, -1, 1, 28, 56, 84, 112, 140, and 168. The mTDS scores decreased from baseline to Week 4 and remained fairly constant from Week 4 to Week 24. The mean subject mTDS scores for each daily timepoint, as well as the mean of the three daily scores (mid-morning, afternoon, and evening) are presented in Figure 5. For comparison, the

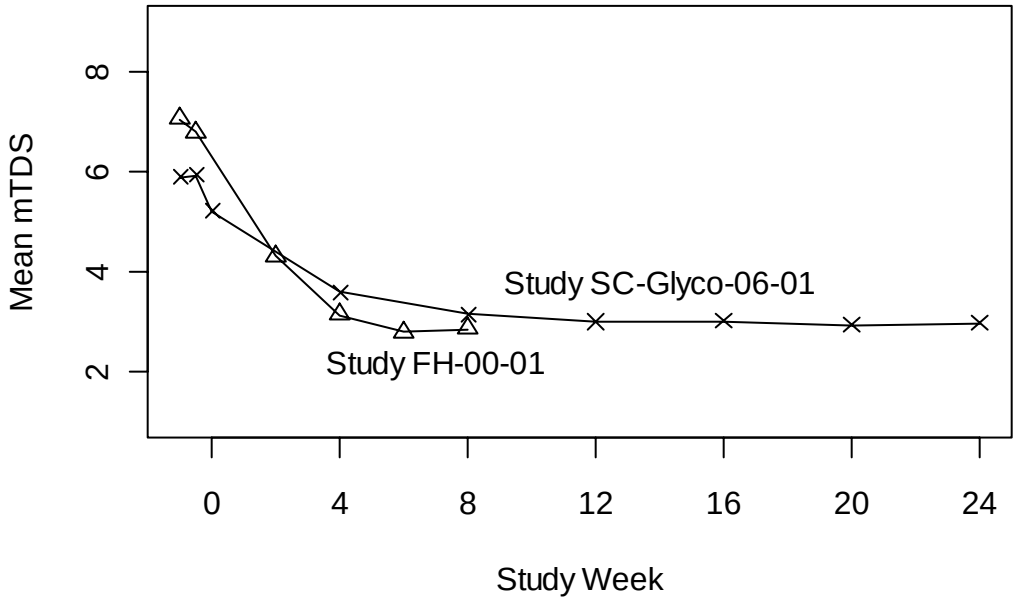
mean daily mTDS scores for glycopyrrolate subjects in both Studies Sc-GLYCO-06-01 and FH-00-01 are presented in Figure 6. Although the baseline scores were slightly higher in Study FH-00-01, at Weeks 4 and 8, both studies had similar results.

Figure 5 - Mean mTDS Scores and Daily Means at each Assessment Timepoint (Sc-GLYCO-06-01)



Note: Daily mean is the mean of the mid-morning, afternoon, and evening scores.

Figure 6 – Daily Mean mTDS Scores for Studies Sc-GLYCO-06-01 and FH-00-01



Note: Daily mean is the mean of the mid-morning, afternoon, and evening scores.

3.2 Evaluation of Safety

3.2.1 Study FH-00-01

3.2.1.1 Extent of Exposure

Subjects were titrated from a starting dose of approximately 0.02 mg/kg (maximum dose of 1 mg) three times per day in steps of 0.02 mg/kg up to a maximum of 0.1 mg/kg (with a maximum dose of 3 mg) three times per day. Investigators could increase the dose level every 5-7 days if adequate response had not been achieved. If intolerable side effects were observed, investigators or parents could reduce the dose level. The protocol encouraged finding a tolerable dose by Day 28 and remaining on that dose for the remainder of the study. Doses were measured in milliliters (1 mg/ 5 mL). The dose titration levels for various weights are given in Table 22.

Table 22 – Dose Titration Levels

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

Source: pg 26 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\fh-00-01\report-body.pdf.

The doses (in milliliters) received by each subject on the glycopyrrolate and placebo arms by study day are presented in Figure 7. The graphs also display the subject's baseline weight.

