CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-212

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 18, 2008
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	22-212
Applicant	Sirion Therapeutics
Date of Submission	December 21, 2007
PDUFA Goal Date	June 26, 2008
Proprietary Name / Established (USAN) names	Durezol (difluprednate ophthalmic emulsion) 0.05%
Dosage forms / Strength	ophthalmic emulsion
Proposed Indication(s)	for the treatment of inflammation and pain associated with ocular surgery
Recommended:	Approval

1. Introduction

Durezol (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).

Table of Currently Available Treatments

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.

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

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.

This proposed indication, the treatment of inflammation and pain associated with ocular surgery, is acceptable and supported by the submitted data. The design of the trials submitted by Sirion (ST-601A-002a and ST-601A-002b) provides sufficient information to approve an indication for all ocular surgery, not just cataract surgery.

2. Background

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.

3. CMC

DRUG SUBSTANCE:
The drug substance is covered by DMF [redacted] and a Letter of Authorization to refer to this DMF is supplied. This DMF, as amended, has been reviewed and found to be adequate. Some details are supplied in the NDA. Difluprednate is 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17- butyrate. It is a [redacted] with a melting point of [redacted] and a specific rotation of [redacted]

A reasonable specification, including tests for appearance, identity, melting point, [redacted] assay, and [redacted] The analytical methods are fully described. No validation details are supplied but the sponsor has agreed to carry out appropriate studies. Sirion Therapeutics' commitment to carry out this work is sufficient.

Satisfactory Certificates of Analysis are provided for three batches of drug substance used to make drug product for clinical studies.

DRUG PRODUCT:
The drug product is a sterile ophthalmic emulsion containing 0.05% difluprednate as the active component and 0.1% sorbic acid as a preservative. Inactive ingredients are glycerin, sodium acetate, boric acid, castor oil, polysorbate 80, sodium edetate, sodium hydroxide, and water for injection. The excipients are all of compendial quality.

The product was originally developed by Senju Pharmaceuticals in Japan and a number of product development reports are supplied. Phase 2 and 3 trials were carried out using product manufactured by Senju in Japan. Phase 3 trials were also carried out using product manufactured by [redacted] the proposed commercial manufacturer. The same formulation was used for all clinical trials. The product is isotonic to slightly hypertonic to tears. The tonicity is governed [redacted]. The product is preserved with 0.1% sorbic acid. This has not changed during the drug development process. The stability of the emulsion is governed by [redacted] In this case the emulsion appears to be [redacted]

Drug product manufacturing, packaging, and labeling will be carried out by [redacted] Drug substance testing and drug product release and stability testing will be carried out by [redacted] An Establishment Evaluation Request was made via EES and an Overall Recommendation of

Acceptable has been made.

DRUG PRODUCT COMPOSITION:

From the original CMC review, page 19.

P.1 Description and Composition of the Drug Product [Durezol (difluprednate ophthalmic emulsion) 0.05%]

Component	Function	Quantity
Difluprednate	Active	0.05%
Glycerin, USP	Tonicity agent	2.20%
Sodium acetate, USP	Buffer	0.05%
Boric acid, USP	Buffer	0.10%
Castor oil, USP	Oil phase	5.00%
Polysorbate 80, USP	Emulsifier	4.00%
Sodium edetate, USP	Stabilizer	0.02%
Sorbic acid, USP	Preservative	0.10%
Sodium hydroxide, USP	pH adjustment	✓
Water for injection, USP	Water phase	qs

The emulsion is [redacted] packaged in 5 mL [redacted] bottle with a dropper. The bottles are contained in cardboard boxes.

REGULATORY SPECIFICATIONS:

From the May 19, 2008, Quality Information Amendment, Section 3.2.P.5.1:

Table 1. Specifications

Test Items	Methods	Method Location	Release Criteria	Shelf Life Criteria
		3.2.R.2.1.1		
		3.2.R.2.1.2		
		3.2.R.2.1.2		
		3.2.R.2.1.4		
		3.2.R.2.1.3		

Appears This Way
On Original

Table 1. Specifications

Test Items	Methods	Method Location	Release Criteria	Shelf Life Criteria
		3.2.R.2.1.5		
		3.2.R.2.1.6		
		3.2.R.2.1.7		
		3.2.R.2.1.8		
		3.2.R.2.1.9		
		3.2.R.2.1.10		
		3.2.R.2.1.11		
		3.2.R.2.1.12		
		3.2.R.2.1.13		
		3.2.R.2.1.14		
		Pending		

, less than; NA, not applicable; NMT, no more than; Rf, reference standard; USP-EU, USP

4. Nonclinical 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 appears to be low. 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.

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 of rabbits.

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 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 significant ocular toxicity. 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.

