CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-212

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-212
Submission Code	Original
Letter Date	12/21/07
Stamp Date	12/26/07
PDUFA Goal Date	6/28/08
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	April 14, 2008
Established Name	difluprednate ophthalmic emulsion 0.05%
(Proposed) Trade Name	Durezol
Therapeutic Class	steroid
Applicant	Sirion Therapeutics
Priority Designation	P
Formulation	Ophthalmic solution
Dosing Regimen	Treatment of inflammation and pain following ocular surgery
Intended Population	Patients s/p ocular surgery with inflammation

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 22-212 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of difluprednate ophthalmic emulsion 0.05% for the treatment of inflammation and pain following cataract surgery.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

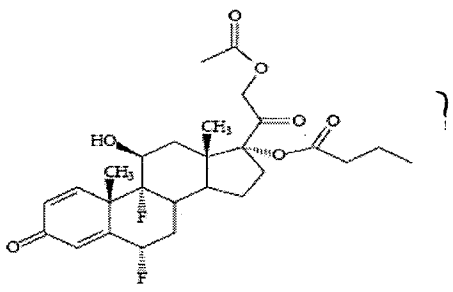
1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

ST-601 is a topical formulation of difluprednate that is an ophthalmic emulsion for ocular instillation. Difluprednate (6α, 9-difluoro-11β,17,21,-trihydroxypregna-1,4-diene-3,20-dione 21 acetate 17-butyrate) is a synthetic, glucocorticoid receptor agonist, a difluorinated derivative of prednisolone that has anti-inflammatory activity.



In addition, the emulsion formulation of ST-601 enables consistent dosing without the need for shaking (as is the case with the ophthalmic prednisolone acetate suspension).

2.2 Tables of Currently Available Treatments for Proposed Indications

Name of Drug	Indication
Xibrom	XIBROM ophthalmic solution is indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
Voltaren	VOLTAREN Ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
Acular LS	ACULAR LS ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.
Acular	ACULAR ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® ophthalmic solution is also indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction.
Nevanac	NEVANAC ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.
Vexol	VEXOL 1% is indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.

2.3 Availability of Proposed Active Ingredient in the United States

Difluprednate is not an approved product in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Difluprednate is a topical corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, systemic hypercorticoidism, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation, and ptosis.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Difluprednate was originally developed by Warner-Lambert in 1970, and licensed to Porcher-Lavril in France in 1976, where it was developed as a dermatologic product and first marketed by Clin-Midy as Epitopic cream and ointment in Europe. Currently Epitopic cream, 0.02% and 0.05%, and Epitopic gel, 0.05%, are marketed in Europe by Laboratoire Gerda of France. In 1979, Mitsubishi Yuka-Yakuhin also obtained rights to develop a dermatologic formulation, which was marketed in Japan by Mitsubishi-Tokyo Pharmaceuticals Inc. as Myser cream and ointment (now marketed as Myser, 0.05%, ointment and cream by Mitsubishi Pharma Corporation). These products are used for treating allergic dermatitis, eczema, psoriasis, prurigo, etc, in the same manner as other dermatologic corticosteroids.

The development of difluprednate to combat inflammation in a dermatologic formulation subsequently led to its reformulation as an ophthalmic product by Senju Pharmaceutical Co. In Japan, Senju has conducted non-clinical and clinical ophthalmic studies in patients with ocular inflammation resulting from ocular surgery or from uveitis. Sirion Therapeutics has acquired the US rights to ST-601, and has conducted two Phase 3 studies examining its safety and effectiveness in the treatment of post-surgical inflammation. A Phase 3 study by Sirion testing the safety and effectiveness of ST-601 for endogenous anterior uveitis is also underway; since this study is masked and ongoing, data from this study is not included in this NDA.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. They investigated 2 sites which were high enrollers.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no investigators with proprietary interest or with any significant interest in the drug product.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Components	Weight (mg/mL)	% w/v
Difluprednate		0.05%
Polysorbate 80		4.0%
Glycerin		2.2%
Sorbic acid		0.1%
Sodium acetate,		0.05%
Boric acid		0.1%
Sodium EDTA		0.02%
Castor oil		5.0%
Water for injection		–
Sodium hydroxide		As needed

qs. sufficient quantity; w/v, weight/volume

The study drug (ST-601 and matching placebo) were manufactured under the current good manufacturing practices (cGMP) requirements by [redacted] The filled bottles were then packaged and labeled for clinical supplies by [redacted], in accordance with the protocol and study randomization schedule.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology studies revealed that difluprednate ophthalmic emulsion suppressed uveitis in animals in a dose-dependent manner. The systemic absorption of ocularly administered difluprednate is very small. During the 7 days ocular instillation studies in rabbits of 0.05% ^{3}H-difluprednate, the C_{max} in the plasma was not more than 10 ng/g dry wet. The conducted safety pharmacology studies did not show any significant effect. Only small effects were observed at drug levels (10^{-4} and 10^{-3} g/mL) much higher than those obtained by ocular route. Therefore, there is no safety concern. Difluprednate (DFBA) is

rapidly metabolized by deacetylation (at 21-position) in the rabbit eye tissues to the metabolite DFB (active metabolite), which is in turn converted to DF. No quantifiable difluprednate or DFB reaches the blood following a single ocular instillation (50 µl/eye) of difluprednate 0.05% in rabbits. The C_{max} in the eye was observed within 1 hour of ^{3}H-difluprednate instillation.
The assay method using ^{3}H-difluprednate is sensitive enough to measure difluprednate and its metabolites at the levels of 0.3 ng equivalent/gm tissue. By autoradiography, difluprednate was cleared from the ocular tissues after a single instillation within 24 hours. Over 99% of radioactivity was excreted within 7 days. These results indicated that difluprednate and its metabolites did not remain in the body and were mainly excreted in the feces. After repeated instillation, radiolabelled difluprednate and its metabolites did not tend to accumulate in ocular tissues.

Difluprednate has been marketed as a topical dermatological ointment in Japan. The toxicity data from the completed dermatological studies in animals were for a longer duration than the ophthalmic studies. The NOELs in the 6-month dermatological studies in rats and dogs were 1.0 µg/kg/day and 1.25 µg/kg/day, respectively. Neither deaths nor serious toxicologic findings were noted in the studies. Many changes at higher doses were those generally observed in glucocorticoid-treated animals. Ocular administration of 0.05% difluprednate ophthalmic emulsion (0.1 ml/eye) QID for up to 4 weeks in dogs and in rabbits did not cause any ocular toxicity. The recommended clinical dose to the affected eye is one drop (0.03-0.05 ml) BID for two weeks. Therefore, it appears that there is a sufficient margin of safety. Instillation of heat-degraded difluprednate 0.05% in rabbits was tolerated as well as the normal difluprednate 0.05%. The instillation of polysorbate 80 excipient for 7 days was tolerated at concentrations up to 4% in rabbit eyes. Mutagenesis and chromosomal aberration tests of difluprednate and difluprednate metabolites were negative. In the bacterial

reverse mutation tests and the *in vitro* mammalian cell clastogenicity tests, difluprednate, metabolites, degradants, and impurities (DF17C, DF21B, and DFB) were all negative. An *in vivo* micronucleus test of difluprednate in mice was also negative. No carcinogenicity studies of difluprednate have been performed. During the IND and pre-NDA submission, no reproductive toxicity studies for difluprednate were submitted. At that time this reviewer recommended that the class labeling of glucocorticoid may be acceptable for difluprednate when approved. However, reproductive toxicity studies conducted in Japan (in 1981-1984) during the development of dermatologic formulation of difluprednate were submitted in this NDA.

Reproductive toxicity tests were performed with difluprednate in rats and rabbits. Fetal death and malformations such as cleft palate (commonly associated with high-dose administration of GCs) were observed during the organogenic period in rabbits. The effects of difluprednate on rat fetuses were weak; fetal death and/or malformed fetuses were not found.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Difluprednate is a glucocorticoid receptor agonist, a difluoronated derivative of prednisolone. Corticosteroids suppress the inflammatory response by inhibiting or disrupting the action of leukocytes and other mediators of inflammation including cytokines, chemokines, lipid and glucolipid agents, and macrophages. Corticosteroids further affect the inflammatory process by inhibiting prostaglandin and leukotriene production through the reduction of cyclooxygenase and lipoxygenase, respectively, as well as disrupting platelet-activating factor synthesis resulting from inhibition of phospholipase A2.

4.4.2 Pharmacodynamics

Two clinical pharmacology studies of ST-601 were conducted as sub-studies of a single Phase 1 trial (Study 9): a pharmacokinetic study evaluating systemic exposure following repeated ocular instillation, and a pharmacodynamic study examining the effect of repeated ocular instillation on serum cortisol levels in the same subjects.

Study 9 investigated the degree of serum cortisol suppression as the result of multiple ocular instillation of difluprednate. A summary of mean cortisol levels in subjects receiving multiple ocular doses of difluprednate ophthalmic emulsion 0.01% and 0.05% QID for 7 days is presented in Table 2.2.4.2-2 (see Clinical Pharmacology review). No significant changes in mean serum cortisol levels were noted following multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days.

