CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-212

STATISTICAL REVIEW(S)

NDA 22-212 ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%)

MEMORANDUM

DATE: June 10, 2008

FROM: Mohammad Huque, Ph.D.
Division Director
Division of Biometrics IV
Office of Biostatistics/OTS

SUBJECT: Division Director's Decisional Memo for NDA 22-212, ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%)

Background:

This Memorandum is to evaluate the overall evidence of efficacy based on NDA 22-212 (Sirion Therapeutics, Inc.) to support the approval for the use of ST-601 (difluprednate Ophthalmic Emulsion, 0.05%) dosed either BID or QID, in subjects with inflammation following ocular surgery.

The phase 3 drug development program consisted of two phase 3 studies (ST-601A-002A, ST- 601A-002B) of identical study design. The primary objective was to assess the efficacy and safety of ST-601 compared to placebo for the treatment of inflammation and pain following ocular surgery. The primary efficacy endpoint as recommended by the Agency was the difference in the proportions of subjects with an anterior chamber cell grade of 0 on Day 8 between the difluprednate QID group and the placebo group. Subjects were randomized to 1 of 4 treatment arms: one drop of either difluprednate or placebo, either twice a day (BID) or four times a day (QID).

As stated in the statistical reviews and based on the ITT results from the two phase 3 studies indicate that a statistically persuasive evidence supports difluprednate therapy (QID) as effective in clearing anterior inflammation (as evidenced by the primary endpoint, proportion of subjects with an anterior chamber cell grade of 0 on Day 8) and the clearing achieved on Day 8 was sustainable. The proportion of ITT Subjects with pain /discomfort score of 0 on Day 3 was statistically significant for difluprednate QID compared to placebo. There was no major safety issues reported.

Note that for the BID regimen, though the above endpoint was statistically significant for the ST-601A-002B, but it failed to achieve statistical significance for the second study ST-601A-002A.

Conclusions and Recommendations

In conclusion, based on evaluating the overall evidence of efficacy and safety, Difluprednate QID regimen demonstrated statistically persuasive evidence, as an effective treatment in subjects with pain and inflammation following ocular surgery.

Mohammad Huque, Ph.D.
Director,
Division of Biometrics IV
Office of Biostatistics

APPENDIX:

Table 1: ITT analysis results for study ST-601A-002A

FDA Recommended/ Sponsor's Primary Endpoint		Dosing Regimen	ST-601 n/N %	Placebo n/N %	Difference (95%CI)[1]	p-value[2]
Proportion of ITT Subjects with Clearing (= 0) of AC Cells by Day 8	FDA	QID	13/55 23.6	11/105 10.5	13.2 (-0.9, 27.2)	0.0302
		BID	9/57 15.8	11/105 10.5	5.3 (-7.2, 17.8)	0.3584
Proportion of ITT Subjects with Clearing (≤ 1) AC Cells by Day 8	Sponsor's Primary	QID	19/55 34.5	13/105 12.4	22.2 (6.7, 37.6)	0.0014
	Sponsor's Secondary[3]	BID	17/57 29.8	13/105 12.4	17.4 (2.6, 32.2)	0.0066

[1] 95% confidence limits on the difference (unstratified). [2]P-value is two-sided and is based on stratified analysis using investigative site(s) as pre-specified and LOCF was used to impute missing values.
[3]Sponsor's proposed dosing is BID but the statistical analysis was based on a sequential testing in the order of QID and BID

Table 2: ITT analysis results for study ST-601A-002B

FDA Recommended/ Sponsor's Primary Endpoint		Dosing Regimen	ST-601 n/N %	Placebo n/N %	Difference (95%CI)[1]	p-value[2]
Proportion of ITT Subjects with Clearing (= 0) of AC Cells by Day 8	FDA	QID	11/52 21.2	6/113 5.3	15.8 (2.6, 29.1)	0.0012
		BID	10/53 18.9	6/113 5.3	13.6 (0.9, 26.3)	0.0075
Proportion of ITT Subjects with Clearing (≤ 1) of AC Cells by Day 8	Sponsor's Primary	QID	18/52 34.6	7/113 6.2	28.4 (13.3, 43.5)	<0.0001
	Sponsor's Secondary [3]	BID	16/53 30.2	7/113 6.2	24.0 (9.5, 38.5)	<0.0001

[1] 95% confidence limits on the difference (unstratified). [2]P-value is two-sided and is based on stratified analysis using investigative site(s) as pre-specified and LOCF was used to impute missing values.
[3]Sponsor's proposed dosing is BID but the statistical analysis was based on a sequential testing in the order of QID and BID

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Mohammad Huque
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NDA 22-212 ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%)

MEMO TO FILE

DATE: June 9, 2008

FROM: Thamban Valappil, Ph.D.
Statistical Team Leader
Division of Anti-infective and Ophthalmology Products

DRUG NAME: ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%)

INDICATION: Treatment of pain and inflammation following ocular surgery

APPLICANT: Sirion Therapeutics, Inc.

SUBJECT: NDA 22-212, Secondary Statistical Review and Evaluation

1.1 Introduction:

This secondary review is based on NDA 22-212 to support approval for the use of ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%), dosed either BID or QID, in subjects with inflammation following ocular surgery. Sirion's proposed dosing regimen of ST-601 is BID. In this submission, Sirion has included two identical double-blind, placebo-controlled Phase 3 U.S. studies (ST-601A-002A and ST-601A-002B) which used both the BID and QID dosing regimens of ST-601. Sirion considers results from these two trials as the primary support for approval of ST-601. The primary focus of this statistical review is on the efficacy results based on studies, ST-601A-002A (Study 002A) and ST-601A-002B (Study 002B). More details on the analysis can be found in Dr. Kadoorie's statistical review.

Table 1: ITT analysis results for study ST-601A-002A

FDA Recommended/ Sponsor's Primary Endpoint		Dosing Regimen	ST-601 n/N %	Placebo n/N %	Difference (95%CI)[1]	p-value[2]
Proportion of ITT Subjects with Clearing (= 0) of AC Cells by Day 8	FDA	QID	13/55 23.6	11/105 10.5	13.2 (-0.9, 27.2)	0.0302
		BID	9/57 15.8	11/105 10.5	5.3 (-7.2, 17.8)	0.3584

Proportion of ITT Subjects with Clearing (≤ 1) AC Cells by Day 8	Sponsor's Primary	**QID**	19/55 34.5	13/105 12.4	22.2 (6.7, 37.6)	0.0014
	Sponsor's Secondary[3]	**BID**	17/57 29.8	13/105 12.4	17.4 (2.6, 32.2)	0.0066

[1] 95% confidence limits on the difference (unstratified). [2]P-value is two-sided and is based on stratified analysis using investigative site(s) as pre-specified and LOCF was used to impute missing values. [3]Sponsor's proposed dosing is BID but the statistical analysis was based on a sequential testing in the order of QID and BID