5. Clinical Pharmacology/Biopharmaceutics

To support product approval, 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.

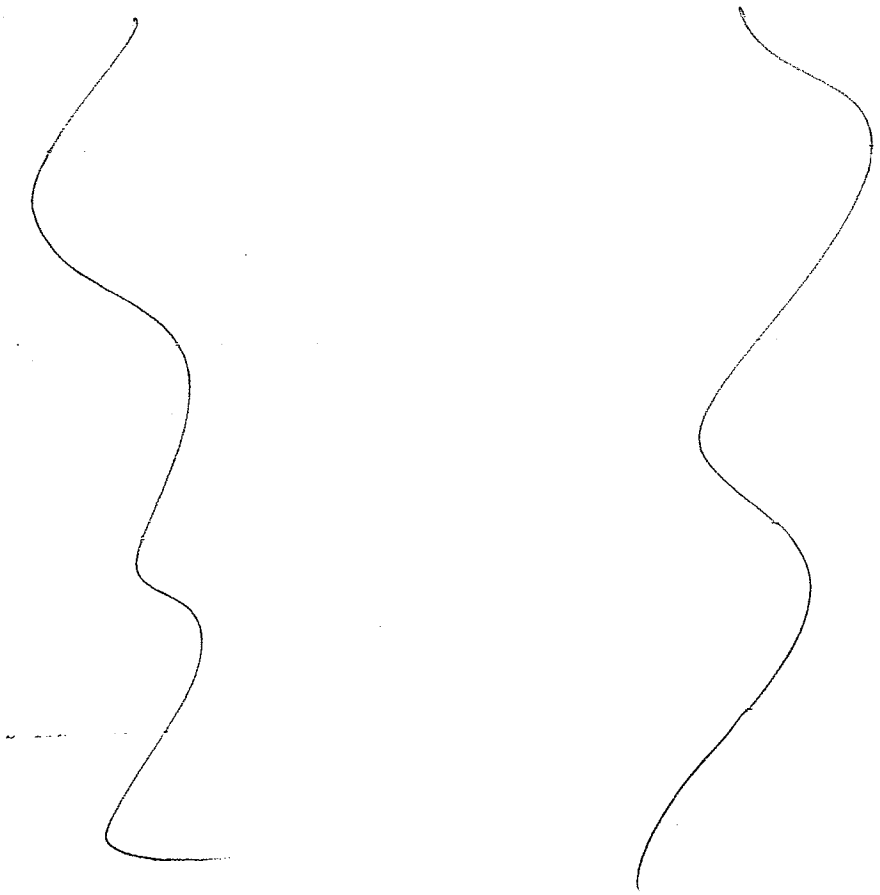
Difluprednate has negligible systemic absorption following multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days, as evidenced by undetectable concentrations of the active metabolite 6α,9-difluoroprednisolone 17-butyrate (DFB). No significant changes in mean serum cortisol levels were noted following multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days.

In studies evaluating the efficacy and safety of difluprednate 0.05% administered either BID or QID for up to 14 days, a dose-response relationship was suggested between the BID and QID dose groups for the primary efficacy endpoint of the proportion of subjects in the ST-601 group with an anterior chamber cell grade of "0" on Day 8 compared with the placebo (vehicle) group. Based on the suggested dose-response for the primary and secondary efficacy endpoints in the Phase 3 trials conducted in the US, the QID regimen of difluprednate 0.05% ophthalmic emulsion appears more effective than the BID regimen.

6. Sterility Assurance

Per the Product Quality Microbiology Review dated June 16, 2008:

The product quality microbiology deficiencies identified in the first review (i.e. micro review dated May 9, 2008) were conveyed to the applicant via e-mail. The deficiencies are provided below in bold type. The applicant's responses to the deficiencies are provided in regular type.



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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Cross Dis. 1

Satisfactory

5. **Provide the following information regarding sterilization of the tips and caps:**

b. **Methods used for monitoring production sterilization cycles**

Satisfactory

The application is recommended for approval by the Product Quality Microbiology Reviewer.

7. Clinical/Statistical - Efficacy

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 surgery (ST-601A-002b) January 2007–August 2007	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
Safety and efficacy	***Study 3***-Difluprednate	Safety and efficacy for post-	Randomized, double-	ST-601: 1 drop QID	200 subjects	Post-ocular surgery;	14 days	Completed; Legacy