4.4.3 Pharmacokinetics

Study 9 investigated systemic exposure as whole blood concentrations of the active difluprednate metabolite, DFB (6α,9-difluoroprednisolone 17-butyrate), following ocular administration QID for up to 7 days. DFB was not detected in whole blood at any time point, indicating that multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days has negligible systemic absorption.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Clinical Studies With Ophthalmic Administration of Difluprednate (ST-601=Difluprednate 0.05%)

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product	No. of Subjects	Healthy Subject of Diagnosis of Patients	Duration of Treatment	Study Status
Safety and Efficacy	***Study 1***-A Phase 3 multi-center, randomized, double-masked, placebo-controlled study of the safety and efficacy of Difluprednate in the treatment of inflammation following ocular surgery (ST-601A-002a)	Safety and efficacy of ST-601 BID or QID vs. placebo for treatment of inflammation following ocular surgery	Randomized, double-masked, parallel-group, placebo controlled	ST-601: 1 drop BID or QID Placebo (vehicle): 1 drop BID or QID Tapering after Day 14 Ocular instillation	220 subjects ST-601 BID: 58 ST-601 QID: 55 Placebo: 107	Post-ocular surgery US males and females	Up to 14 days	Completed; Full report
Safety and efficacy	***Study 2***-A Phase 3 multi-center, randomized, double-masked, placebo controlled study of the safety and efficacy of difluprednate in the treatment of inflammation following ocular	Safety and efficacy of ST-601 BID or QID vs. placebo for treatment of inflammation following ocular surgery	Randomized, double-masked, parallel-group, placebo controlled	ST-601: 1 drop BID or QID Placebo (vehicle): 1 drop BID or QID Tapering after Day 14 Ocular instillation	220 subjects ST-601 BID: 54 ST-601 QID: 52 Placebo: 114	Post-ocular surgery; US males and females	Up to 14 days	Completed; Full report

	surgery (ST-601A-002b) January 2007– August 2007							
Safety and efficacy	***Study 3***-Difluprednate Phase 3 clinical study—A confirmatory study on post-operative inflammation (SJE2079/3-03) April 2004– March 2005	Safety and efficacy for post-surgical inflammation	Randomized, double-masked, parallel group, comparative	ST-601: 1 drop QID BM (betamethasone) ophthalmic solution 0.1%: 1 drop QID	200 subjects ST-601: 100 BM: 100	Post-ocular surgery; Japanese adult males & females	14 days	Completed; Legacy abbreviated report
Safety and efficacy	***Study 4***-Phase 2 exploratory study of difluprednate ophthalmic emulsion in the treatment of post-operative inflammation (SJE2079/2-03-PC) April 2003– July 2003	Safety and efficacy for post-operative inflammation	Randomized, double-masked, parallel-group, comparative	ST-601: 1 drop QID BM ophthalmic solution 0.1%: 1 drop QID	24 subjects ST-601: 11 BM: 13	Post-ocular surgery; Japanese adult males and females	14 days	Completed; Legacy abbreviated report
Safety and efficacy	***Study 6***-Phase 3 confirmatory study of difluprednate ophthalmic emulsion in the treatment of uveitis (SJE2079/3-01-PC) August 2002– November 2003	Safety and efficacy for anterior uveitis	Randomized, double-masked, parallel-group, comparative	ST-601: 1 drop QID BM ophthalmic solution 0.1%: 1 drop QID	137 subjects ST-601: 69 BM: 68	Uveitis; Japanese adult males and females	14 days	Completed; Legacy abbreviated report
Safety and Efficacy	***Phase 7***-Phase 2a study of	Safety and efficacy for	Randomized, double-	ST-601: 1 drop QID	15 subjects	Uveitis; Japanese adult	14 days	Completed; Legacy

	difluprednate ophthalmic emulsion in the treatment of anterior uveitis (SJE2079/2- 02-PC) March 2000–April 2001	anterior uveitis	masked, parallel-group, comparative	BM ophthalmic solution 0.1%: 1 drop QID	ST-601: 8 BM: 7	males and females		abbreviated report
Safety	***Study 8***-Phase 1 clinical study of difluprednate ophthalmic emulsion - single instillation study (SJE2079/1-01-PC-5); May 1998–June 1998	Safety evaluation	Randomized, single-masked, placebo-controlled	Difluprednate 0.002%, 0.01%, or 0.05%: 2 drops single, ocular instillation	18 subjects Difluprednate 0.002%: 6 eyes Difluprednate 0.01%: 6 eyes Difluprednate 0.05%: 6 eyes Placebo: 18 eyes	Healthy adult male subjects	Single dose	Completed; Legacy abbreviated report
PD/PK	***Study 9***-Phase 1 clinical study of difluprednate ophthalmic emulsion—repeated instillation study (SJE2079/1-02-PC-2) August 1998- October 1998	Safety evaluation, blood levels of difluprednate and cortisol following repeated ocular instillation	Double-masked, placebo-controlled	Difluprednate 0.01% or 0.05% 2 drops QID for 7 days in 1 eye, with placebo (vehicle) in contralateral eye	12 subjects Difluprednate 0.01%: 6 eyes Difluprednate 0.05%: 6 eyes	Healthy adult Japanese male subjects	7 days	Completed; Legacy abbreviated report
Safety and efficacy	***Study 10***-Phase 2a exploratory study of difluprednate ophthalmic emulsion in the	Safety and efficacy for post-operative inflammation	Randomized, double-masked, parallel-group, comparative	Difluprednate 0.002% or 0.05%: 1 drop QID	Difluprednate 0.002%: 2 Difluprednate 0.05%: 4	Post-ocular surgery; Japanese adult males and females	7 days	Completed; Legacy abbreviated report

	treatment of post-operative inflammation (SJE2079/2-01-PC) December 1999– October 2000		group					
Safety and Efficacy	***Study 11***-Phase 3 open-label clinical study of difluprednate ophthalmic emulsion in the treatment of severe uveitis (SJE2079/3- 02-PC) August 2002– June 2003	Phase 2 safety and efficacy study for anterior uveitis	Open-label	ST-601: 1 drop QID Ocular instillation	19 subjects	Refractory uveitis; Japanese adult males and females	14 days	Completed; Legacy abbreviated report

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

Two Phase 3 clinical trials were conducted to demonstrate efficacy (Studies 1 and 2) and 7 studies were analyzed to demonstrate safety (Studies 1-4, 6, 7, and 11). The efficacy studies were 2 double-masked, randomized, placebo-controlled clinical trials evaluating ST-601 in the treatment of inflammation and pain 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 for 14 days, was compared with vehicle in subjects who had undergone unilateral ocular surgery. On Day 15, after completion of the planned treatment course, subjects who had an anterior chamber cell grade of "0" or who had responded satisfactorily to treatment as judged by the investigator began graduated tapering of the study drug, which successively halved the number of doses per day at each step. Beginning at Day 15, the subjects who were initially assigned to the QID dosing group instilled study medication BID from Days 15 to 21, and QD from Days 22 to 28. If further tapering was required after Day 28, the investigator discontinued study drug and prescribed a suitable drug, as deemed appropriate. Beginning at Day 15, the subjects who were initially assigned to the BID dosing group instilled study medication QD from Days 15 to 28. If further tapering was required after Day 28, the investigator discontinued study drug and prescribed a suitable drug, as deemed appropriate.

Tapering Schedule

	Study: Days 1–14	Tapering: Days 15–21	Tapering: Days 22–28
ST-601 or vehicle	QID	BID	QD
ST-601 or vehicle	BID	QD	QD

In Study 1 and 2 the total number of subjects included in the intent-to-treat (ITT)/safety population was 438. Of these, 111 subjects were assigned to receive treatment with ST-601 BID, 107 were assigned to receive ST-601 QID treatment, and 220 were assigned to the vehicle group.

As specified in the protocol and the SAP, the analysis was to be conducted strictly geographically, with sites located north of latitude 37° in Study ST-601A-002b and sites located south of latitude 37° in Study ST-601A-002a. Four sites were initially allocated to the opposite study from a geographical perspective to balance enrollment. One site was north of latitude 37° (Site 34) but assigned to Study ST-601-A-002a, and 3 sites were south of latitude 37° (Sites 48, 49, and 54) but assigned to Study ST-601A-002b. However, for all analyses, these sites have been assigned to the correct study based on geographic location.

Study Schedule:

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 documentation		X	X	X	X	X	X

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.

All subjects self-administered their allocated treatments. One drop of the study drug was instilled into the affected eye either BID or QID, depending on the subject's group assignment.

Group	Time of Day (Approximate), Days 1-14 ± 2							
	8 AM	10 AM	Noon	2 PM	4 PM	6 PM	8 PM	10 PM
Study drug								
ST-601 QID	X		X		X		X	
ST-601 BID	X						X	
Control								
Placebo QID	X		X		X		X	
Placebo BID	X						X	

Study 1: List of Investigators

Site No.	Principal Investigator	Location	Total Randomized
021	Carlos Buznego, MD	Miami, FL	29
0032	G. Richard Cohen, MD	Boca Raton, FL	9
0050	George Fournier, MD	Ft. Lauderdale, FL	2
0054	Robert DaVanzo, MD	High Point, NC	34
0049	Harvey B. DuBiner, MD	Morrow, GA	9
0039	Ronald E.P. Frenkel, MD	Stuart, FL	2
0033	Charles A. Garcia, MD	Houston, TX	11
0031	Barrett R. Ginsberg, MD	Ft. Meyers FL	0
0024	Richard E. Hector, MD	Bradenton, FL	1
0025	Gregory L. Henderson, MD	Brandon, FL	18
0019	Charles A. Kirby, MD	Chattanooga, TN	36
0029	Bernard R. Perez, MD	Tampa, FL	27
0012	Michael H. Rotberg, MD	Charlotte, NC	28
0048	Kenneth N. Sall, MD	Artesia, CA	14
			TOTAL=220

Study 2: List of Investigators

Site No.	Principal Investigator	Location	Total Randomized
0018	Marc A. Abrams, MD	Cleveland, OH	1
0020	Jeffrey A. Boomer, MD	Overland Park, KS	1
0023	David L. Cooke, MD	St. Joseph, MI	53
0022	Y. Ralph Chu, MD	Edina, MN	14
0056	John C. Galanis, MD	St. Louis, MO	10
0026	David W. Karp, MD	Louisville, KY	3
0034	Michael S. Korenfeld, MD	Washington, MO	58
0009	Howard S. Lazarus, MD	New Albany, IN	4
0027	Parag A. Majmudar, MD	Hoffman Estates, IL	18
0028	Matthew D. Paul, MD	Danbury, CT	0
0030	Steven M. Silverstein, MD	Kansas City, MO	38
0002	Timothy A. Walline, MD	Kansas City MO	20
			TOTAL=220

*There were 26 total sites that got IRB approval for the study and 24 of these sites enrolled patients.