Table 2: ITT analysis results for study ST-601A-002B

FDA Recommended/ Sponsor's Primary Endpoint		**Dosing Regimen**	**ST-601 n/N %**	**Placebo n/N %**	**Difference (95%CI)[1]**	**p-value[2]**
Proportion of ITT Subjects with Clearing (= 0) of AC Cells by Day 8	FDA	**QID**	11/52 21.2	6/113 5.3	15.8 (2.6, 29.1)	0.0012
		BID	10/53 18.9	6/113 5.3	13.6 (0.9, 26.3)	0.0075
Proportion of ITT Subjects with Clearing (≤ 1) of AC Cells by Day 8	Sponsor's Primary	**QID**	18/52 34.6	7/113 6.2	28.4 (13.3, 43.5)	<0.0001
	Sponsor's Secondary [3]	**BID**	16/53 30.2	7/113 6.2	24.0 (9.5, 38.5)	<0.0001

[1] 95% confidence limits on the difference (unstratified). [2]P-value is two-sided and is based on stratified analysis using investigative site(s) as pre-specified and LOCF was used to impute missing values. [3]Sponsor's proposed dosing is BID but the statistical analysis was based on a sequential testing in the order of QID and BID

1.2 Conclusions and Recommendations

Overall findings from studies 002A and 002B provided adequate evidence of efficacy in the QID regimen but not in the BID regimen. Overall findings were primarily based on an analysis of 'the proportion of ITT subjects with complete clearing (count = 0) of anterior chamber cells by day 8' as a clinically meaningful primary endpoint recommended by the Agency, although the Sponsor's definition of complete clearance was based on count ≤ 1. For the QID regimen, the Agency recommended endpoint was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B. In addition, for the QID regimen, both studies 002A and

002B showed significance for a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3.'

In summary, based on evaluating the Agency recommended primary and secondary analysis results and other considerations, a statistically persuasive evidence was presented only for the QID regimen as an effective treatment in subjects with pain and inflammation following ocular surgery.

Thamban Valappil, Ph.D.
Statistical Team Leader,
CDER/OTS/OB/DBIV

Concur:

Mohammad Huque, Ph.D.
Director,
Division of Biometrics IV
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/s/

Thamban Valappil
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Secondary Statistical Review

Mohammad Huque
6/10/2008 04:43:30 PM
BIOMETRICS

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

CLINICAL STUDIES

NDA # :	22-212
Drug Name:	ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%)
Indication(s):	Treatment of pain and inflammation following ocular surgery
Applicant:	Sirion Therapeutics, Inc.
Stamp Date:	December 26, 2007
PDUFA Goal Date:	June 26, 2008
Reviewer Completion Date:	May 23, 2008
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products
Documents Reviewed:	\\CDSESUB1\N22212\N_000\2007-12-26
Statistical Reviewer:	Christopher Kadoorie, Ph.D.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Clinical Reviewer(s):	Sonal Wadhwa, M.D.
Project Manager:	Jane Dean, RN, MSN.

TABLE OF CONTENTS

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Introduction

Sirion Therapeutics, Inc. has submitted NDA 22-212 to support approval for the use of ST-601 (Difluprednate Ophthalmic Emulsion, 0.05%), dosed either BID or QID, in subjects with inflammation following ocular surgery. Sirion's proposed dosing regimen of ST-601 is BID. In this submission, Sirion has included two identical double-blind, placebo-controlled Phase 3 U.S. studies (ST-601A-002A and ST-601A-002B) which were conducted evaluating both the BID and QID dosing regimens of ST-601. Sirion considers results from these two trials as the primary support for approval of ST-601. Additional supportive evidence is also presented from 8 clinical efficacy and safety studies conducted by Senju Pharmaceuticals which included two randomized, controlled studies conducted in post-surgical inflammation (one phase 3 and one phase 2). The primary focus of this statistical review is on efficacy results presented in Phase 3 studies, ST-601A-002A and ST-601A-002B, hereinafter referred to as Studies 002A and 002B.

1.2 Conclusions and Recommendations

Overall findings from studies 002A and 002B provided adequate evidence of efficacy in the QID regimen but not the BID regimen. Overall findings were primarily based on an analysis of 'the proportion of ITT subjects with complete clearing (count = 0) of anterior chamber cells by day 8' which had been previously recommended by the Agency as a clinically meaningful primary endpoint. For the QID regimen, this endpoint was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B.

For the QID regimen, both studies 002A and 002B also showed significance in a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3.' In the BID regimen, neither Study 002A nor Study 002B showed significance for this endpoint. Similarly for several other secondary endpoints of Studies 002A and 002B, patients on the QID regimen were observed to have more favorable outcomes compared to patients on a BID regimen (Table 10). Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QID regimen but not the BID regimen as an effective treatment in subjects with inflammation following ocular surgery.

1.3 Brief Overview of Clinical Studies 002A and 002B

Studies 002A and 002B were double-masked, randomized, placebo-controlled clinical trials evaluating ST-601 in the treatment of inflammation following ocular surgery. Each study was conducted under an identical but separate protocol. In each study, the efficacy and safety of ST-601, dosed either BID or QID, was compared with placebo (vehicle) in subjects who had undergone unilateral ocular surgery.

Study Endpoints

The primary efficacy endpoint was the proportion of subjects with an anterior chamber cell grade of "0" (anterior chamber cells ≤ 1) on Day 8 as compared between the ST-601 QID and placebo groups. This primary endpoint and an additional 5 secondary endpoints were compared in a hierarchical manner:
1. The proportion of subjects with an anterior chamber cell grade of "0" on Day 8 for ST-601 BID;
2. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 QID;
3. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 BID;
4. The proportion of subjects with an anterior chamber cell grade of "0" on Day 15 for ST-601 QID;
5. The proportion of subjects with an anterior chamber cell grade of "0" on Day 15 for ST-601 BID.

Study Duration

Studies 002A and 002B included a 14-day tapering period following the 14-day treatment period, which began on the first day after ocular surgery. Follow-up safety and efficacy evaluations also were conducted on Days 29 ± 2 and at 1 week after the last dose of study medication.

1.4 Statistical Issues and Findings

Statistical issues were identified by the following:

- The Sponsor's primary endpoint defined as 'the proportion of subjects with clearing (grade of "0" with count ≤ 1) of anterior chamber cells by day 8' was not considered by the FDA to be clinically relevant.

  Statistical Reviewer Comments: *The Agency had recommended that the Sponsor define the primary endpoint as 'the proportion of ITT subjects with complete clearing (count = 0) of anterior chamber cells by day 8'. Therefore, overall study results were evaluated based on meeting the FDA recommended primary endpoint.*

- Study 002B failed to show significance in the BID arm based on the FDA recommended endpoint of 'the proportion of subjects with clearing (count = 0) of anterior chamber cells by day 8.' Both Study 002A and Study 002B also failed to show significance in the BID arm for a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3'.

  Statistical Reviewer Comments: *Based on primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QID regimen but not the BID regimen as an effective treatment in subjects with inflammation following ocular surgery.*

- Sirion's proposed dosing regimen of ST-601 is BID, however, Studies 002A and 002B define the primary endpoint in terms of the QID regimen rather than the BID regimen.

  Statistical Review Comments: *Sirion's specification of primary and secondary endpoints in the design of studies 002A and 002B may weaken overall evidence presented for the BID regimen since BID regimen findings are based on secondary rather than primary endpoints.*

- Sirion's prioritized hypothesis testing alternates between testing the QID and BID regimens. Lack of significance in the BID regimen can affect significant findings in the QID regimen.