Figure 7 – Doses (mL) Received by Study Day for Subjects on Glycopyrrolate (FH-00-01)

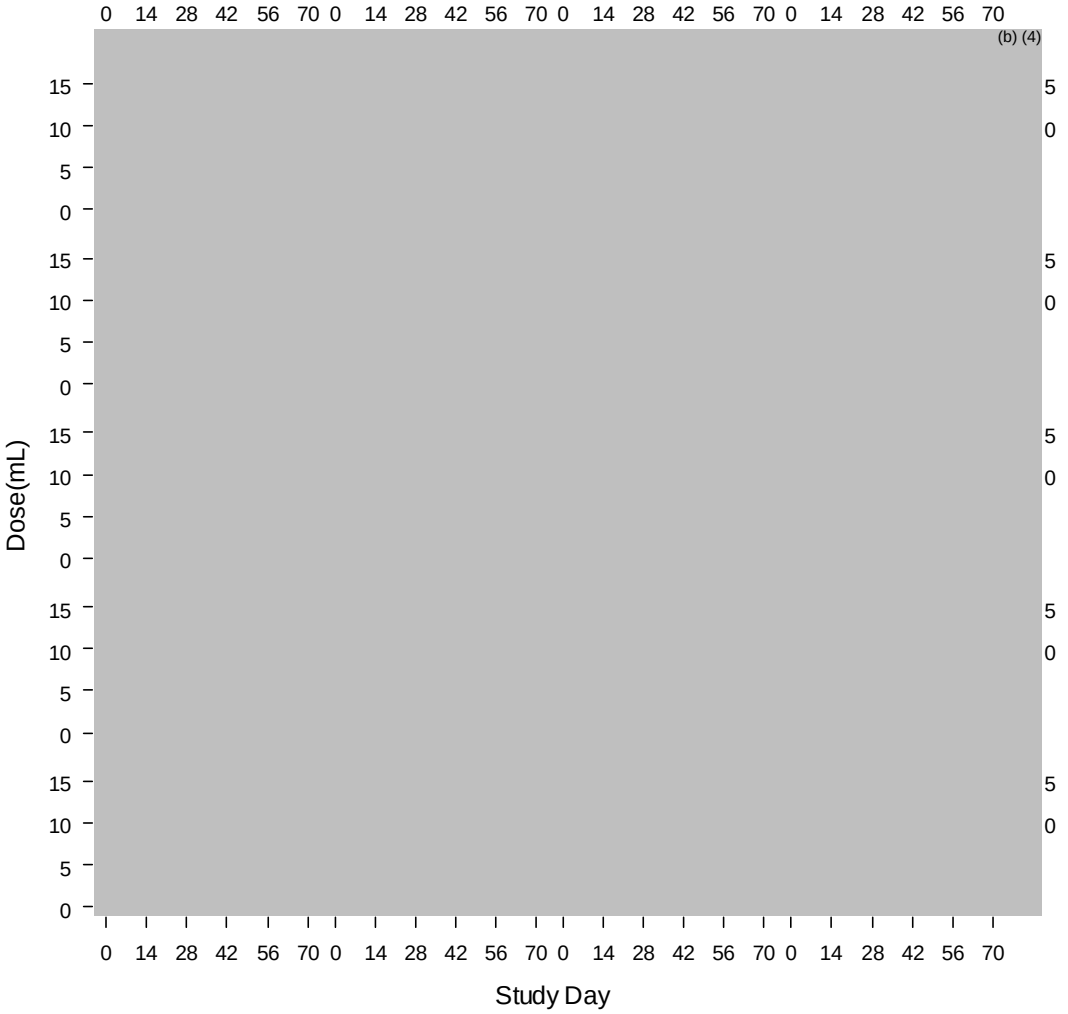
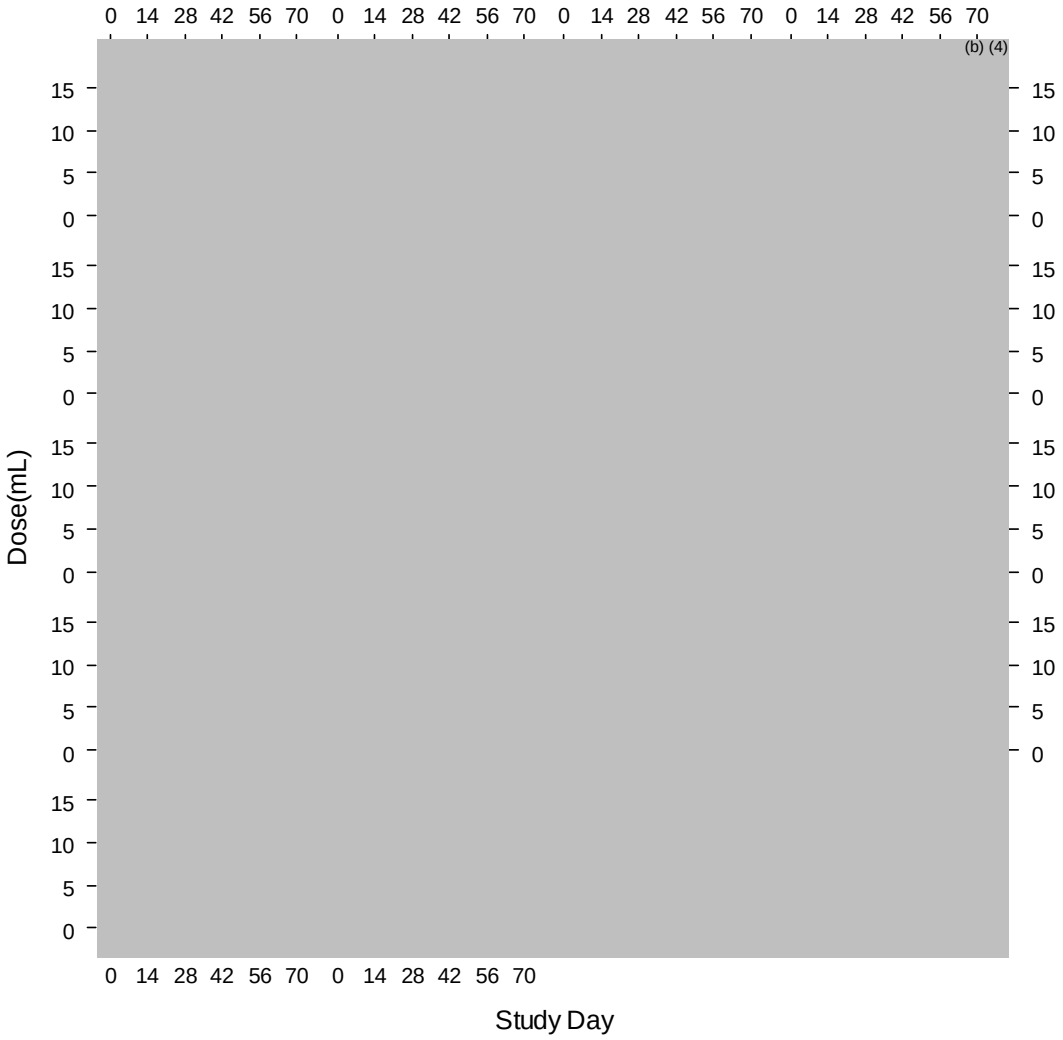