Inclusion Criteria:

- Unilateral ocular surgery on the day prior to study enrollment
- Anterior chamber cell grade ≥ "2" on the day after surgery (Day 1)
- Age 2 years or older on the day of consent
- Negative urine pregnancy test on Day 1 for post-menarchal subjects; negative urine pregnancy test for pre-menarchal subjects at the investigator's discretion
- 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

Exclusion Criteria:

- Systemic administration of any corticosteroid in the 2 weeks prior to study enrollment
- 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
- 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 pre-surgical administration of a topical NSAID to prevent miosis
- Any history of glaucoma or ocular hypertension in the study eye
- History or presence of endogenous uveitis
- Any current corneal abrasion or ulceration
- Any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease
- Allergy to similar drugs, such as other corticosteroids
- History of steroid-related IOP increase
- Scheduled surgery on the contralateral eye during the treatment period
- Unwilling to discontinue use of contact lenses during the study period
- Pregnancy or lactation
- 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
- Prior participation in the study described in this protocol
- Unable or unwilling to give signed informed consent prior to participation in any study-related procedures
- Ocular hemorrhage which interferes with evaluation of post-surgery inflammation
- Injection of gas into the vitreous body during surgery
- Presence of IOP ≥24 mmHg on Day 1 after surgery

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication: Durezol is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery.

Reviewer's Comments:
This proposed indication is not acceptable. In the 2 trials to support efficacy of this product, over 95% of the patients underwent cataract surgery, therefore the data supports an indication for the treatment of inflammation and pain s/p cataract surgery. there is insufficient information to approve an indication for all ocular surgery. See section 6.1.7 for further discussion, and refer to Labeling section for additional information.

6.1.1 Methods

The support for the efficacy of ST-601 is the two Sirion studies, Protocol ST-601A-002a and ST-601A-002b. In the efficacy analyses of Studies 1 and 2, treatments were compared in a pair-wise manner using the chi-square test stratified by study site. The primary and multiple secondary hypotheses involving multiple dose regimens and endpoints were tested in a pre-specified order with a two-sided alpha of 0.05. Testing continued until a *P* value of greater than 0.05 was obtained.

6.1.2 Demographics

Study 1: Demographics by Treatment Group, Study ST-601A-002a (ITT/Safety Population)

Parameter	ST-601 BID (N=57)	ST-601 QID (N=55)	Vehicle (N=107)	Over All Regimens (N=219)
Gender				
Male	27	24	56	107
Female	30	31	51	112
Age				
Mean	70.8	68.1	69.1	69.3
Race				
White	46	48	96	190
African-American	9	7	8	24
American Indian/ Alaskan	0	0	0	0
Asian	1	0	2	3
Other race	1	0	1	2
Ethnicity				
Hispanic/Latino	10	12	28	50
Not Hispanic/Latino	47	43	79	169
Iris Color				
Blue	18	9	27	54
Brown	24	33	50	107
Green	6	3	8	17
Hazel	6	8	17	31
Gray	0	0	2	2
Unknown	3	2	3	8

Study 2: Demographics by Treatment Group, Study ST-601A-002b (ITT/Safety Population)

Parameter	ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo (N=113)	Over All Regimens (N=219)
Gender				
Male	24	23	43	90
Female	30	29	70	129
Age				
Mean	70.7	68.4	69.9	69.8
Race				
White	43	47	100	190
African-American	7	4	6	17
American Indian/ Alaskan	1	0	0	1
Asian	1	0	2	3
Other race	2	1	5	8
Ethnicity				
Hispanic/Latino	0	1	2	3
Not Hispanic/Latino	54	51	111	216
Iris Color				
Blue	20	22	44	86
Brown	22	10	33	65
Green	8	7	11	26
Hazel	3	10	20	33
Gray	1	2	5	8
Unknown	0	1	0	1

6.1.3 Patient Disposition

Study 1: Disposition of Subjects Entering Trial ST-601A-002a (ITT/Safety Population)

	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	Over All Regimens (N=219)
Completed Study	52 (91.2%)	51 (92.7%)	68 (63.6%)	171 (78.1%)
Total subjects withdrawn early	5	4	39	48
Adverse event	0	2	3	5
Lack of efficacy	4	1	33	38
Lost to follow-up	0	0	2	2
Protocol Violation	0	0	0	0
Withdrew Consent	1	0	1	2
Early Termination of Study	0	1	0	1

Study 2: Disposition of Subjects Entering Trial ST-601A-002b (ITT/Safety Population)

	ST-601 BID (N=54)	ST-601 QID (n=52)	Vehicle (N=113)	Over All Regimens (N=219)
Completed Study	48 (88.9%)	48 (92.3%)	56 (49.6%)	152 (69.4%)
Total subjects withdrawn early	6	4	57	67
Adverse event	0	0	1	1
Lack of efficacy	5	2	54	61
Lost to follow-up	1	0	0	1
Protocol Violation	0	1	1	2
Withdrew Consent	0	1	1	2

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Studies 1 and 2 was the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 as compared between the ST-601 QID and placebo groups.

Efficacy endpoints were calculated from the following assessments:

- Slit-lamp examination for signs of anterior ocular inflammation was conducted using a slit beam of 1.0 mm height and 1.0 mm width with maximum luminance, viewed through the high power lens.
- The anterior chamber cell *count* was recorded as the actual number of cells observed if fewer than 10 cells were seen (red blood cells and pigment cells were not counted), and the anterior chamber cell *grade* was determined according to the following "0" to "4" scale:
    - "0" ≤1 cell
    - "1" 2 to 10 cells
    - "2" 11 to 20 cells
    - "3" 21 to 50 cells
    - "4" >50 cells
- Flare was graded according to the following "0" to "4" scale:
    - "0" None
    - "1" Mild (trace to clearly noticeable, visible)
    - "2" Moderate (without plastic aqueous humor)
    - "3" Marked (with plastic aqueous humor)
    - "4" Severe (with fibrin deposits and/or clots)
- The following signs were graded according to a "0" to "3" scale ("0" = absent,"1" = mild, "2" = moderate, "3" = severe):
    - Chemosis
    - Bulbar conjunctival injection
    - Ciliary injection
    - Corneal edema
    - Keratic precipitates
- Symptoms of anterior ocular inflammation were also collected using the Visual Analogue Scale (VAS). Each symptom was scored according to a 0–100 VAS using a mark on a 100

mm line (with the anchor points of 0 = absent, 100 = maximal pain or discomfort). The symptoms measured were:

- Eye pain/discomfort
- Photophobia

The ITT population comprised all randomized subjects that received at least 1 dose of the study drug. Following the ITT principle, subjects were analyzed according to the treatment they were assigned to at randomization, irrespective of compliance or any deviations from the study protocol. The PP population included all randomized subjects who had no protocol violations (ie. subjects who complied with the protocol sufficiently to ensure that the data exhibited the effects of the active substance when administered as intended). According to the study protocol, the term "protocol violations" denoted those deviations from the protocol that led to the exclusion of the subject from the PP analysis, while "protocol deviations" subsumed minor deviations that had no impact on the PP analyses. Protocol violations included violation of entry criteria, lack of compliance, and the use of prohibited medications. The safety population consisted of all subjects who received at least 1 dose of study drug. Subjects were analyzed according to the treatment they received. No data was excluded from safety analysis because of protocol deviations.

Study 1: Subjects in the Analysis Populations by Treatment Group (ST-601A-002a)

	ST-601 BID (N=58)	ST-601 QID (n=55)	Vehicle (N=107)	Over All Regimens (N=220)
Randomized	58	55	107	220
ITT Population	57	55	107	219
PP Population	57	52	105	214
Safety Population	57	55	107	219

Study 2: Subjects in the Analysis Populations by Treatment Group (ST-601A-002b)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Vehicle BID (N=57)	Vehicle QID (N=57)	Over All Regimens (N=220)
Randomized	54	52	57	57	220
ITT Population	54	52	56	57	219
PP Population	54	51	56	57	218
Safety Population	54	52	56	57	219

Study 1: Proportion of Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	3	4	0	0.0180	0.0075
Day 8 (LOCF)	9 (15.8%)	13 (23.6%)	11 (10.3%)	0.3584	0.0302
Day 15 (LOCF)	25	25	15	<0.0001	<0.001
Day 29 (LOCF)	35	32	26	<0.0001	<0.001
Follow-up	35	36	51	0.2200	0.0148

Study 1: Proportion of Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: PP Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=52)	Vehicle (N=105)	ST-601 BID P value	ST-601 QID P value
Day 3	3	3	0	0.0168	0.0169
Day 8	9	13	11	0.9535	0.1652
Day 15	24 (46.2%)	23 (48.9%)	15 (21.1%)	0.0074	0.0020
Day 29	34	28	25	0.0003	0.0060
Follow-up	35	34	50	0.1969	0.0138

Study 2: Proportion of Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=54)	ST-601 QID (n=52)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	1	1	2	0.8706	1.0000
Day 8 (LOCF)	10 (18.9%)	11 (21.2%)	6 (5.3%)	0.0075	0.0012
Day 15 (LOCF)	20	19	10	<0.0001	<0.0001
Day 29 (LOCF)	29	33	20	<0.0001	<0.0001
Follow-up	33	32	48	0.0209	0.0101

Study 2: Proportion of Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: PP Population

Subjects Cleared	ST-601 BID (N=54)	ST-601 QID (n=51)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	1	1	2	0.9101	0.9029
Day 8	10	11	6	0.0283	0.0042
Day 15	18 (39.1%)	19 (38.8%)	10 (15.4%)	0.0214	0.0164
Day 29	26	31	19	0.0404	0.0081
Follow-up	33	31	48	0.0209	0.0165

Reviewer's Comments:

When looking at the ITT results of the 2 clinical trials examining Grade 0=0 cells in the anterior chamber, QID dosing "wins" at both day 8 and day 15. QID dosing also "wins" in the proportion of subjects with pain/discomfort score=0 on Day 3.

When looking at the results examining Grade 0=0 cells in the anterior chamber with BID dosing at Day 8, BID dosing only "wins" in one study (Study 2). At Day 15, BID dosing wins in both studies. BID dosing also loses in one study on proportion of patients with pain/discomfort score=0 at Day 8 and only wins in both studies with this endpoint at Day 15.

Therefore, the QID dose is the optimal dose with respect to efficacy for the treatment of inflammation and pain after cataract surgery.