  Statistical Reviewer Comments: *Due to a lack of significance in the fourth endpoint tested in Studies 002A and 002B, 'the proportion of subjects with pain/discomfort on Day 3 for ST-601 BID', significance could not be shown for the fifth and sixth tested endpoint, 'proportion of subjects with an AC cell grade of "0" on Day 15' for ST-601QID and for ST-601 BID, respectively.*

- The Sponsor's pre-specified primary analysis was based solely upon a Mantel-Haenszel chi-square test stratified on investigative sites and did not consider an unstratified analysis.

  Statistical Reviewer Comments: *The Agency generally recommends an unstratified analysis as providing the most useful and conservative comparison. While a stratified approach may provide useful information in cases where the initial randomization was also stratified on investigative site (e.g. Studies 002A and 002B), unstratified analyses should be included for comparison and should provide consistent information.*

- The actual randomization allocations among treatment arms were not carried out as planned. This failure to appropriately randomized patients as planned resulted in a loss of study power.

  Statistical Reviewer Comments: *The planned randomization was 2:2:1:1 with a larger numbers of patients randomized to the ST-601 treatment versus placebo. The randomization conducted was 1:1:1:1 with equal numbers of patients randomized to placebo and ST-601 treatment arms. Since the placebo BID and placebo QID arms were pooled for comparisons, comparisons of ST-601 BID versus placebo (pooled) and ST-601 QID versus placebo (pooled) each involved approximately twice as many placebo treated patients in comparison to ST-601 treated patients. This is an inefficient study design.*

- Additionally, the Sponsor's methodology for allocating study sites to either study 002A and study 002B was neither consistent with the final Statistical Analysis Plan (SAP) nor agreed upon by the Agency.

  Statistical Reviewer Comments: *The final SAP states that sites located north of latitude 37° would be allocated in study 0002B while sites located south of latitude 37° to be allocated in Study 002A. However, 4 sites (#034, #048, #049 and #054) were not allocated according to this guideline as reflected by subject identifications in these sites. In the analyses, however,*

these subjects were analyzed in groups consistent with the protocol. Since changes in site allocation were made in a blinded manner and based on evaluability considerations (as reported by the sponsor), there is less of a concern for potential treatment biases.

- Some investigative sites contributed a disproportionately large number of cases or had unusually high rates of complete clearing (=0) of anterior chamber cells by Day 8. This raises concerns regarding the robustness of study findings and the degree to which study findings may be influenced by potential biases.

  Statistical Reviewer Comments: *In Study 002A, sites #029 and #054 contributed a disproportionately large number of cases of complete clearing (=0) of anterior chamber cells by Day 8. Of the total number of 33 cases, site #029 had 11 (33.3%) of these cases while Site #054 had 8 (24.2%). In Study 002B, of the 21 cases for ST-601 treated patients, site #030 had 8 (38.1%) cases while the next highest site had 3 (14.3%) cases. Of the 10 ST-601 BID cases, there were 5 (50.0%) cases from site #030 and 2 (20%) from the next highest site.*

  In Study 002A, site #029 had unusually high rates of complete clearing (=0) of anterior chamber cells by Day 8.The proportion of ITT subjects with clearing (= 0) of AC cells was higher at 11/26 (42.3%) versus 33/217 (11.5%) for all other sites (p=.0007). Similarly, in Study 002B for site #030, the proportion of ST-601 BID treated subjects with clearing (= 0) of AC cells was higher at 5/9 (55.6%) versus 5/44 (11.4%) (p=.002).

- The Division of Scientific Inquiry (DSI) has noted opposite extremes in primary efficacy endpoint data coming from sites #030 (Dr. Silverstein) and #034 (Korenfeld) of Study 002B and has investigated these sites.

  Statistical Reviewer Comments: *Based on recent discussions with DSI on their preliminary investigations, opposite extremes in primary efficacy endpoint data coming from sites #030 and #034 appear to be chance variation. Also, no significant finds were observed in either site and no FDA 483 was issued. Dr. Silverstein (site #030) was advised to develop procedures for avoiding data entry errors and to ensure/document that all employees recording study data are properly trained in the eCaseLink data system. Please refer to DSI investigational report for more updated information.*

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Difluprednate is a synthetic steroidal prednisolone derivative first developed by Mitsubishi Chemical Corporation (currently Tokyo Mitsubishi Pharmaceutical Co., Ltd.). Difluprednate

was first developed as a dermatological preparation (marketed in Japan under the product name Myser®), and subsequently was developed in Japan as an ophthalmic emulsion by Senju Pharmaceutical Co., Ltd., of Osaka, Japan.

2.1.2 Sponsor's Rationale

There are currently several steroidal anti-inflammatory ophthalmic solutions used for treating ocular inflammation, but these treatments may show insufficient therapeutic outcomes when used according to the labeled dosing regimens. Thus, the most potent ocular steroid currently in the US formulary, prednisolone acetate, is empirically deemed by physicians to less effective than needed, as evidenced by the recommendation to use it up to 4 times an hour, instead of the indicated 4 times a day.

ST-601 (difluprednate ophthalmic emulsion 0.05%) was developed to meet the need for a more potent ophthalmic topical corticosteroid therapy. According to the Sponsor, Difluprednate has a potency closely equivalent to betamethasone and greater potency at the glucocorticoid receptor than prednisolone (Wyatt, 2001). Thus, ST-601 may reduce the amount of damage done to the eye from the sequelae of inflammation. The Sponsor also mentions that the emulsion formulation of ST-601 enables consistent dosing without the need for shaking (as is the case with the ophthalmic prednisolone acetate suspension), while providing better corneal penetration than a difluprednate suspension.

2.2 Data Sources

Files of \\Cdsesub1\n22212\N_000\2007-12-26

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The primary efficacy endpoint was the proportion of subjects with an anterior chamber cell grade of "0" (anterior chamber cells ≤ 1) on Day 8 as compared between the ST-601 QID and placebo groups. This primary endpoint and an additional 5 secondary endpoints were compared in a hierarchical manner according to the following pre-specified order:

1. The Proportion of subjects with an AC cell grade of "0" on Day 8 for ST-601 BID;
2. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 QID;
3. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 BID;
4. The proportion of subjects with an AC cell grade of "0" on Day 15 for ST-601 QID;
5. The proportion of subjects with an AC cell grade of "0" on Day 15 for ST-601 BID.

Table 1: Prioritized Hypothesis Testing (Studies 002A & 002B)

	Day 3/4		Day 8		Day 15		Day 29	
	QID	BID	QID	BID	QID	BID	QID	BID
Cell grade = 0"	1st(1)	2nd	5th	6th				
Pain/discomfort score=0	3rd	4th						

(1) This was the primary endpoint. Secondary endpoints are 2nd, 3rd, etc.
Source: Sponsor Table

Table 2: Schedule of Events (Studies 002A & 002B)