Figure 8 - Doses (mL) Received by Study Day for Subjects on Placebo (FH-00-01)



Eight (40%) of glycopyrrolate subjects down-titrated their dose or discontinued from the study before completing the full dosing period. Of the 8 glycopyrrolate subjects who down-titrated at any time or discontinued treatment, 3 (38%) were classified as non-responders (1003, 2004, 6009), while of the 12 subjects who did not down-titrate during the study, only 2 (17%) were non-responders (7001, 6011). See Table 23.

Table 23 – Titration Status and Response for Glycopyrrolate Subjects (FH-00-01)

	Glycopyrrolate (N=20)		
	Responder	Non-Resp.	Total
Increased dose to maximum level and did not titrate downward	6 (30%)	1 (5%)	7 (35%)
Increased dose to less than the maximum level and did not titrate downward	4 (20%)	1 (5%)	5 (25%)
Down titrated at any time (including treatment discontinuation before Week 6)	5 (25%)	3 (15%)	8 (40%)

3.2.1.2 Adverse Events

All glycopyrrolate subjects and most placebo subjects experienced at least one adverse event during the study. The most common adverse events (and occurring at a rate greater than placebo) were dry mouth, vomiting, constipation, flushing, and nasal congestion. The sponsor classified adverse events using 'reported' (verbatim) terms, 'modified' reported terms (sponsor-defined), and 'dictionary-derived' terms (this reviewer could not identify which dictionary was used). The study report used the 'modified' reported terms while this review (Table 24) uses the dictionary terms. Thus there are a few discrepancies for the counts of similar terms. For example, the reviewer's table combines 'constipation' and 'constipation-aggravated' into one category, while the study report[5] reports these categories separately.

Table 24 – Adverse Events occurring in at Least 10% of Glycopyrrolate Subjects (FH-00-01)

	Glycopyrrolate N=20	Placebo N=18
Any Adverse Event	20 (100%)	16 (89%)
Most Common Adverse Events		
Dry Mouth	8 (40%)	2 (11%)
Vomiting	8 (40%)	2 (11%)
Constipation	7 (35%)	4 (22%)
Flushing	6 (30%)	3 (17%)
Nasal Congestion	6 (30%)	2 (11%)
Somnolence	4 (20%)	5 (28%)
Pyrexia	3 (15%)	5 (28%)
Diarrhea	3 (15%)	4 (22%)
Headache	3 (15%)	1 (6%)
Sinusitis	3 (15%)	1 (6%)
Upper Resp. Tract Infection	3 (15%)	0 (0%)
Urinary Retention	3 (15%)	0 (0%)
Mood Altered	2 (10%)	2 (11%)
Agitation	2 (10%)	1 (6%)
Heart Rate Increased	2 (10%)	1 (6%)
Seasonal Allergy	2 (10%)	0 (0%)

Source: Reviewer's analysis

3.2.2 Study Sc-GLYCO-06-01

3.2.2.1 Extent of Exposure

Study Sc-GLYCO-06-01 used the same dosing titration schedule as Study FH-00-01. The planned exposure in Study Sc-GLYCO-06-01 was 24 weeks. Approximately 75% of the subjects continued dosing for at least 22 weeks, while approximately 9% of subjects dosed for less than 4 weeks. The minimum dosing duration was 2 days and the maximum was 197 days (28 weeks).

[5] pg 179 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5351-stud-rep-contr\fh-00-01\fh-00-01\report-body.pdf

Table 25 – Duration of Exposure (Sc-GLYCO-06-01)

Weeks of Exposure	N=137
≥ 22 Weeks (154 days)	103 (75%)
≥ 16 Weeks (112 days)	108 (79%)
≥ 10 Weeks (70 days)	114 (83%)
≥ 4 Weeks (28 days)	124 (91%)

3.2.2.2 Adverse Events

Many of the more common adverse events observed in Study FH-00-01 were also the more common adverse events observed in Study Sc-GLYCO-06-01, such as constipation, vomiting, diarrhea, dry mouth, flushing, and nasal congestion. The adverse events observed in at least 5% of subjects in Study Sc-GLYCO-06-01 are presented in Table 26.

Table 26 – Adverse Events occurring in at least 5% of Subjects (Sc-GLYCO-06-01)

	Glycopyrrolate N=137
Any Adverse Event	122 (89%)
Most Common Adverse Events	
Constipation	28 (20%)
Vomiting	24 (18%)
Diarrhea	24 (18%)
Pyrexia	20 (15%)
Nasal Congestion	15 (12%)
Dry Mouth	15 (11%)
Flushing	15 (11%)
Otitis Media	12 (9%)
Upper Resp. Tract Infection	11 (8%)
Rash	11 (8%)
Convulsion	11 (8%)
Urinary Tract Infection	11 (8%)
Dysuria	9 (7%)
Irritability	8 (6%)
Influenza	7 (5%)
Somnolence	7 (5%)
Epistaxis	7 (5%)
Pharyngitis Streptococcal	7 (5%)
Pneumonia	7 (5%)

Source: pg 46-47 of \\CDSESUB1\EVSPROD\NDA022571\\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-sialorrhea-in-children\5352-stud-rep-uncontr\sc-glyco-06-01\sc-glyco-06-01\report-body.pdf

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Due to the small sample size of Study FH-00-01, the gender, age, and race subgroups also have very small sample sizes and thus it is difficult to draw meaningful comparisons. However, in all subgroups, the proportion of glycopyrrolate responders was greater than the proportion of placebo responders. See Figure 9 and Figure 10.