Study 1: Proportion of Subjects With Clearing (Grade "0") of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	4	5	2	0.1126	0.0540
Day 8 (LOCF)	17 (29.8%)	19 (34.5%)	13 (12.4%)	0.0066	0.0014
Day 15 (LOCF)	35	36	18	<0.0001	<0.001
Day 29 (LOCF)	45	45	36	<0.0001	<0.001
Follow-up	40	42	62	0.3381	0.0096

Study 2: Proportion of Subjects With Clearing (Grade "0") of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=54)	ST-601 QID (n=52)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	1	2	2	0.8706	0.4093
Day 8 (LOCF)	16 (30.2%)	18 (34.6%)	7 (6.2%)	<0.0001	0<0.0001
Day 15 (LOCF)	26	31	17	<0.0001	<0.0001
Day 29 (LOCF)	37	41	28	<0.0001	<0.0001
Follow-up	39	38	56	0.0032	0.0010

Reviewer's Comments:

The primary endpoint of the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 as compared between the ST-601 QID and placebo groups although achieved statistical significance in the 2 trials is not a clinically meaningful endpoint. As was discussed in the comments to the original IND 75,713 and discussed at subsequent meetings, a clinically meaningful endpoint would be complete clearing of anterior chamber cells where a grade 0=0 cells in the anterior chamber.

6.1.5 Analysis of Secondary Endpoints(s)

Hierarchal Testing of Endpoints

	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.

The primary endpoint listed above and an additional 5 secondary endpoints were compared in a hierarchical manner to control for family wise Type I error. Specifically, these 6 endpoints were tested in a pre-specified order with a 2-sided alpha of 0.05, and testing continued until a *P* value >0.05 was obtained, at which time the hierarchical testing ended. The hierarchy-terminating

endpoint (ie. the first with a *P* value >0.05) and the subsequent (yet untested) endpoints became investigative secondary endpoints.

The primary endpoint was tested first, followed in order by:

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 1: Proportion of Patients With a Pain/Discomfort Score of 0 (ITT Population)

	ST-601 BID (N=57)	ST-601 QID (N=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	23 (40.4%)	27 (50%)	29 (27.6%)	0.0772	0.0026
Day 8 (LOCF)	23 (40.4%)	38 (69.1%)	32 (30.5%)	0.2250	<0.0001
Day 15 (LOCF)	36 (63.2%)	42 (76.4%)	47 (44.8%)	0.0209	0.0001
Follow-up	41	44	75	0.3961	0.2516

Study 2: Proportion of Patients With a Pain/Discomfort Score of 0 (ITT Population)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	19 (35.8%)	21 (40.4%)	25 (22.1%)	0.0800	0.0116
Day 8 (LOCF)	23 (43.4%)	24 (46.2%)	27 (23.9%)	0.0121	0.0027
Day 15 (LOCF)	23 (43.4%)	25 (48.1%)	29 (25.7%)	0.0150	0.0021
Follow-up	30	36	56	0.4282	0.0088

6.1.6 Other Endpoints

Additionally, 15 exploratory secondary endpoints were compared between the ST-601 groups and the vehicle placebo groups. In all cases the comparison was with the placebo group.

1. The proportion of subjects with an anterior chamber cell grade of "0" on Days 3 and 29 (BID and QID)
2. The observed cell grade and change from baseline in anterior chamber cell grade on Days 3, 8, 15, and 29 (BID and QID)
3. The proportion of subjects with a sustained anterior chamber cell grade of "0" (BID and QID)
4. The proportion of subjects to relapse from an anterior chamber cell grade of "0" (BID and QID)
5. The proportion of subjects with an anterior chamber cell count of 0 on Day 8 (QID)
6. The proportion of subjects with an anterior chamber cell count of 0 on Day 8 (BID)

7. The proportion of subjects with an anterior chamber cell count of 0 on Days 3, 15, and 29 (BID and QID)
8. The observed cell count and change from baseline in anterior chamber cell count on Days 3, 8, 15, and 29 (BID and QID)
9. The proportion of subjects with an anterior chamber flare grade of "0" on Days 3, 8, 15, and 29 (BID and QID)
10. The observed flare grade and change from baseline in anterior chamber flare grade on Days 3, 8, 15, and 29 (BID and QID)
11. The proportion of subjects with total signs = "0" at Days 3, 8, 15, and 29 (BID and QID)
12. The observed total score and change from baseline total score of signs on Days 3, 8, 15, and 29 (BID and QID)
13. The proportion of subjects reporting no pain/discomfort (0 on the ocular pain/discomfort VAS) at Days 8, 15, and 29 (BID and QID)
14. The observed pain/discomfort VAS score and change from baseline on the ocular pain/discomfort VAS score on Days 3, 8, 15, and 29 (BID and QID)
15. The proportion of subjects reporting no photophobia (0 on the photophobia VAS) at Days 3, 8, 15, and 29 (BID and QID)
16. The observed photophobia VAS score and change from baseline in photophobia VAS score on Days 3, 8, 15, and 29 (BID and QID)

6.1.7 Subpopulations

The primary endpoint was analyzed for the following subgroups: age (≤65 years vs. >65 years), sex (male vs. female), race (white vs. non-white), and iris color (light vs. dark).

Study 1: The study population was largely elderly (median age, 71 years, range 29–96 years), and there were slightly more women (51.4%) than men (48.6%). The subjects were mostly non-Hispanic white. Light eye color (blue, grey, green) was seen in 35% of the subjects, and dark eye color (hazel, brown) in 65% of the subjects. Cataract surgery was the type of ocular surgery performed in nearly all subjects (96.8%).

Study 1: Subpopulation Analysis

Type of Surgery	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	Total (N=219)
Cataract	56	54	106	216
Iridoplasty	0	0	0	0
Vitrectomy	1	1	1	3
Wound Modification	0	0	0	0

Study 2: The study population was largely elderly (mean age, 71 years; range, 24–88 years), mostly women (59%), and mostly non-Hispanic white. Light eye color (blue, grey, green) was seen in 55% of subjects, and dark eye color (hazel, brown) in 45%. Cataract surgery was the type of ocular surgery performed in nearly all subjects (98.2%).

Study 2: Subpopulation Analysis

Type of Surgery	ST-601 BID (N=54)	ST-601 QID (n=52)	Vehicle (N=113)	Total (N=219)
Cataract	52	51	112	215
Iridoplasty	1	0	0	1
Vitrectomy	1	1	0	2
Wound Modification	0	0	1	1

Reviewer's Comment:
Subject baseline demographics were comparable between treatment groups in Studies 1 and 2. There were no marked differences between treatment groups on ethnic or physical characteristics, including eye color.

The proposed indication: Durezol is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery is not acceptable. In the 2 trials to support efficacy of this product, over 95% of the patients underwent cataract surgery, therefore the data supports an indication for the treatment of inflammation and pain s/p cataract surgery. There is insufficient information to approve an indication for all ocular surgery. Refer to Labeling section for additional information.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See reviewer's comments in section 6.1.4.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was no longer than 14 days. In the studies conducted in the US, a 14-day tapering period was used after the 14 days of treatment. ST-601 is intended for short-term use for the treatment of inflammation and pain following ocular surgery.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Seven clinical trials were used to support safety of difluprednate. Studies 1, 2, 3, and 4 were in patients s/p intraocular surgery with moderate inflammation. Studies 6, 7, and 11 were conducted in patients with a diagnosis of endogenous anterior uveitis or panuveitis.

There were 5 Phase 3 studies (Studies 1, 2, 3, 6, and 11), one Phase 2a study (Study 7), and one Phase 2 study (Study 4). In Studies 3, 4, 6, and 7, the comparator drug was betamethasone ophthalmic emulsion 0.1%, which is used for the treatment of ocular inflammation in countries outside of the US. In Studies 1 and 2, vehicle was selected as the control treatment. All of these trials evaluated ST-601 at the dosing regimen of 1 drop of ST-601 QID for 14 days. In Studies 1 and 2, subjects also could be randomized to receive 1 drop BID for 14 days and there was tapering of study drug during a 2-week period following the 14 day treatment period. Safety assessments in these 7 studies included palpebral injection, corneal endothelial cell density, IOP, BCVA, slit lamp examination, ophthalmoscopy, and the collection of AEs. In addition, the Senju trials evaluated hematological changes.

7.1.2 Adequacy of Data

Between the 7 studies there were 314 patients in the safety database in which patients received ST-601 QID for at least 14 days. All of these trials were randomized, multi-center, double-masked, parallel-group, and comparative, except for Study 11, which was an open-label trial.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Studies Used to Establish Safety

Sirion Post-surgical Studies	Study 1	US	55
	Study 2	US	52
Senju Post-surgical Studies	Study 3	Japan	100
	Study 4	Japan	11
Senju Uveitis Studies	Study 6	Japan	69
	Study 7	Japan	8
	Study 11	Japan	19
Total No. of Patients Treated with ST-601 QID for 14 days			314

7.2 Adequacy of Safety Assessments

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

Overall, a total of 425 subjects in the 4 post-surgical (Studies 1, 2, 3, and 4) and 3 uveitis (Studies 6, 7, and 11) studies have been exposed to at least 1 dose of ST-601 for 14 days (BID or QID dosing), as defined in the individual study protocols. Of these 314 were treated with ST-601 QID for approximately14 days. In the studies that investigated post-surgical inflammation (Studies 1, 2, 3, and 4), treatment with the study drug was initiated 1 day following surgery. Subjects in Sirion post-surgical Studies 1 and 2 were exposed to study drug for a period of 14 days followed by a tapering regimen that was defined by the protocol. Total duration of exposure included both the 14-day treatment period and the tapering period. In Senju post-surgical Studies 3 and 4, subjects were treated with study drug for 14 days without a tapering period. In the studies that investigated endogenous anterior uveitis (Senju uveitis Studies 6, 7, and 11), study drug treatment was initiated on the day after written informed consent was obtained. Subjects in these studies were exposed to study drug for 14 days without a tapering period. The vast majority of subjects in the Senju post-surgical and uveitis studies were treated for at least 12 days (94.6% and 99%, respectively).