Evaluation	Day 0	Screening/ Baseline/ Treatment Day 1 (Visit 1)	Treatment Period			Follow-up	
			Day 3 (or 4) (Visit 2)	Day 8 ± 1 (Visit 3)	Day 15 ± 2 (Visit 4)	Day 29 ± 2 (Visit 5)	1 Week After Last Study Drug Dose (Visit 6)
Surgery	X						
Informed consent (1)		X					
Inclusion/exclusion criteria		X					
Demographics (1)		X					
Medical/ocular history (1)		X					
Urine pregnancy test (2)		X					
Randomization		X					
Slit lamp exam (signs)							
Anterior chamber cell (3)		X	X	X	X	X	X
Anterior chamber Flare		X	X	X	X	X	X
Chemosis		X	X	X	X	X	X
Bulbar conjunctival injection		X	X	X	X	X	X
Ciliary injection		X	X	X	X	X	X
Corneal oedema		X	X	X	X	X	X
Keratic precipitates		X	X	X	X	X	X
VAS (symptoms)							
Eye pain/discomfort		X	X	X	X	X	X
Photophobia		X	X	X	X	X	X
IOP		X	X	X	X	X	X
Corneal endothelial cell Density		X					X
BCVA		X	X	X	X	X	X
Ophthalmoscopy		X			X		X
Drug dispensing		X					
AE assessment		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X

documentation							

AE, adverse event; BCVA, best-corrected visual acuity; IOP, intraocular pressure; VAS, Visual Analogue Scale
(1) May be done prior to surgery or on Day 1, at investigator's option.
(2) May be done on Day 0 or Day 1.
(3) Anterior chamber cell count and grade.
Source: Sponsor Table

Inclusion Criteria

Each subject had to meet all of the following criteria to be eligible for the study.
1. Unilateral ocular surgery on the day prior to study enrollment.
2. Anterior chamber cell grade ≥ "2" on the day after surgery (Day 1).
3. Aged 2 years or older on the day of consent.
4. Negative urine pregnancy test on Day 1 for postmenarchal subjects; negative urine pregnancy test for premenarchal subjects at the investigator's discretion.
5. Provide signed written consent prior to entering the study or signed written consent from parent or legal guardian if subject is a minor and signed assent from minor subject, if appropriate.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study.

Presurgical Criteria
1. Systemic administration of any corticosteroid in the 2 weeks prior to study enrollment.
2. Periocular injection in the study eye of any corticosteroid solution within 4 weeks prior to instillation of the study drug, or of any corticosteroid depot within 2 months prior to instillation of the study drug.
3. Instillation of any topical ocular corticosteroid or NSAID within 24 hours prior to instillation of the study drug or during the course of the study, with the exception of presurgical administration of a topical NSAID to prevent miosis.
4. Any history of glaucoma or ocular hypertension in the study eye.
5. History or presence of endogenous uveitis.
6. Any current corneal abrasion or ulceration.
7. Any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease.
8. Allergy to similar drugs, such as other corticosteroids.
9. History of steroid-related IOP increase.
10. Scheduled surgery on the contralateral eye during the treatment period.
11. Unwilling to discontinue use of contact lenses during the study period.
12. Pregnancy or lactation.
13. Participation in any study of an investigational topical or systemic new drug or device within 30 days prior to screening, or at any time during the study.
14. Prior participation in the study described in this protocol.
15. Unable or unwilling to give signed informed consent prior to participation in any study-related procedures.

Postsurgical Criteria

1. Ocular hemorrhage which interferes with evaluation of postsurgery inflammation.
2. Injection of gas into the vitreous body during surgery.
3. Presence of IOP ≥24 mm Hg on Day 1 after surgery.

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition Study 002A

Table 3: Number (%) of Subjects in the Analysis Populations by Treatment Group (Study 002A)

	ST-601 BID (N=58)	**ST-601 QID** (N=55)	**Placebo** (N=107)	**Over All Regimens** (N=220)
Randomized	58 (100.0%)	55 (100.0%)	107 (100.0%)	220 (100.0%)
ITT population	57 (98.3%)	55 (100.0%)	107 (100.0%)	219 (99.5%)
PP population	57 (98.3%)	52 (94.5%)	105 (98.1%)	214 (97.3%)
Safety population	57 (98.3%)	55 (100.0%)	107 (100.0%)	219 (99.5%)

N, the number of subjects randomized, in each column was used as the denominator for all percentage calculations.
Source: Adapted from Sponsor Table 12 of Study Report

In Study 002A, one subject was included in the randomized population but excluded from the ITT population. Subject (0019004) was re-enrolled with the second eye under new subject ID (0019011). Data from 0019011 were excluded from the ITT, PP, and safety populations. There were five ITT subjects excluded from the PP population, three subjects (0012010, 0050001, and 0050002) enrolled with a cell grade <"2" and two subjects (0019032 and 0024001) used disallowed medications.

Table 4: Number (%) of Subjects in the Analysis Populations by Treatment Group (Study 002A)

	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)	Over All Regimens (N=219)
Completed study, N (%)	52 (91.2%)	51 (92.7%)	68 (63.6%)	171 (78.1%)
Total subjects withdrawn early	5 (8.8%)	4 (7.3%)	39 (36.4%)	48 (21.9%)
Adverse event	0	2 (3.6%)	3 (2.8%)	5 (2.3%)
Lack of efficacy	4 (7.0%)	1 (1.8%)	33 (30.8%)	38 (17.4%)
Lost to follow-up	0	0	2 (1.9%)	2 (0.9%)
Protocol violation	0	0	0	0
Withdrew consent	1 (1.8%)	0	1 (0.9%)	2 (0.9%)
Early termination of study	0	1 (1.8%)	0	1 (0.5%)

N, number of subjects in the ITT/safety population that is used as the denominator for all percentage calculations.
(1) The ITT and safety populations are identical.
Source: Adapted From Sponsor's Table 9 of Study Report

Statistical Reviewer Comments: *In Study 002A, the number of subjects who withdrew early due to lack of efficacy was largest in the placebo arms 33 (31%) and smallest in the ST-601 QID arm 1 (2%). The overall percentage of subjects withdrawing early due to lack of efficacy was smaller in Study 002A than in Study 002B at 17.4% vs. 27.9% respectively.*

Demographics and Baseline Characteristics Study 002A:

Table 5: Demographic Summary by Treatment Group: ITT/Safety (Study 002A)

Subject Characteristic		ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)	Over All Regimens (N=219)
Age (yrs)	n	57	55	107	220
	Mean	70.8	68.1	69.1	69.3
Gender	n	55	107	219	57
	Male	24 (43.6%)	56 (52.3%)	107 (48.9%)	27 (47.4%)
	Female	31 (56.4%)	51 (47.7%)	112 (51.1%)	30 (52.6%)

Ethnicity	n	55	107	219	57
	Hispanic/Latino	12 (21.8%)	28 (26.2%)	50 (22.8%)	10 (17.5%)
	Not Hispanic/Latino	43 (78.2%)	79 (73.8%)	169 (77.2%)	47 (82.5%)
Race	White	46 (80.7%)	48 (87.3%)	96 (89.7%)	190 (86.6%)
	Black/African-American	9 (15.8%)	7 (12.7%)	8 (7.5%)	24 (11.0%)
	Other	4 (7.4%)	1 (1.9%)	7 (6.2%)	12 (5.5%)
Iris color	n	57	55	107	219
	Blue	18 (31.6%)	9 (16.4%)	27 (25.2%)	54 (24.7%)
	Brown	24 (41.1%)	33 (60.0%)	50 (46.7%)	107 (48.95%)
	Green	6 (10.5%)	3 (5.5%)	8 (7.5%)	17 (7.8%)
	Hazel	6 (10.5%)	8 (14.5%)	17 (15.9%)	31 (14.2%)
	Gray	0	0	2 (1.9%)	2 (0.9%)
	Unknown	3 (5.3%)	2 (3.6%)	3 (2.8%)	8 (3.7%)
Surgery	n	57	55	107	219
	Cataract	55 (96.5%)	53 (96.4%)	104 (97.2%)	212 (96.8%)
	Other	2 (3.5%)	2 (3.6%)	3 (2.8%)	7 (3.2%)