Figure 9 – Proportion of Responders by Gender and Age Group (Study FH-00-01)

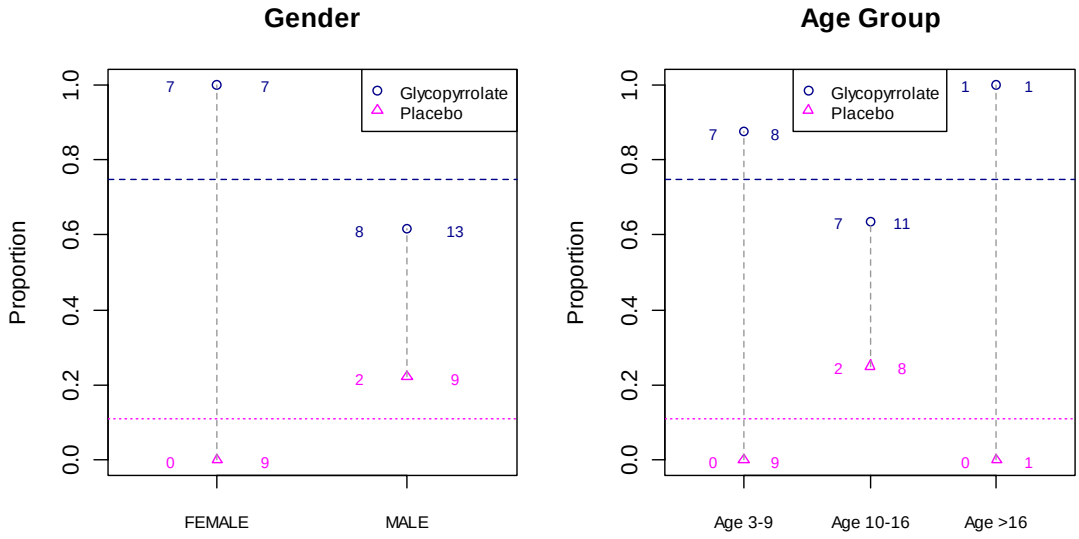
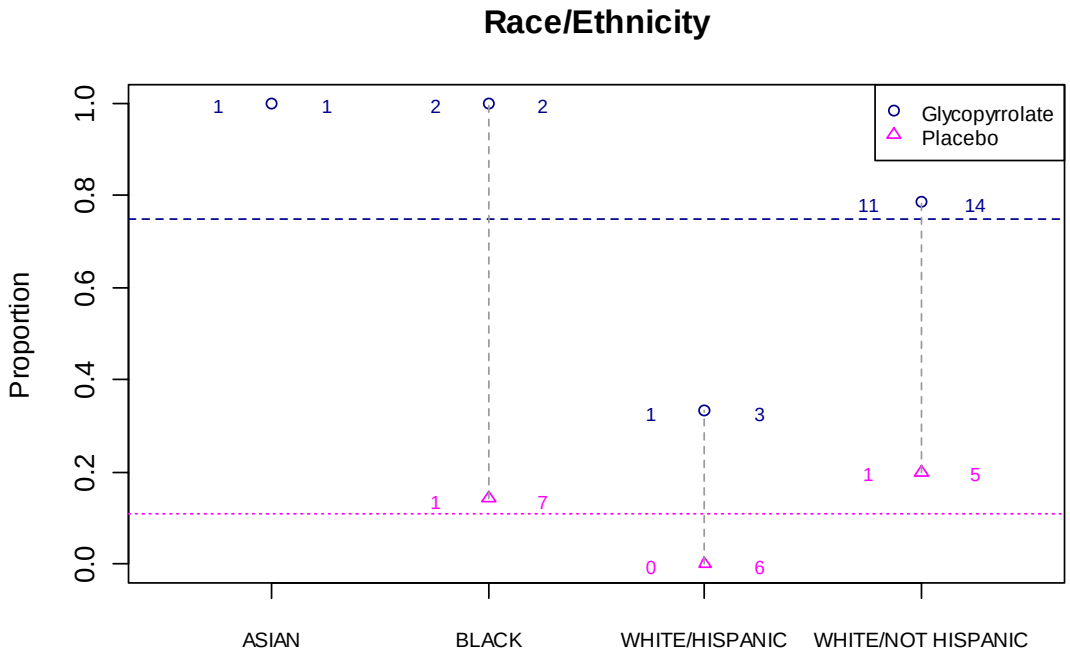