Study 1: Mean Duration of Exposure to Study Drug (ITT/Safety Population)

	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)
Mean Exposure (Days)	26.3	26.5	20.1

Study 1: Distribution of Exposure Durations to Study Drug (ITT/Safety Population)

Exposure Time (Days)	ST-601 BID (N=57)	ST-601 QID (N=55)	Placebo (N=107)
0-4 Days	2	0	20
5-11 Days	1	3	12
12-18 Days	2	0	4
19-33 Days	51	52	71
>33 Days	1	0	0

Study 2: Mean Duration of Exposure to Study Drug (ITT/Safety Population)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo (N=113)
Mean Exposure (Days)	26.1	26.2	17.9

Study 2: Distribution of Exposure Durations to Study Drug (ITT/Safety Population)

Exposure Time (Days)	ST-601 BID (N=54)	ST-601 QID (N=52)	Placebo (N=113)
0-4 Days	2	2	23
5-11 Days	3	0	22
12-18 Days	0	3	10
19-33 Days	48	47	58
>33 Days	1	0	0

Integrated Summary of Exposure (7 Safety Studies): Safety Population

	Sirion post-surgical studies ST-601 QID (N=107)	Senju post-surgical studies ST-601 QID (N=111)	Senju uveitis studies ST-601 QID (N=96)
Exposure			
Mean	26.9	13.2	14.0
Median	28.0	14.0	14.0
Min/Max	2/34	0/16	12/17
Duration of Exposure			
0-4 days	2	6	0
5-11 days	3	0	0
12-18 days	3	104	95
>=19 days	99	0	1

7.2.2 Explorations for Dose Response

There were no marked differences between the ST-601 BID and QID treatment groups in the frequency or type of AEs, or in the many safety parameters observed. The incidence of severe AEs in this study was low, and with similar frequency in both ST-601 treatment groups. Both of the dosing regimens of ST-601 were well tolerated.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

See section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

One PK study was performed. See section 4.4.

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

See section 7.4.5.

7.3 Major Safety Results

7.3.1 Deaths

One subject who was enrolled in Study 1 and assigned to the placebo treatment group experienced a stroke while on study, the outcome of which was fatal. The narrative for this event is provided below:

Death secondary to Stroke (ST-601A-002A-0019026/ —— Age: 61 years; Gender: Male)
Two days following randomization into the study, the subject was admitted to the hospital after experiencing a stroke. The subject started taking Coumadin once every other day in 1990 for atrial fibrillation. The subject's primary care physician advised him to discontinue Coumadin 5 days prior to cataract surgery to prevent excessive bleeding that could result from the surgical procedure. Upon notification of the subject's involvement in the study, the hospital physician discontinued the study medication 2 days after the subject was admitted to the hospital. The hospital physician then prescribed PredForte to resolve the remaining inflammation post-cataract extraction. The subject passed away, 7 days after being admitted to the hospital, as a result of the stroke. The subject had a history of atrial fibrillation following heart catheterization in 1990, as well as hyperlipidemia.

7.3.2 Nonfatal Serious Adverse Events

The overall incidence of SAEs in the 7 clinical studies was 11 of 425 subjects (2.6%) exposed to ST-601. Of the 329 subjects who were treated with ST-601 in the combined Senju and Sirion post-surgical studies, SAEs were reported for 8 subjects (2%), 1 SAE each.

In the Sirion post-surgical studies (Studies 1 and 2), 1 of 111 subjects (<1%) treated with ST-601 BID experienced 1 SAE (syncope), 4 of 107 subjects (37%) treated with ST-601 QID had 1 SAE each, and 2 of 220 subjects (<1%) in the placebo group had 1 SAE. The narratives for these 6 events are listed below:

1. Syncope Secondary to Atrial Fibrillation (ST-601A-002A-0019020/ —— Age: 86 years, Male), ST-601 BID

On Day 14 of the study, the subject was admitted to the hospital after experiencing syncope secondary to atrial fibrillation. The subject had a history of atrial fibrillation, hypertension, stroke, triple heart bypass, and carotid endarterectomy. Hospital physicians also suspected an internal bleed from an unknown origin because the subject's fecal matter was dark. Esophageal endoscopy and colonoscopy were inconclusive in regard to the suspected bleed. The subject received 6 units of fresh frozen plasma and 2 units of packed red blood cells due to progressive anemia, coagulopathy, and intermittent black stools. Concomitant medications were: vitamin K, Lasix, Benadryl, Labetalol, Lisinopril, Pepcid, levothyroxine sodium, Lisinopril, Coumadin, hydralazine HCL, and Nexium. This AE was considered resolved with sequelae of atrial

fibrillation and anemia, and the subject was discharged from the hospital on Day 18. The subject did not interrupt study drug, he completed the study.

2. Syncope Secondary to Dehydration Resulting from Vomiting and Diarrhea (ST-601A-002A-0025014/ ; Age: 72, Female), ST-601 QID

The subject fainted and suffered a concussion from falling on Day 7 of the study. She was admitted to the hospital for syncope secondary to dehydration associated with a gastrointestinal virus causing vomiting and diarrhea in the days preceding the event. While admitted, the subject underwent orthostatic testing and received the following medications: aspirin, Protonix, Lovenox, lidocaine, potassium, sodium chloride, and Tylenol. The subject was discharged 3 days later and she followed-up with her primary care physician, where she reported that she had dizzy spells since the fall. She was told that this was related to the concussion and was told to stay off the concomitant medication, Lisinopril, for a while; the dizzy spells subsequently improved. The subject did not interrupt study drug and she completed the study.

3. Urinary Tract Infection (ST-601A-002A-0034031/ , Age: 64, Male), ST-601 QID

The subject had an initial diagnosis of foot pain 2 years prior to participation in the study. The subject started taking Darvocet for right foot pain on Day 27 of the study, after completion of study treatment. The following day he was admitted to the hospital for urinary retention and urinary tract infection requiring catherization and intravenous antibiotics. While admitted, the subject received intravenous antibiotics for the infection and Vicodin as needed for the foot pain. The event resolved, the subject was discharged from the hospital 3 days later, with Levaquin and Flomax listed as the discharge medications. The subject did not interrupt study drug and he completed the study.

4. Cerebrovascular Accident (ST-601A-002A-0019026/ Age: 61, Male), vehicle
See narrative in Section 7.3.1.

5. Respiratory Distress (ST-601A-002A-0033002/ ; Age: 67, Male), vehicle

This subject had a history of depression and was on Effexor until the day prior to the study related surgery. The subject was to begin taking Paxil post-surgically but at his own discretion decided not to do so. On Day 4 of the study the subject began experiencing difficulty breathing, became depressed and sought treatment at a local emergency room. On the following day (Day 5 of the study), he was admitted to the hospital with respiratory problems as a result of an anxiety attack. The subject was dismissed 2 days later, and prescribed Paxil once again. The subject did not interrupt treatment with the study drug. The event was considered resolved when the subject was discharged from the hospital.

6. Headache (ST-601A-002B-0048009/ Age: 66, Female), ST-601 QID

On Day 16 of the study, the subject went into the hospital with the chief complaint of pain in the neck that had been intractable for 3 days, resulting in a severe headache. She was given

morphine sulfate in the emergency room with no relief, and was admitted to the hospital for a magnetic resonance imaging (MRI) and a neurological consultation. The MRI showed a severely degenerated C4-C5 disk, which was causing encroachment upon the spinal canal, and a diskectomy and fusion surgery of the C3-C4 and C4-C5 was performed. While admitted, the subject received Zofran and Vicodin. The subject was discharged from the hospital on Day 33 of treatment with difluprednate. The subject did not interrupt study drug and she completed the study.

7. Pneumonia (ST-601A-002B-0054005/ ; Age: 77, Female), ST-601 QID

The subject was admitted to the hospital with pneumonia on Day 17 of the study. Chest X-rays showed a mild opacity in the medial left lung base with possible early infiltrates. While admitted, the subject received intravenous Levaquin and Mucinex. The subject was discharged from the hospital 3 days later, and the event was considered resolved without sequelae. The subject did not interrupt ST-601 and completed the study.

In the Senju post-surgical studies (Studies 3 and 4), 3 of 110 subjects (3%) treated with ST-601 QID reported 1 SAE each (maculopathy, retinal detachment, and iris adhesions). The narratives for these 3 events are listed below:

1. Maculopathy (Study 3, Subject #21-1; Age: 64 years, Female)

Although maculopathy manifested at Day 3 of the study, the administration of difluprednate was continued for the full course of 14 days. Decreased IOP (4 mm Hg) was reported at Days 5 and 14. The subject was hospitalized for surgery at 89 days (after termination of difluprednate treatment), and she underwent vitreous displacement at 90 days. The IOP increased to 42 mm Hg at Day 91 (a day after surgery) and decreased to 24 mm Hg at Day 98; discharge from the hospital occurred at Day 99. Although the IOP was stabilized at less than 21 mmHg, the signs of maculopathy were unchanged. Low IOP occasionally occurs after vitreous surgery, and rarely, maculopathy is complicated by sustained IOP decrease.

2. Retinal Detachment (Study 3, Subject #22-2; Age: 61 years, Female)

Although retinal detachment manifested at Day 13 of the study, the instillation of difluprednate was continued until Day 15. The subject was hospitalized for surgery 3 days after termination of the treatment, underwent retinopexy at Day 19, and was discharged from the hospital on Day 23. The post-surgical course was found to be good at the Day 31 follow-up evaluation, and the event was considered resolved by the Day 38 follow-up evaluation.

3. Iris Adhesions (Study 3, Subject #53-1; Age: 69 years, Male)
Although iris adhesions manifested at Day 2 of the study, administration of difluprednate was continued until Day 12. Thereafter, the iris adhesions progressed; and the subject underwent posterior synechiotomy 5 days after termination of treatment, with a prolonged hospitalization period. The iris adhesions were resolved by the surgery.