N, number of subjects in the ITT/safety population.
(1) The ITT and safety populations are identical.
Sources: Adapted From Sponsor Table 13 of Study Report

Statistical Reviewer Comments: *In Study 002A, the distributions of males and females in the ST-601 BID and QID arms differed slightly with approximately 56% females and 44% males in the BID arm and 48% females and 52% males in the QID arm. In the ST-601 BID arm vs. the ST-601 QID arm, there was a larger proportion of patients with blue iris color 18 (32%) vs. 9 (16%) and a smaller proportion with brown iris color, 24 (41%) vs. 33 (60%).*

Subject Disposition Study 002B

Table 6: Number (%) of Subjects in the Analysis Populations by Treatment Group (Study 002B)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo BID (N=57)	Placebo QID (N=57)	Over All Regimens (N=220)
Randomized	54 (100.0%)	52 (100.0%)	57 (100.0%)	57 (100.0%)	220 (100.0%)
ITT population	54 (100.0%)	52 (100.0%)	56 (98.2%)	57 (100.0%)	219 (99.5%)
PP population	54 (100.0%)	51 (98.1%)	56 (98.2%)	57 (100.0%)	218 (99.1%)
Safety population	54 (100.0%)	52 (100.0%)	56 (98.2%)	57 (100.0%)	219 (99.5%)

Source: Adapted from Sponsor Table 12 of Study Report

In Study 002B, there was one subject (#027008) excluded from the ITT population and another subject (#023051) excluded from the PP population. Subject (#027008) was never treated and subject (#023051) failed to comply with study medication.

Table 7: Disposition of Subjects Entering Trial: ITT Population (Study 002B)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo (N=113)	Over All Regimens (N=219)
Completed study, n (%)	48 (88.9%)	48 (92.3%)	56 (49.6%)	152 (69.4%)
Total subjects withdrawn early	6 (11.1%)	4 (7.7%)	57 (50.4%)	67 (30.6%)
Adverse event	0	0	1 (0.5%)	1 (0.5%)
Lack of efficacy	5 (9.3%)	2 (3.8%)	54 (47.8%)	61 (27.9%)
Lost to follow-up	1 (1.9%)	0	0	1 (0.5%)
Protocol violation	0	1 (1.9%)	1 (0.5%)	2 (0.9%)
Subject withdrew consent	0	1 (1.9%)	1 (0.5%)	2 (0.9%)

N, number of subjects in the ITT/safety population that is used as the denominator for all percentage calculations.
Source: Adapted from Sponsor Table 9 of Study Report

Statistical Reviewer Comments: *In Study 002B, the number of subjects who withdrew early due to lack of efficacy was largest in the placebo arms at 54 (47.8%) and smallest in the ST-601 BID and QID arms at 5 (9.3%) and 2 (3.8%) respectively. The overall percentage of subjects withdrawing early due to lack of efficacy was larger in Study 002B than in Study 002A at 27.9% vs. 17.4% respectively.*

Demographics and Baseline Characteristics Study 002B:

Table 8: Demographic Summary by Treatment Group: ITT/Safety (Study 002B)

Subject Characteristic		ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo (N=113)	Over All Regimens (N=219)(1)
Age (yrs)	n	54	52	113	219
	Mean	70.7	68.4	69.9	69.8

Gender	n	54	52	113	219
	Male	24 (44.4%)	23 (44.2%)	43 (38.1%)	90 (41.1%)
	Female	30 (55.6%)	29 (55.8%)	70 (61.9%)	129 (58.9%)
Ethnicity	n	54	52	113	219
	Hispanic/Latino	0	1 (1.9%)	2 (1.8%)	3 (1.4%)
	Not Hispanic/Latino	54 (100.0%)	51 (98.1%)	111 (98.2%)	216 (98.6%)
Race	n	54	52	113	219
	White	43 (79.6%)	47 (90.4%)	100 (88.5%)	190 (86.8%)
	Black/African-American	7 (13.0%)	4 (7.7%)	6 (5.3%)	17 (7.8%)
	American Indian/Alaskan Native	1 (1.9%)	0	0	1 (0.5%)
	Asian	1 (1.9%)	0	2 (1.8%)	3 (1.4%)
	Other race	2 (3.7%)	1 (1.9%)	5 (4.4%)	8 (3.7%)
Iris color	n	54	52	113	219
	Blue	20 (37.0%)	22 (42.3%)	44 (38.9%)	86 (39.3%)
	Green	8 (14.8%)	7 (13.5%)	11 (9.7%)	26 (11.9%)
	Gray	1 (1.9%)	2 (3.8%)	5 (4.4%)	8 (3.7%)
	Brown	22 (40.7%)	10 (19.2%)	33 (29.2%)	65 (29.7%)
	Hazel	3 (5.6%)	10 (19.6%)	20 (17.5%)	33 (15.1%)
	Unknown	0	1 (1.9%)	0	1 (0.5%)
Surgery	n	54	52	113	219
	Cataract	52 (96.3%)	51 (98.1%)	112 (99.1%)	215 (98.2%)
	Iridoplasty	1 (1.9%)	0	0	1 (0.5%)
	Vitrectomy	1 (1.9%)	1 (1.9%)	0	2 (0.9%)
	Wound modification	0	0	1 (0.9%)	1 (0.5%)

N, number of subjects in the ITT/safety population.
(1) The ITT and safety populations are identical.
Sources: Adapted From Sponsor Table 13 of Study Report

Statistical Reviewer Comments: *In Study 002B, there was a larger percentage of white subjects in the ST-601 QID arm versus the ST-601 BID arm, approximately 90% vs. 80% respectively. There was a larger percentage of subjects with iris color of brown in the ST-601 BID arm versus the ST-601 QID arm, 41% vs. 19% respectively.*

3.1.3 Statistical Methodologies

Hypothesis Testing

The SAP specified that a series of hypotheses would be tested using a closed, sequential testing procedure. The overall significance level would be maintained at 0.025; one-tailed, but each hypothesis would be tested at the 0.025 level.