Figure 10 – Proportion of Responders by Race/Ethnicity (Study FH-00-01)



4.2 Other Special/Subgroup Populations

None.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has conducted a single placebo-controlled clinical study with support from an open-label single-arm study. The Agency agreed at the Pre-IND meeting for this product that a single controlled study with additional supportive information may be acceptable for filing. Although the study findings are highly statistically significant, the study does have a number of issues which make the interpretation of the findings challenging. These issues include changes to the study population and endpoints during the study and lack of detail in the protocol leading to a variety of ways to classify subjects as responders or non-responders. The protocol underwent a fairly substantial revision after approximately half of the subjects were enrolled. The protocol revision modified the inclusion criteria and the list of secondary endpoints. Two of the key changes to the inclusion criteria were

- to change the age range [redacted] (b) (4) to 3 – 16 years
- to expand the underlying diagnosis [redacted] (b) (4) to cerebral palsy, [redacted] (b) (4) or any other neurologic impairment or condition

The amendment also proposed restricting the analysis to subjects age 3 – 16 years. Prior to the amendment, two subjects >16 years of age had already completed the study. This review provides results from both the pediatric subset and the full enrolled population; there were no substantial differences between the two analyses.

The protocol specified that the primary efficacy endpoint was the change from baseline to Week 8 evaluations of the mTDS administered by parents/caregivers. An analysis of the proportion of responders (subjects with at least a 3-point improvement from baseline in mTDS) at Week 8 was listed in the protocol as a secondary endpoint. At the guidance meeting held with the Agency on 3/20/2007, the Agency recommended using the mTDS responder analysis at Week 8 as the primary efficacy endpoint.

Another issue which impacted the analysis was the handling of missing data—both single missing observations within an assessment day and completely missing assessment days due to dropout. The protocol and SAP provided inconsistent directions for handling missing assessment days. In addition, the neither the protocol nor the SAP provided any information about how to handle missing observations within an assessment day. Different interpretations of the way to handle missing data as well as different ways to compute the baseline means led to different analyses in the study report, ISE and reviewer's analysis. However, all of the various analyses led to statistically significant results.

Although the inclusion criteria stated that subjects were to have 'profuse, severe drooling in the absence of treatment so that clothing becomes damp on most days (5-7 days per week),' mTDS scores were not actually used to determine eligibility. With a responder defined as subjects whose mean daily score reduced by at least 3 units, baseline scores have an impact as to whether a subject is classified as a responder. The three subjects with the lowest baseline mTDS mean scores in Study FH-00-01 were all non-responders (there were a total of 5 non-responders on the glycopyrrolate arm).

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

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

5.2 Conclusions and Recommendations

Glycopyrrolate oral solution had demonstrated efficacy versus placebo in the treatment of pathologic drooling in patients with cerebral palsy or other neurologic conditions in one study. The applicant conducted a placebo-controlled study in 38 subjects and a single-arm, open-label study in 137 subjects.

Study FH-00-01 treated 38 subjects age 3 to 23 with either glycopyrrolate or placebo for 8 weeks. Parents or caregivers assessed drooling levels using the 9-point Modified Teacher's Drooling Scale (mTDS). On designated assessment days, the parents and caregivers recorded mTDS scores 4 times per day (before the morning dose and then 2 hours after each dose. Daily mTDS scores were summarized with the mean of the three post-dose assessments (mid-morning, afternoon, evening). Treatment response was defined as at least a 3-point improvement from baseline to Week 8 in daily mean mTDS scores. The reviewer's analyses for the number of responders as well as the mean change from baseline are presented in Table 27.