In the Senju uveitis studies (Studies 6, 7, and 11), 3 of 96 subjects (3%) treated with ST-601 QID reported 1 SAE each (monoarthritis, corneal perforation, and necrotizing retinitis). The narratives for these 3 events are listed below:

1. Corneal Perforation (Study 6, Subject #19-1; Age: 69 years, Male)

This subject was receiving difluprednate in 1 eye for uveitis. On Day 6, corneal perforation occurred in the fellow eye due to aggravation of his underlying disease (corneal herpes in the contralateral eye). This eye was not receiving ST-601. Treatment with difluprednate was continued in the opposite study eye for 14 days. On Day 7, the subject was hospitalized to undergo conjunctival flap. Therapeutic medicines used for conjunctival flap included Atarax injection), intravenous Flumarin, physiological saline, Xylocaine, intravenous Fosmicin, xylocaine 2%, and Decadron. In addition, during the hospitalization, the following drugs were administered: Cravit, Rinderon , Tarivid, atropine ophthalmic solution, Voltaren, and Loxonin. On Day 11, the subject was discharged from the hospital; the event was resolved on Day 14 (final day of the study treatment; 3 days after discharge from the hospital).

2. Necrotizing Retinitis (Study 6, Subject #30-2; Age: 43 years, Female)

On Day 13 (final day of the study treatment), the subject was hospitalized due to occurrence of necrotizing retinitis in the study eye. Therapeutic medicines administered included Predonine tablets and Valtrex tablets on the day of hospitalization, intravenous Vicclox and dose-tapering drip infusion of Predonine from Days 1 to 10 post-treatment, Predonine tablets from Days 11 to 13 post-treatment, and Rinderon and Mydrin throughout the treatment period. The event was resolved 13 days post-treatment, and the subject was discharged from the hospital. At the time of inclusion in the study, the etiology of the subject's uveitis was unknown. The subject was later diagnosed with an aggravation of an underlying viral acute retinal necrosis.

3. Monoarthritis (Study 11, Subject #1O-1; Age: 25 years, Female)

The subject was hospitalized with monoarthritis on the day of completion of the study treatment (Day 14). The following drugs were administered during the hospital stay: Voltaren, Myonal, Loxonin, Voltaren, Seltouch, Mohrus, Indacin, Tsumura Goshajinkigan (herbal supplement), and prednisolone; the event resolved 54 days later.

Overall Listing of Serious Adverse Events

Organ system	Subject/Study	Age	Sex	Treatment	Time of Onset (Days)	Drug continued?	Outcome and duration of event
Cardiac Disorders							
Atrial fibrillation	19120/Study 1	86	M	ST-601 BID	14	Yes	Resolved with sequelae
Eye Disorders							
Iris Adhesions	53-1/Study 3	69	M	ST-601 QID	2	Yes	Posterior synechitomy performed- Resolved after 3 days
Maculopathy	21-1/Study 3	64	F	ST-601 QID	3	Yes	Unchanged
Retinal Detachment	22-2/Study 3	61	F	ST-601 QID	13	Yes	Retinopexy- Resolved after 25 days
Necrotizing retinitis	30-2/Study 6	43	F	ST-601 QID	13	Yes	Relieved after 13 days of treatment with anti-virals
Infections							
Pneumonia	54005/Study 2	77	F	ST-601 QID	17	Yes	Resolved after 3 days of treatment with antibiotics
UTI	34031/Study 1	64	M	ST-601 QID	27	Yes	Resolved after 3 days of treatment with antibiotics
Injury and procedural complications							
Corneal perforation	19-1/Study 6	69	M	ST-601 QID	6	Yes	Resolved after 8 days
Metabolism							
Dehydration	25014/Study 1	72	F	ST-601 QID	10	Yes	Resolved after 3 days
Musculoskeletal							
Monoarthritis	10-1/Study 11	25	F	ST-601 QID	14	Yes	Relieved after 54 days of treatment
Nervous system							
Headache	48009/Study 2	66	F	ST-601 QID	16	Yes	Resolved after 15 days
Respiratory							
Respiratory distress	33002/Study 1	67	M	Placebo	6	Yes	Resolved after 2 days

7.3.3 Dropouts and/or Discontinuations

Adverse Events That Required Discontinuation of Study Drug

	Sirion Surgical Study ST-601 QID (N=107)	Sirion Surgical Study Vehicle (N=220)	Senju Post-surgical Studies ST-601 QID (N=111)	Senju Uveitis Studies ST-601 QID (N=96)	Total Studies ST-601 (N=314)
Subjects reporting AEs leading to withdrawal	4	58	3	0	7
Eye Disorders					
Photophobia	0	13	0	0	0
Visual acuity reduced	0	10	0	0	0
Anterior chamber cell	1	14	0	0	1
Eye pain	0	15	0	0	0
Conjunctival hyperemia	1	16	0	0	1
Eye inflammation	1	12	0	0	1
Anterior chamber flare	0	15	0	0	0
Iritis	0	3	0	0	0
Macular edema	1	5	0	0	1
Choroidal detachment	0	0	1	0	1
Foreign body sensation	0	2	0	0	0
Vitreous opacities	0	1	0	0	0
Ciliary hyperemia	0	17	0	0	0
Corneal edema	0	9	0	0	0
Trichiasis	0	1	0	0	0
Conjunctivitis allergic	0	1	0	0	0
Corneal striae	0	1	0	0	0
Lacrimation increased	0	1	0	0	0
Conjunctival edema	0	4	0	0	0
Eyelid ptosis	0	1	0	0	0
Iridocyclitis	0	1	0	0	0
Uveitis	0	1	0	0	0
Vision blurred	0	1	0	0	0
Eye pruritis	0	0	0	0	0
Eyelid edema	0	1	0	0	0
Keratitis	0	1	0	0	0
Investigations					
IOP increased	0	1	2	0	2
IOP decreased	0	0	1	0	1
GI disorders					
Diverticulum	0	0	0	0	0
Hemorrhoids	0	0	0	0	0
Injury					
Superficial injury of the eye	0	0	0	0	0
General disorders					
Application site disorders	0	1	0	0	0

Immune system disorders					
Hypersensitivity	0	1	0	0	0
Infections					
Pneumonia	0	1	0	0	0
Nervous system disorders					
CVA	0	1	0	0	0
Headache	0	1	0	0	0

7.3.4 Significant Adverse Events

See section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Result

7.4.1 Common Adverse Events

Integrated Summary of Treatment-Emergent Adverse Events Occurring in >=2% of Subjects of 7 Studies to Support Safety (Studies 1, 2, 3, 4, 6, 7, and 11)

Organ Class	Sirion Post-Surgical Studies ST-601 BID N=111 Studies 1&2	Sirion Post-Surgical Studies ST-601 QID N=107 Studies 1&2	Sirion Post-Surgical Studies Placebo N=220 Studies 1&2	Senju Post-Surgical Studies ST-601 QID N=111 Studies 3&4	Senju Uveitis Studies ST-601 QID N=96 Studies 6, 7, 11	Total Studies ST-601 BID and QID dosing N=425	Total Studies ST-601 QID dosing N=314
Eye disorders							
Posterior capsular opacification	17	12	32	0	0	29	12
Conjunctival hyperemia	11	16	76	1	0	28	17
Punctate keratitis	8	6	8	2	9	25	17
Eye pain	12	5	44	2	3	22	10
Photophobia	11	10	45	0	0	21	10
Corneal edema	12	5	56	0	0	17	5
Ciliary hyperemia	6	10	62	0	0	16	10
Conjunctival edema	7	5	27	0	0	12	5
Visual acuity reduced	6	2	37	0	2	10	4
Anterior chamber cell	5	4	40	0	0	9	4
Eye inflammation	3	5	17	0	0	8	5
Vitreous floaters	3	5	5	0	0	8	5
Iritis	5	2	3	0	0	7	2
Foreign body sensation	3	2	16	2	0	7	4
Vitreous detachment	3	2	4	0	0	5	2
Conjunctival hemorrhage	3	1	1	0	0	4	1
Anterior chamber flare	3	1	31	0	0	4	1
Macular edema	1	2	5	0	0	3	2
Blepharitis	1	2	12	0	0	3	2
Trichiasis	0	2	6	0	0	2	2
Vision blurred	1	0	4	0	0	1	0
Corneal deposits	0	0	5	0	0	0	0
Eyelid edema	0	0	5	0	0	0	0

Congenital, familial, and genetic d/o							
Corneal dystrophy	1	0	6	0	0	1	0
General disorders							
Application site irritation	0	1	3	5	9	15	15
Application site pruritis	0	1	0	3	1	5	5
Application site pain	0	0	0	0	2	2	2
Investigations							
IOP increased	3	2	2	9	9	23	20
GI disorders							
Constipation	0	0	0	9	0	9	9
Nervous system d/o							
Headache	0	2	2	5	1	8	8
Psychiatric d/o							
Insomnia	0	0	0	5	1	6	6
Musculoskeletal d/o							
Back pain	0	0	0	3	1	4	4

7.4.2 Laboratory Findings

No clinical laboratory evaluations were conducted in Sirion Studies 1 or 2, except for urine pregnancy tests conducted at screening.

Hematologic examinations were performed in Studies 3, 4, 6, 7, 8, 9, 10, and 11, and included RBC, WBC, hemoglobin, hematocrit, and platelet count. Only 3 abnormal findings were reported in any of the studies. In Study 3, a reduction in platelet count in subject #61-2 was back to a more normal value 8 days after completion of dosing. In Study 9, an elevated WBC count was reported in subject 7. In Study 11, subject #10-1, a 25-year-old female, had a WBC count elevation that reached Grade 1. The subject also had a fever.

Clinical chemistry studies were conducted in Studies 3, 4, 6, 7, 8, 9, 10, and 11, and they included AST, ALT, LDH, alkaline phosphatase, leucine aminopeptidase (LAP), gamma glutamyl transpeptidase (γ-GTP), total protein, albumin, BUN, and uric acid. Study 3 also evaluated blood sugar levels. Abnormal findings were reported in Studies 3 and 7 (see Table 16 and 17 in Applicant's Integrated Summary of Safety). The elevation of AST and ALT seen in subject #53-1 returned to within the normal range within 30 days of completion of dosing. Subject #61-2 had a Grade 1 elevation of blood glucose levels at baseline, which suggests this subject could have had diabetes. However, fasting values were not obtained. Subject #3-1 had elevation of the γ-GTP and ALT at baseline. ALT and AST were within the normal range by 27 days after dosing was completed, and γ-GTP had fallen, although still elevated.