Determination of Sample Size

The planned sample size was 216 subjects to achieve 195 evaluable subjects based on a 2:1

randomization. The Sponsor's rationale for the sample size was as follows:

Previous clinical trials had shown ST-601 to be an effective treatment for inflammation and as effective as betamethasone, a strong steroid. On the primary endpoint, the response rate to placebo treatment was expected to be 35%, and the difference between ST-601 and placebo was expected to be 30% for the main outcome measure (proportion of subjects with an anterior chamber cell grade of "0" at Day 8). With an 85% power (1-β) and a significance (α) level of 0.0125 (one-tailed, chi-square test, continuity corrected), the number of subjects required per treatment group was 65. Attrition was expected to be low in both groups (10%), and so the number of subjects to be enrolled was 72 in each ST-601 group, with half that in each placebo group, for 216 in all. This sample size was deemed to be sufficient to demonstrate the superiority of ST-601 at either dosage regimen, or at both regimens. Subjects were to be randomized in a 2:1 ratio of active drug to vehicle into 4 treatment groups, as follows:

- Treatment Group 1 = Approximately 72 subjects to receive 1 drop of ST-601 in the affected eye BID for 14 days
- Treatment Group 2 = Approximately 72 subjects to receive 1 drop of ST-601in the affected eye QID for 14 days
- Treatment Group 3 = Approximately 36 subjects to receive 1 drop of vehicle in the affected eye BID for 14 days
- Treatment Group 4 = Approximately 36 subjects to receive 1 drop of vehicle in the affected eye QID for 14 days

3.1.4 Results and Conclusions

Efficacy Results

Table 8: FDA Recommended Primary Endpoints and Sponsor Pre-specified Primary and Secondary Endpoints (Study 002A)

Study 002A Endpoint	Endpoint Classification	Dosing Regimen	ST-601 n/N %	Placebo n/N %	Difference (95%CI)[2]	p-value[3]
Proportion of ITT Subjects with Clearing (≤ 1) of AC Cells by Day 8[3]	FDA Recommended Primary	QID	13/55 23.6	11/105 10.5	13.2 (-0.9, 27.2)	0.0302
	FDA Recommended Primary	BID	9/57 15.8	11/105 10.5	5.3 (-7.2, 17.8)	0.3584

Proportion of ITT Subjects with Clearing (= 0) AC Cells by Day 8[3]	**Sponsor's Primary**	**QID**	19/55 34.5	13/105 12.4	22.2 (6.7, 37.6)	0.0014
	Sponsor's Secondary	**BID**	17/57 29.8	13/105 12.4	17.4 (2.6, 32.2)	0.0066
Proportion of ITT Subjects with pain /discomfort score of 0 on Day 3	**Sponsor's Secondary**	**QID**	27/54 50.0	29/105 27.6	22.4 (5.1, 39.6)	0.0026
	Sponsor's Secondary	**BID**	23/57 40.4	29/105 27.6	12.7 (-4.0, 29.4)	0.0772
Proportion of Subjects with Clearing ($\leq$ 1) of AC Cells by Day 15[3]	**Exploratory[1]**	**QID**	36/55 65.5	18/105 17.1	48.3 (32.4, 64.2)	< 0.0001
	Exploratory[1]	**BID**	35/57 61.4	18/105 17.1	44.3 (28.4, 60.2)	< 0.0001

[1]Considered exploratory rather than secondary since the 4th test of the Sponsor's hierarchical testing strategy failed to show significance. [2]P-value is two-sided: significance level is stratified on investigative site and 95% confidence limits on the difference (unstratified). [3]LOCF was used to impute missing values

Source: FDA Table

Statistical Reviewer Comments: In Study 002A, *The BID regimen failed to show significance in the FDA recommended primary endpoint 'Proportion of ITT Subjects with Clearing (= 0) AC Cells by Day 8' (P=.3584) and a key secondary endpoint 'Proportion of ITT Subjects with pain/discomfort score of 0 on Day 3' (p=.0772). Since this secondary endpoint did not show significance, the next prioritized endpoint tested, 'Proportion of Subjects with Clearing ($\leq$ 1) of AC Cells by Day 15', was considered exploratory rather than secondary. Note that the sponsor's primary endpoint is not considered clinically meaningful by the Agency. It should also be noted that two ITT patients in the placebo arm were not included in this analysis. This is not a concern since excluding these patients rather than including them as failures would offer a more conservative analysis.*

The QID regimen showed significance in the FDA recommended primary endpoint 'Proportion of ITT Subjects with Clearing (= 0) AC Cells by Day 8' using a stratified analysis as pre-specified by the Sponsor. However, an analysis with continuity correction and without stratifying by site, yielded a treatment difference of 13.2% with the corresponding 95% CI= (-0.9, 27.2) which did not exclude 0 (i.e. no treatment difference). The p-value for this test was

.0476. Note that in this analysis if we make a conservative assumption that the treatment difference is normally distributed, statistical inferences regarding significance may be unclear.

Table 9: FDA Recommended Primary Endpoints and Sponsor Pre-specified Primary and Secondary Endpoints (Study 002B)

Study 002B Endpoint	Endpoint Classification	Dosing Regimen	ST-601 n/N %	Placebo n/N %	% Difference (95%CI)	P-value
Proportion of ITT Subjects with Clearing (= 0) of AC Cells by Day 8	**FDA Recommended Primary**	**QID**	11/52 21.2	6/113 5.3	15.8 (2.6, 29.1)	0.0012
	FDA Recommended Primary	**BID**	10/53 18.9	6/113 5.3	13.6 (0.9, 26.3)	0.0075
Proportion of ITT Subjects with Clearing (≤ 1) of AC Cells by Day 8	**Sponsor's Primary**	**QID**	18/52 34.6	7/113 6.2	28.4 (13.3, 43.5)	<0.0001
	Sponsor's Secondary	**BID**	16/53 30.2	7/113 6.2	24.0 (9.5, 38.5)	<0.0001
Proportion of ITT Subjects with pain /discomfort score of 0 on Day 3	**Sponsor's Secondary**	**QID**	21/52 40.4	25/113 22.1	18.3 (1.5, 35.0)	0.0116
	Sponsor's Secondary	**BID**	19/53 35.8	25/113 22.1	13.7 (-2.7, 30.1)	0.0800
Proportion of Subjects with Clearing (≤ 1) of Anterior Chamber Cells by Day 15	**Exploratory[1]**	**QID**	31/52 59.6	17/113 15.0	44.6 (28.3, 60.9)	<0.0001
	Exploratory[1]	**BID**	26/53 49.1	17/113 15.0	34.0 (17.6, 50.4)	<0.0001

[1]Considered exploratory rather than secondary since the 4th test of the Sponsor's hierarchical testing strategy failed to show significance. [2] LOCF was used to impute missing values

Source: FDA Table

Statistical Reviewer Comments: *In Study 002B, the QID and BID regimens did show significance in the FDA recommended primary endpoint 'Proportion of ITT Subjects with Clearing (= 0) AC Cells by Day 8' (p=.0012 and p=.0075, respectively). In a key secondary endpoint 'Proportion of ITT Subjects with pain/discomfort score of 0 on Day 3,' the QID regimen did show significance (p=.0116) whereas the BID regimen failed to show significance (p= .0800). Due to this finding, the next prioritized test 'Proportion of Subjects with Clearing (≤ 1) of AC Cells by Day 15' was considered exploratory rather than secondary.*

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Table 10: Significance of Endpoints Analyzed: P-values of ST-601 regimen (BID or QID) versus Pooled Placebo in each of Studies 002A and 002B