Table 27 – Reviewer's Efficacy Analyses (FH-00-01)

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

The protocol and statistical analysis plan did not provide adequate detail about how to calculate the baseline mean mTDS score for each subject (data were collected on two baseline assessment days) and was not sufficiently clear about how to handle missing data. Due to the lack of detail in the protocol, the original study report and the integrated summary of effectiveness (ISE) present the results in two different ways. In addition, this reviewer's analyses differ from both of the applicant's analysis. The issues leading to the variations in the analyses result from:

- the choice of which observations to include in a subject's baseline mean calculation
- the handling of missing data
- the handling of subjects over age 16

The applicant's results are restricted to subjects age 3 to 16 and to subjects with at least one pre-baseline and one post-baseline assessment. As can be seen in Table 28, the applicant's responder rate estimates for glycopyrrolate range from 47% to 78% and thus the analysis issues regarding the baseline mean calculation and handling of missing data do have an impact on the estimates. However, all of the analyses lead to statistically significant results and the conclusion that glycopyrrolate is superior to placebo in the treatment of pathologic drooling.

Table 28 – Applicant's Responder Analyses for Ages 3 – 16 (FH-00-01)

	Glycopyrrolate	Placebo	p-value
Study Report	9/19 (47%)	1/17 (6%)	0.004
ISE	14/18 (78%)	3/16 (19%)	0.0016

The applicant also conducted an open-label, single-arm, 24-week study (SC-Glyco-06-01) in 137 subjects. Approximately half of the subjects met the responder definition at Week 24 in this uncontrolled study.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, PhD
Date: 5/20/2010

Statistical Team Leader: Mohamed Alosh, PhD

cc:
DDDP/Walker
DDDP/Kelsey
DDDP/Hyman
DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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/

KATHLEEN S FRITSCH
05/20/2010

MOHAMED A ALOSH
05/20/2010
Concur with the primary reviewer's conclusion/recommendation.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-571/0 **Applicant:** Sciele **Stamp Date:** 9/28/09

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

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

	Content Parameter for RTF	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Only final protocol
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?__Yes_____

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		X		'Daily Mean' vague
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		Common subj. not id'd
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Requests to the Applicant for the 74-Day Letter

Review Issues

1. In Study FH-00-01, the method for calculating endpoints based on mean mTDS values (change from baseline and responders) is not clear. The mean values appear to be calculated differently for the original study report and the ISE. The results from the *study report* for Study FH-00-01 cannot be replicated from the analysis datasets provided. It is difficult to interpret study findings when an endpoint is not clearly or uniquely defined.

2. The integrated summary of safety does not provide information on or account for subjects who may have participated in both Studies FH-00-01 and SC-GLYCO-06-01.

Information Request

1. Provide a detailed algorithm for how mean daily mTDS values (both the baseline value and for follow-up visits), change from baseline values, and responders were calculated for the Study Report for Study FH-00-01 and the ISE. Include the rules for handling missing data. Provide an analysis dataset (in SAS transport format) for Study FH-00-01 (similar to the submitted datasets ade2.xpt and adef.xpt) that uses the definitions of mean mTDS and responders used in the study report (including baseline). Include the treatment assignments. This dataset should be suitable for replicating the analyses based on mTDS for each visit as reported in the study report.

2. Provide a dataset (in SAS transport format) that includes a unique subject identifier that indentifies subjects who participated in both Studies FH-00-01 and SC-GLYCO-06-01 using a single subject ID. The dataset should include, at a minimum, the current variables USUBJID and STUDYID, and a new variable that is unique to each subject and links subjects that participated in both studies.

3. Submit all earlier versions of Protocol FH-00-01 (Original, Amendment 1, and Amendment 2).

4. Provide a listing which links the investigator names to the investigator numbers in Study FH-00-01 (or identify where to find this information in the submission).

Reviewing Statistician Date

Supervisor/Team Leader Date

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/s/

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10/28/2009

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10/28/2009