Urinalysis testing was performed in the Phase 1 Study 8, which studied a single administration of 2 drops of ophthalmic difluprednate at concentrations of 0.002%, 0.01%, and 0.05%. The categories of the tests included specific gravity, qualitative analysis (pH, glucose, protein, occult blood, ketone body, bilirubin, and urobilinogen), and sediment. Out of the 18 healthy subjects, 1 subject in the difluprednate 0.002% group and 1 subject in the difluprednate 0.05% group had abnormal urinary sediment rates.

Plasma cortisol levels were obtained in subjects across Studies 3, 4, 6, 7, 8, 9, 10, and 11. Only 1 abnormal finding considered related to ST-601 was reported in any of the studies, an elevated cortisol level in Subject 9 in Study 9.

7.4.3 Vital Signs

Vital signs were not measured in these studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in the studies.

7.4.5 Special Safety Studies

An increase in IOP is a common treatment-related AE resulting from corticosteroid use, especially with the use of topical ophthalmic steroids. The following are all IOP increases that were had an IOP of ≥21 mmHg that was also ≥10 mmHg higher than baseline. In all subjects, IOP elevation either was controlled with medication or did not require treatment.

In the Sirion post-surgical studies (Studies 1 and 2), a total of 8 subjects (3 on ST-601 BID, 3 on ST-601 QID, and 2 on placebo) had IOP increases that were IOP of ≥21 mmHg that and was also ≥10 mmHg higher than baseline. None of these subjects discontinued study drug as a result of IOP increase. The 8 events are described below:

a. Subject ST-601A-002A-0012023 (ST-601 BID)
This subject had an IOP of 7 mmHg at baseline, which rose to 26 mmHg at Day 15 and decreased to 24 mmHg at Day 29 and to 15 mmHg at the last study visit (Day 36). The subject was not given medication to treat the IOP increase.

b. Subject ST-601A-002A-0029027 (ST-601 BID)
Patient had an IOP of 17 mmHg at baseline, which increased to 27 mmHg at Day 8 before decreasing to 21 mmHg at Day 15 and 19 mm Hg at the last study visit (Day 37). The subject was given Trusopt to treat the IOP increase.

c. Subject ST-601A-002B-0023028 (ST-601 BID)
Patient had an IOP of 22 mmHg at baseline, 24 mmHg at Day 3, and 32 mmHg at Day 8. The IOP decreased to 29 mmHg at Day 15, and 15 mmHg at the last study visit (Day 38). The subject was not given medication to treat the IOP increase.

d. Subject ST-601A-002A-0029009 (ST-601 QID)
This subject had an IOP of 20 mmHg at baseline, which decreased to 14 mmHg on Day 3 but increased to 39 mmHg at an unscheduled visit (Day 10). The subject was given Istalol to treat the IOP increase.

e. Subject ST-601A-002A-0029015 (ST-601 QID)
Patient had an IOP of 6 mmHg at baseline, which increased to 19 mmHg on Day 8, 18 mmHg on Day 15, and 21 mmHg on Day 29 before decreasing to 11 mmHg at the last study visit (Day 36). This subject was not given medication to treat the IOP.

f. Subject ST-601A-002B-0023006 (ST-601 QID)
This subject had an IOP of 8 mmHg at baseline, which increased to 21 mmHg at Day 8, and 18 mmHg at Day 15 and which returned to normal range, 14 mmHg, at the last study visit (Day 36). The subject was not given medication to treat the IOP.

g. Subject ST-601A-002B-0030028 (placebo)
The baseline value was 13 mmHg. The IOP increased to 30 mmHg at an unscheduled visit (Day 7). This subject was withdrawn from study medication for lack of efficacy on Day 3. The IOP

increase was first diagnosed and treated with Istalol on Day 7. The IOP decreased to 19 mmHg at the last study visit (Day 10).

h. Subject ST-601A-002A-0021012 (placebo)
Patient had an IOP of 10 mmHg at baseline, which increased to 24 mmHg at Day 8 and decreased to 14 mmHg at the last study visit (Day 13). This subject was given Lumigan to treat the IOP.

In the Senju post-surgical studies (Studies 3 and 4), 6 subjects (5.5%) treated with ST-601 QID in Study 3 had an IOP increase that was IOP of $\geq$21 mmHg that and was also $\geq$10 mmHg higher than baseline. None of these subjects discontinued study drug as a result of IOP increase. All 6 events are described below:

a. Subject 41-2 had an IOP of 12 mmHg at baseline, and an increase to 34 mmHg at Day 7 and 40 mmHg at Day 14. The IOP decreased to 23 mmHg at the last study visit (Day 261 after termination). This subject was given followings medications: carteolol, Diamox tablet, bunazosin, Xalatan, and Trusopt.

b. Subject 44-2 had an IOP of 17 mmHg at baseline, which increased to 27 mmHg at Day 7 and decreased to 20 mmHg at Day 14 and 13 mmHg at the last study visit (Day 21 after termination). This subject was given medication to treat IOP (Mikelan).

c. Subject 46-3 had an IOP of 9 mmHg at baseline, which increased to 21 mmHg at Day 14 and decreased to 16 mmHg at the last study visit (Day 14 after termination). This subject was not given medication to treat the IOP increase.

d. Subject 51-4 had an IOP of 17 mmHg at baseline, which rose to 28 mmHg at Day 14 and decreased to 18 mmHg at the last study visit (Day 17 after termination). This subject was given medication to treat IOP (Mikelan).

e. Subject 69-4 had an IOP of 9 mmHg at baseline that increased to 20 mm Hg at Day 7 and decreased to 13 mm Hg at Day 14. This subject was not given medication to treat the IOP increase.

f. Subject 72-3 had an IOP of 11 mmHg at baseline that increased to 32 mmHg at Day 7 and decreased to 23 mmHg at Day 14 and 20 mm Hg at the last study visit (Day 42 after termination). This subject was given medication to treat IOP (Mikelan and Timoptol).

In the Senju uveitis studies (Studies 6, 7, and 11), 5 subjects (5.2%) treated with ST-601 QID had an IOP increase that was an IOP of $\geq$21 mmHg that and was also $\geq$10 mmHg higher than baseline (2 in Study 6, 2 in Study 7, and 1 in Study 11). None of these subjects discontinued study drug as a result of IOP increase. The 5 events are described below:

a. Subject 4-2 (Study 6) who received treatment in both eyes had a significant IOP increase in both eyes. In both eyes, the IOP was 14 mmHg at baseline, which increased to 45 mmHg in the

right eye and 38 mmHg in the left eye at Day 14 and decreased to 18 mmHg in both eyes at the follow-up visit (Day 28 after termination). This subject was given medication to treat IOP (Mikelan).

b. Subject 30-4 (Study 6) who received treatment in both eyes had a significant IOP increase in both eyes. In both eyes, the IOP at baseline was 16 mmHg, which increased to 31 mmHg in the right eye and 29 mmHg in the left eye at Day 14 and decreased to 13 mmHg in both eyes at the follow-up visit (Day 28 after termination). This subject was given the following medications: Mikelan, Diamox tablets, Mannitol S and Azopt.

c. Subject 7-1 (Study 7) had an IOP in the study eye of 15 mmHg at baseline, which increased to 30 mmHg at Day 14 and decreased to 14 mm Hg after 13 days. This subject was given Milekan to treat IOP. The IOP further decreased to 12 mmHg at Day 20, 7 days after the IOP medication was discontinued.

d. Subject 8-1 (Study 7) had an IOP in the study eye at baseline of 12 mmHg that increased to 22 mmHg at Day 3 and decreased to 14 mmHg at Day 7 and 13 mmHg at Day 14. This subject was not given medication to treat the IOP increase.

e. Subject O-6-04 (Study 11) who received treatment in both eyes had an IOP increase in the left eye. The IOP at baseline was 18 mmHg, which increased to 30 mmHg at Day 3, decreased to 22 mmHg at Day 7, increased slightly to 23 mmHg at Day 14, and decreased to 15 m Hg and 16 mmHg after 19 and 33 days. This subject was given Milekan to treat IOP.

The overall incidence of an IOP increase was 4%. These results indicate a slightly lower incidence of IOP increases in subjects treated with ST-601 in the Sirion studies compared with subjects in the Senju studies; 6 subjects (3 ST-601 BID [2.7%] and 3 ST-601 QID [2.8%]) with a significant increase in IOP in the Sirion post-surgical studies, and 6 subjects (5.4%) in the Senju post-surgical studies, and 5 subjects (5.2%) in the Senju uveitis studies. In conclusion, it is apparent that some investigators in the Senju post-surgical (Studies 3 and 4) and Senju uveitis (Studies 6, 7, and 11) studies considered relatively small IOP increases as an AE although those events did not meet the criteria for clinically significant IOP increases. Moreover, in 1 subject treated with ST-601 QID in the Sirion studies (Studies 1 and 2), the investigator did not consider the IOP increase as an AE, yet it met the criteria for a clinically significant IOP increase.