ST-601 vs. Placebo (pooled) for Study Endpoint (below) by Study Day (3, 8, 15, 29), Regimen (BID, QID) and Study p-value (002A or 002B)	**Study Day:**							
	Day 3		Day 8		Day 15		Day 29	
Regimen:	BID	QID	BID	QID	BID	QID	BID	QID
Study Endpoint (below):	**Study p-values:** upper cell row (Study002A) lower cell row (Study002B)							
Proportion of Subjects, AC grade="0"[3](Sponsor's primary)	.1126 .8706	.0540 .4093	**.0066** **.0001**	**.0014** **.0001**	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Observed and change from baseline, AC cell grade	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Proportion of Subjects, AC cell count=0[2] (FDA primary)	.0180 .8706	.0075 1.000	**.3584** **.0075**	**.0302** **.0012**	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Observed and Change from baseline, mean AC cell count	.0001 .0009	.0001 .0722	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Proportion of Subjects, AC cell count ≤5	.0007 .2568	.0022 .3453	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Proportion of Subjects, AC cell count ≤5 and flare grade ="0"	.0006 .9449	.0006 .3891	.0042 .0001	.0029 .0118	.0209 .0150	.0001 .0001	.0001 .0001	.0001 .0001
Proportion of Subjects, pain/discomfort=0[4]	**.0772** **.0800**	**.0026** **.0116**	.2250 .0121	.0001 .0027	.0022 .0004	.0001 .0021	.0116 .0007	.0001 .0002
Observed and Change from baseline, pain/discomfort	.1422 .0005	.0001 .0005	.0005 .0001	.0001 .0001	.0024 .1856	.0002 .0001	.0051 .0001	.0001 .0001
Proportion of Subjects, photophobia = 0	.1369 .7751	.0675 .5973	.0428 .0065	.0103 .0037	.0010 .0090	.0002 .0002	.0108 .0227	.0001 .0001
Observed and Change from baseline, photophobia	.0152 .1156	.0017 .0049	.0009 .0119	.0006 .0089	.0001 .0001	.0003 .0032	.0002 .0069	.0002 .0109
Proportion of Subjects, AC flare grade ="0"	.0007 .1716	.0037 .7931	.0007 .0020	.0001 .0141	.0001 .0001	.0001 .0001	.0005 .0001	.0005 .0001
Observed and Change from baseline, AC flare grade	.0001 .0001	.0001 .0256	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0004 .0001	.0001 .0001
Proportion of Subjects, Total signs = "0"	.0073 .7129	.0567 .1791	.0131 .0001	.0125 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001
Observed and Change from baseline, total score of signs	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001	.0001 .0001

[1]P-values of controlled primary and secondary endpoints as well as FDA recommended endpoints are shown in bold.
[2] FDA recommended primary analysis at Day 8; [3]Sponsor primary (QID) and 1st tested secondary (BID) endpoint at Day 8
[4] Sponsor 2nd tested (QID) and 3rd tested (BID) secondary endpoint at Day 3. [5]Proportion of Subjects sustaining AC grade of "0" was also analyzed at Day 29 with a p-value of .0001 in both the BID and QID regimens.
Source: FDA Table

Statistical Reviewer Comments: *Based upon the observed primary and secondary endpoints in Studies 002A and 002B, findings in the QID regimen provided more substantial evidence of efficacy in comparison to findings in the BID regimen. This was evidenced by generally lower p-values in the QID regimen. It should also be noted that several endpoints included in Table 10 were not controlled for by the Sponsor. Statistical inferences for these endpoints may be limited due to potential inflation of the overall type I error rate associated with multiple endpoint testing.*

Conclusions:
For the QID regimen, the FDA recommended primary endpoint of 'the Proportion of Subjects with AC cell count=0 at Day 8' was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B. For the QID regimen, both studies 002A and 002B also showed significance in a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3.' In the BID regimen, neither Study 002A nor Study 002B showed significance for this endpoint. Similarly for several other secondary endpoints of Studies 002A and 002B, patients on the QID regimen were observed to have more favorable outcomes compared to patients on a BID regimen (Table 10). Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QID regimen but not the BID regimen as an effective treatment in subjects with inflammation following ocular surgery.

3.4 Evaluation of Safety

Table 11: Overall Summary of Treatment-Emergent Adverse Events: Safety Population (Study 002A)

Study 002A	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)
Number of AEs	67	77	276
Number (%) of subjects reporting			
Any AEs	30 (52.6%)	28 (50.9%)	81 (75.7%)
1 AE	14 (24.6%)	11 (20.0%)	24 (22.4%)
>1 AEs	16 (28.1%)	17 (30.9%)	57 (53.3%)
Maximum intensity: n (%)			
Mild	20 (35.1%)	13 (23.6%)	37 (34.6%)
Moderate	8 (14.0%)	12 (21.8%)	37 (34.6%)
Severe	2 (3.5%)	3 (5.5%)	7 (6.5%)
Relationship to study drug: n (%)			
Not related	24 (42.1%)	25 (45.5%)	62 (57.9%)
Related	6 (10.5%)	3 (5.5%)	19 (17.8%)
AEs leading to discontinuation: n (%)	5 (8.8%)	2 (3.6%)	31 (29.0%)

AEs leading to interruption of study medication: n (%)	1 (1.8%)	1 (1.8%)	4 (3.7%)
SAEs: n (%)	1 (1.8%)	3 (5.5%)	2 (1.9%)
Number (%) of deaths	0	0	1 (0.9%)
AEs in the study eye: n (%)	30 (52.6%)	25 (45.5%)	79 (73.8%)
AEs in the fellow (untreated) eye: n (%)	3 (5.3%)	6 (10.9%)	11 (10.3%)

Source: Adapted From Sponsor's Table 23 of Study Protocol

Table 12: Overall Summary of Treatment-Emergent Adverse Events: Safety Population (Study 002B)

Study 002B	**ST-601 BID (N=54)**	**ST-601 QID (N=52)**	**Placebo (N=113)**
Number of AEs	95	84	376
Number (%) of subjects reporting			
Any AEs	36 (66.7%)	34 (65.4%)	101 (89.4%)
1 AE	16 (29.6%)	15 (28.8%)	22 (19.5%)
>1 AEs	20 (37.0%)	19 (36.5%)	79 (69.9%)
Maximum intensity: n (%)			
Mild	25 (46.3%)	22 (42.3%)	45 (39.8%)
Moderate	10 (18.5%)	9 (17.3%)	39 (34.5%)
Severe	1 (1.9%)	3 (5.8%)	17 (15.0%)
Relationship to study drug: n (%)			
Not related	15 (27.8%)	14 (26.9%)	21 (18.6%)
Related	21 (38.9%)	20 (38.5%)	80 (70.8%)
AEs leading to discontinuation: n (%)	4 (7.4%)	2 (3.8%)	27 (23.9%)
AEs leading to interruption of study medication: n (%)			
SAEs: n (%)	0	1 (1.9%)	0
Number (%) of deaths	0	0	0
AEs in the study eye: n (%)	35 (64.8%)	33 (63.5%)	100 (88.5%)
AEs in the fellow (untreated) eye: n (%)	9 (16.7%)	7 (13.5%)	2 (1.8%)

Source: Sponsor's Table 23 of Study Protocol

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The statistical reviewer conducted subgroup analyses by age, gender and race in Study 002A and Study 002B for the FDA recommended primary endpoint of proportion of ITT subjects with clearing (= 0) AC Cells by Day 8. However, due to the small number of cases of complete clearing in most subgroups, inferences based on subgroup comparisons were highly limited. There were no notable differences with respect to age, gender or race in Study 002A and Study 002B.

Table 13: Proportion of ITT Subjects by Subgroup with Clearing (= 0) AC Cells by Day 8: (Study 002A)

Subgroup	Category	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)[1]	Over All Regimens (N=219)[2]
Age	< 65	1/10 (10.0)	5/16 (32.2)	5/30 (16.7)	11/56 (19.6)
	≥ 65	8/47 (17.0)	8/39 (20.5)	6/75 (8.0)	22/161 (13.7)
Gender	Male	2/27 (7.4)	5/24 (20.8)	5/55 (9.1)	12/106 (11.3)
	Female	7/30 (23.3)	8/31 (25.8)	6/50 (12.0)	21/111 (18.9)
Race	White	6/46 (13.0)	12/48 (25.0)	10/96 (10.4)	28/190 (14.7)
	African/American	2/9 (22.2)	1/7 (14.3)	1/6 (16.7)	4/22 (18.2)
	Other	1/2 (50.0)	0/0 (0.0)	0/3 (0.0)	1/5 (20.0)

[1] n=105 patients used in calculations. [2] n=217 patients used in calculations.
[3] LOCF (Last observation carried forward) was used to impute missing data.
Source: FDA Table

Table 14: Proportion of ITT Subjects by Subgroup with Clearing (= 0) AC Cells by Day 8: (Study 002B)

Subgroup	Category	ST-601 BID (N=54)[1]	ST-601 QID (N=52)	Placebo (N=113)[1]	Over All Regimens (N=219)[2]
Age	< 65	1/11 (9.1)	4/15 (26.7)	1/28 (3.6)	6/54 (11.1)
	≥ 65	9/42 (21.4)	7/37 (18.9)	5/85 (5.9)	21/164 (12.8)
Gender	Male	5/24 (20.8)	7/23 (30.4)	3/43 (7.0)	15/90 (16.7)
	Female	5/29 (17.2)	4/29 (13.8)	3/70 (4.3)	12/128 (9.4)
Race	White	7/43 (16.3)	10/47 (24.7)	5/100 (5.0)	22/190 (11.6)
	African/American	1/6 (16.7)	0/4 (0)	0/6 (0)	1/16 (6.3)
	Other	2/4 (50.0)	1/1 (100)	1/7(14.3)	4/12 (33.3)

[1] n=53 patients used in calculations. [2] n=218 patients used in calculations.
[3] LOCF (Last observation carried forward) was used to impute missing data.
Source: FDA Table

Additional analyses were conducted to assess differences in major sites across the two studies. Due to the small number of cases of complete clearing within a site, statistical inferences were limited. However, the influential sites were site #029 and site #054 (Study 002A) and site # 030 (Study 002B).

Table 15: Proportion of ITT Subjects by Study Site with Clearing (= 0) AC Cells by Day 8 (Study 002A)

Study 002-A Site #	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)[1]	Over All Regimens (N=219)[2]
All Sites	9/57 (15.8)	13/55 (23.6)	11/105 (10.5)	33/217 (15.2)
012	1/8 (12.5)	3/7 (42.9)	2/13 (7.1)	6/28 (21.4)
019	0/9 (0)	0/8 (0)	0/18 (0)	0/35 (0)
021	0/7 (0)	3/8 (37.5)	1/13 (7.7)	4/28 (14.3)
025	0/5 (0)	0/4 (0)	0/9 (0)	0/18 (0)
029	4/7 (57.1)	3/7 (42.9)	4/12 (33.3)	11/26 (42.3)
033	0/3 (0)	0/2 (0)	1/6 (16.7)	1/11 (9.1)
048	0/3 (0)	1/4 (25.0)	0/7 (0)	1/14 (7.2)
054	3/9 (33.3)	3/8 (37.5)	2/17 (10.5)	8/34 (23.5)
Other Sites[3]	1/6 (16.7)	0/7 (0)	1/10 (10.0)	2/23 (8.7)

[1]n=105 patients used in calculations. [2]217 patients used in calculations.
[3] Includes Sites: 024, 032, 039, 049, 050
[4] LOCF (Last observation carried forward) was used to impute missing data.
Source: FDA Table

Statistical Reviewer Comments: *In Study 002A, influential sites were site #029 and #054. Of the 33 patients with complete clearing (=0) of AC cells at day 8, site #029 had 11 (33.3%) of these cases while Site #054 had 8(24.2%) of these cases. In site #029, the proportion of ITT subjects with clearing (= 0) of AC cells by day 8 was higher at 11/26 (42.3%) versus 33/217 (11.5%) over all other sites (p=.0007).*

Table 16: Proportion of ITT Subjects by Study Site with Clearing (= 0) AC Cells by Day 8 (Study 002B)

Study 002-B Site #	ST-601 BID (N=54)[1]	ST-601 QID (N=52)	Placebo (N=113)	Over All Regimens (N=219)[2]
All Sites	10/53 (18.9)	11/52 (21.1)	6/113 (5.3)	27/218 (12.6)
002	2/4 (50.0)	0/5 (0)	0/10 (0)	2/19 (10.5)
022	1/4 (25.0)	2/3 (66.7)	1/7 (7.1)	4/14 (28.6)
023	0/12 (0)	0/13 (0)	1/28 (3.6)	1/53 (1.9)
027	2/5 (40.0)	3/4 (75.0)	2/8 (25.0)	7/17 (41.2)
030	5/9 (55.6)	3/9 (33.3)	0/20 (0)	8/38 (21.1)
034	0/14 (0)	3/14 (21.4)	2/30 (6.7)	5/58 (8.6)
Other Sites[3]	0/5 (0)	0/4 (0)	0/10 (0)	0/19 (0)

[1]n=53 patients used in calculations. [2]218 patients used in calculations.
[3] Includes Sites: 009,018, 020, 026, 056

[4] LOCF (Last observation carried forward) was used to impute missing data.
Source: FDA Table

Statistical Reviewer Comments: *In Study 002B, an influential site was site #030. Of the 21 ST-601 treated patients with complete clearing (=0) of AC cells at day 8, 8 (38.1%) of these patients were from site #030. Of the 10 ST-601 BID patients, 5 (50.0%) of patients were from site #030 with the next highest site at 2 (20%).*

Comparing efficacy rates in site #030 versus all other sites, the proportion of ITT subjects in the BID, QID and placebo regimens with clearing (= 0) of AC cells was higher in the BID regimen at 5/9 (55.6%) versus 5/44 (11.4%) (p=.019), higher in the QID regimen at 3/9 (33.3%) versus 8/43 (18.6%) and lower in the placebo regimens at 0/20 (0%) versus 6/93 (6.5%).

5. SUMMARY AND CONCLUSIONS

Overall findings from studies 002A and 002B provided adequate evidence of efficacy in the QID regimen but not the BID regimen. Overall findings were primarily based on an analysis of 'the proportion of ITT subjects with complete clearing (count = 0) of anterior chamber cells by day 8' which had been previously recommended by the Agency as a clinically meaningful primary endpoint. For the QID regimen, this endpoint was significant in Studies 002A and 002B. For the BID regimen, this endpoint was significant in Study 002A but not significant in Study 002B.

For the QID regimen, both studies 002A and 002B also showed significance in a key secondary endpoint, 'the proportion of ITT subjects with pain/discomfort score of 0 on Day 3.' In the BID regimen, neither Study 002A nor Study 002B showed significance for this endpoint. Similarly for several other secondary endpoints of Studies 002A and 002B, patients on the QID regimen were observed to have more favorable outcomes compared to patients on a BID regimen (Table 10). Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QID regimen but not the BID regimen as an effective treatment in subjects with inflammation following ocular surgery.

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