Integrated Summary of IOP Increase of >=10 mmHg from Baseline and Observed IOP >=21 mmHg (Safety Population)

IOP Increase	Sirion Post-Surgical Studies ST-601 BID N=111 Studies 1&2	Sirion Post-Surgical Studies ST-601 QID N=107 Studies 1&2	Sirion Post-Surgical Studies Placebo N=220 Studies 1&2	Senju Post-Surgical Studies ST-601 QID N=111 Studies 3&4	Senju Uveitis Studies ST-601 QID N=96 Studies 6, 7, 11
No. of subjects	3	3	2	6	5

Time to Onset of Clinically Significant IOP Elevation in the Integrated Analysis

	Number of Patients	Mean Time to Onset (Days)	Median Time to Onset (Days)
Sirion Studies	6	12	8
Senju Studies	11	9.25	7
Overall	17	10.4	7

Study 1: Proportion of Subjects with Increase in Intraocular Pressure of 10 mmHg or More

Visit	ST-601 BID (N=54)	ST-601 QID (N=52)	Vehicle (N=113)
Visit 2 (Day ¾)	0 (N=53)	0 (N=52)	0 (N=113)
Visit 3 (Day 8)	1 (N=51)	1 (N=50)	2 (N=101)
Visit 4 (Day 15)	0 (N=48)	1 (N=50)	0 (N=68)
Visit 5 (Day 29)	0 (N=47)	0 (N=48)	0 (N=56)
Visit 6 (Follow-up)	0 (N=53)	0 (N=50)	0 (N=111)

Study 2: Proportion of Subjects with Increase in Intraocular Pressure of 10 mmHg or More

Visit	ST-601 BID (N=57)	ST-601 QID (N=55)	Vehicle (N=107)
Visit 2 (Day ¾)	0 (N=57)	1 (N=54)	0 (N=105)
Visit 3 (Day 8)	1 (N=55)	1 (N=53)	2 (N=108)
Visit 4 (Day 15)	1 (N=54)	1 (N=53)	0 (N=74)
Visit 5 (Day 29)	1 (N=52)	2 (N=51)	0 (N=70)
Visit 6 (Follow-up)	0 (N=57)	1 (N=51)	0 (N=100)

Another special safety study performed was corneal endothelial cell counts at baseline and at Visit 6. This measurement was only performed in Study 1 and 2.

Corneal Endothelial Cell Count Change From Baseline (Integrated Data From Study 1 and 2)

		ST-601 BID (N=111)	ST-601 QID (N=107)	ST-601 BID and QID (N=218)	Vehicle (N=220)
Visit 1- Day 0	Mean	2301.7	2213.4	2257.3	2279.9
	SD	493.7	639.4	571.7	526.9
Visit 6-Follow-up	Mean	2288.6	2180.1	2237.0	2250.5
	SD	633.9	592.5	615.3	633.2
Change From Baseline	Mean	78.8	14.3	47.2	36.3
	SD	529.3	464.4	498.0	521.5
P value based on the difference between ST-601 and vehicle		0.28	0.72	0.52	

Reviewer's Comment:
Corneal endothelial cell counts should be checked 3 months after initiation of treatment. In the protocol, evaluation at Visit 6 (defined as 1 week after last study drug dose) may be too early to discover any endothelial changes.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed.

7.5.2 Time Dependency for Adverse Events

Not performed.

7.5.3 Drug-Demographic Interactions

Study 1: Proportion of Subjects (<65 years old) With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	2/10	2/16	0/29	0.0134	0.0514
Day 8 (LOCF)	1/10	5/16	5/30	0.2720	0.8245
Day 15 (LOCF)	5/10	6/16	6/30	0.0658	0.1980
Day 29 (LOCF)	7/10	7/16	5/30	0.0014	0.0463
Follow-up	6/10	9/13	12/28	0.3514	0.1159

Study 1: Proportion of Subjects (>=65 years old) With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	1/47	2/38	0/75	0.2046	0.0450
Day 8 (LOCF)	8/47	8/39	16/75	0.1282	0.0535
Day 15 (LOCF)	20/47	19/39	9/75	0.0001	<0.0001
Day 29 (LOCF)	28/47	25/39	21/75	0.0005	0.0002
Follow-up	29/47	27/38	39/72	0.4168	0.0856

Study 1: Proportion of Male Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	3/27	1/23	0/55	0.0118	0.1196
Day 8 (LOCF)	2/27	5/24	5/55	0.7976	0.1489
Day 15 (LOCF)	10/26	8/22	6/40	0.0298	0.0542
Day 29 (LOCF)	15/27	12/24	10/55	0.0006	0.0037
Follow-up	16/27	13/20	23/51	0.2340	0.1313

Study 1: Proportion of Female Subjects With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	0/3	3/31	0/49	0	0.0264
Day 8 (LOCF)	7/30	8/31	6/50	0.1834	0.1102
Day 15 (LOCF)	15/30	17/31	9/50	0.0025	0.0006
Day 29 (LOCF)	20/30	20/31	16/50	0.0025	0.0042
Follow-up	19/30	23/31	28/49	0.5865	0.1222

Study 2: Proportion of Subjects (<65 years old) With Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	2/10	2/16	0/29	0.0134	0.0514
Day 8 (LOCF)	1/10	5/16	5/30	0.2720	0.8245
Day 15 (LOCF)	5/10	6/16	6/30	0.0658	0.1980
Day 29 (LOCF)	7/10	7/16	5/30	0.0014	0.0463
Follow-up	6/10	9/13	12/28	0.3514	0.1159

7.5.4 Drug-Disease Interactions

ST-601 was evaluated for the treatment of post-surgical ocular inflammation with no drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between ST-601 and any of the concomitant medications allowed in those studies. Drug interactions, if any, are expected to be similar to those for other corticosteroids. The extremely limited systemic absorption of ST-601 would limit the potential for drug interaction.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of difluprednate in topical preparations, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was not tested on a pediatric population. Height and weight data were not collected as part of this protocol.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Durezol is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

On April 18, 2008 at 4 month safety update was submitted to the NDA. The safety update report covers the period of December 26, 2007 through March 31, 2008 and provides additional clinical safety information from 3 ongoing clinical studies evaluating the safety and efficacy of ST-601. All of these studies are ongoing and the data is still masked.

US Clinical Studies of ST-601 During Reporting Period

Study	Title	Purpose	Patient Population	No. of Subjects Enrolled	Study Status
ST-601A-001 Originally Submitted on November 9, 2006 (IND 75,713, S 0000)	A Phase 2b Multi-center, Randomized, Double-Masked Study of the Safety and Efficacy of Difluprednate 0.05% Ophthalmic Emulsion Compared to Prednisolone Acetate 1% Ophthalmic Suspension in the Treatment of Endogenous Anterior Uveitis	To assess the efficacy and safety of difluprednate 0.05% compared to Prednisolone acetate 1% in subjects with endogenous anterior uveitis	Subjects with endogenous anterior uveitis	57	Study ongoing. The intended treatment duration is 14 days, with 2 weeks of tapering and 2 weeks of follow-up (total 6 weeks) after initiation of treatment.
ST-601-003 12/7/07 (IND 75,713,	A Phase 3 Multi-center, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of	To assess the efficacy and safety of difluprednate 0.05% compared to Placebo (vehicle)	Subjects scheduled for unilateral ocular	125	Study ongoing. Anticipated completion date of study: Q2, 2008

S 0017)	Difluprednate Administered 4 Times Daily in the Management of Inflammation Following Ocular Surgery	administered 4 times daily (QID) for the management of post-surgical ocular inflammation following ocular surgery	surgery aged 2 years or older		
ST-601-004 12/7/07 (S0017)	A Phase 3 Multi-center, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Difluprednate Administered 2 Times Daily in the Management of Inflammation Following Ocular Surgery	To assess the efficacy and safety of difluprednate 0.05% compared to Placebo (vehicle) administered 2 times daily (BID) for the management of post-surgical ocular inflammation following ocular surgery	Subjects scheduled for unilateral ocular surgery aged 2 years or older	124	Study ongoing. Anticipated completion date of study: Q2 2008

In Study ST-601A-001, a total of 98 AEs were reported in 30 subjects. The majority of these AEs were ocular with superficial punctate keratitis, increased ocular pressure (IOP), photophobia, dry eye, and decreased vision being the most commonly reported ocular AEs. Seventeen subjects experienced AEs that were considered to be mild, and 10 experienced AEs that were considered to be moderate in intensity. Three subjects experienced severe AEs and there was 1 serious AE (SAE) of chest pain reported in this study that was considered severe and not related to study medication.

In Study ST-601-003, a total of 115 AEs were reported in 38 subjects. The majority of these AEs were ocular with punctate epithelial erosion, conjunctival hyperemia, IOP increase, decreased vision, and a foreign body sensation in the eyes being the most commonly reported ocular AEs. There was 1 SAE, which was the occurrence of a seizure disorder that was not related to study medication and which resolved with medication.

In Study ST-601-004, a total of 90 AEs were reported in 42 subjects. The majority of these AEs were ocular, with cataract, eye redness, IOP increase, photophobia, and eye pain being the most commonly reported ocular AEs. Nineteen subjects experienced AEs that were rated as possibly due to study medication. The 3 AEs rated as severe were worsening of visual acuity from baseline and photophobia, 2 of which were possibly related to study medication and which required study drug discontinuation. One SAE, a bleeding ulcer, which was considered moderate and unlikely related to study medication, was reported in this study. Study medication was discontinued for this subject, and this SAE resolved with medication.

Serious Adverse Events Occurring Across All Studies During the Reporting Period

Study No./ Subject No.	Treatment Group	Serious Adverse Event	Relationship to Study Drug	Outcome	IND Safety Report
ST-601A-001/ 15011	Masked	Chest pain	Not related	Not recovered	No
ST-601-003/ 23006	Masked	Seizure disorder with postictal state and confusion	Not related	Resolved	No
ST-601-004/ 65023	Masked	Bleeding ulcer	Unlikely related	Resolved	No

No IND safety reports have been submitted to FDA during this period. There have been no deaths in any of the ongoing studies during the reporting period.

64 subjects have withdrawn from the three studies during this reporting period. The most frequent reason for subjects withdrawing from these studies was the apparent lack of efficacy of study medication in the two placebo-controlled post-surgical inflammation studies. The total proportion of subjects withdrawing from the uveitis study was 5.2%, and none of the 3 subjects withdrew for lack of efficacy.

No new information regarding the mechanism of action of ST-601 was obtained during the reporting period. No regulatory actions were taken during this reporting period for this product in any foreign countries.

8 Post-marketing Experience

Because ST-601 is not marketed in any country, no sources of AE information exist, except for clinical study reports of the trials that were conducted for its development. A post-marketing safety report was submitted, however, for the dermatological formulation of difluprednate 0.05%, Myser ointment. The report was prompted by a foreign scientific literature case report of acquired hemophilia resulting in the death of a hospitalized patient receiving multiple medications including difluprednate (Myser ointment). Causality is unknown. There have been no other similar adverse experience reports previously filed. No follow-up written report was submitted for this AE.

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on difluprednate.

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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