	Phase 3 clinical study—A confirmatory study on post-operative inflammation (SJE2079/3-03) April 2004– March 2005	surgical inflammation	masked, parallel group, comparative	BM (betamethasone) ophthalmic solution 0.1%: 1 drop QID	ST-601: 100 BM: 100	Japanese adult males & females		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 difluprednate ophthalmic emulsion in the treatment of anterior uveitis (SJE2079/2- 02-PC) March 2000–April 2001	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	15 subjects ST-601: 8 BM: 7	Uveitis; Japanese adult males and females	14 days	Completed; Legacy 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 treatment of post-operative inflammation (SJE2079/2-01-PC) December 1999– October 2000	Safety and efficacy for post-operative inflammation	Randomized, double-masked, parallel-group, comparative group	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
Safety and Efficacy	***Study 11***-Phase 3 open-label clinical study of difluprednate	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	14 days	Completed; Legacy abbreviated report

	ophthalmic emulsion in the treatment of severe uveitis (SJE2079/3- 02-PC) August 2002–June 2003					females		

Two Phase 3 clinical trials were reviewed to support efficacy (Studies ST-601A-002a and ST-601A-002b).

The efficacy studies (Studies 002a and 002b) were 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. As specified in the protocol and the Statistical Analysis Plan, the analysis was to be conducted strictly geographically, with sites located north of latitude 37° in Study 002b and sites located south of latitude 37° in Study 002a.

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" (defined as $\leq$1 cell) 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.

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.

The primary efficacy endpoint for Studies 002a and 002b 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.

Since the Agency considers that a clinically meaningful endpoint would be complete clearing of anterior chamber cells where a grade 0=0 cells in the anterior chamber, the Agency utilized complete clearing of anterior chamber cells where a grade 0=0 cells in the anterior chamber in our efficacy determinations.

Complete Clearing of Anterior Chamber Cell
Study 002a [Grade 0 = 0 cells] (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

Complete Clearing of Anterior Chamber Cell
Study 002b [Grade 0 = 0 cells] (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

Analysis of Secondary Endpoints-Study 002a: 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

Analysis of Secondary Endpoints-Study 002a: 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

See the Medical Officer's review, pages 20 -23, dated 04 June 2008.

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.

Per the original Stats review Section 1.2:

> 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. 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.

ADDITIONAL ANALYSIS

At the May 29, 2008, Advisory Committee Meeting, an addition analysis was requested to look at between-group differences where both inflammation (no cells) and pain equal zero. A Committee member questioned whether difluprednate was effective in subjects with concomitant pain and inflammation.

The following two tables demonstrate statistically significant differences between difluprednate and vehicle at Day 15 in both 002a and 002b:

Proportion of Subjects with Clearing (Count of "0") of Anterior Chamber Cells and Pain VAS 0 (ITT Population) Protocol ST-601A-002a

Visit		Difluprednate 0.05% BID (N=57)	Difluprednate 0.05% QID (N=55)	Placebo (N=107)	BID Regimen (1)	QID Regimen (1)
Visit 2 - Day 3/4	n	57	54	103		
	No	57(100.0%)	52(96.3%)	103(100.0%)		
	Yes	0	2(3.7%)	0	0%	3.7%, 0.0493, (-1.3, 8.7)
Visit 3 - Day 8	n	55	53	82		
	No	50(90.9%)	42(79.2%)	73(89.0%)		
	Yes	5(9.1%)	11(20.8%)	9(11.0%)	-1.9%, 0.7211, (-12.1, 8.3)	9.8%, 0.1183, (-3.1, 22.6)
Visit 3 - Day 8 (LOCF)	n	57	55	104		
	No	52(91.2%)	44(80.0%)	95(91.3%)		
	Yes	5(8.8%)	11(20.0%)	9(8.7%)	0.1%, 0.9797, (-9.0, 9.2)	11.3%, 0.0401, (-0.5, 23.2)
Visit 4 - Day 15	n	54	53	74		
	No	36(66.7%)	32(60.4%)	64(86.5%)		
	Yes	18(33.3%)	21(39.6%)	10(13.5%)	19.8%, 0.0074, (5.0, 34.6)	26.1%, 0.0007, (10.8, 41.4)
Visit 4 - Day 15 (LOCF)	n	57	55	104		
	No	39(68.4%)	34(61.8%)	94(90.4%)		
	Yes	18(31.6%)	21(38.2%)	10(9.6%)	22.0%, 0.0004, (8.6, 35.3)	28.6%, <.0001, (14.5, 42.6)
Visit 5 - Day 29	n	52	51	70		
	No	26(50.0%)	23(45.1%)	50(71.4%)		
	Yes	26(50.0%)	28(54.9%)	20(28.6%)	21.4%, 0.0157, (4.2, 38.7)	26.3%, 0.0035, (9.1, 43.6)
Visit 5 - Day 29 (LOCF)	n	57	55	104		
	No	31(54.4%)	26(47.3%)	84(80.8%)		
	Yes	26(45.6%)	29(52.7%)	20(19.2%)	26.4%, 0.0004, (11.4, 41.4)	33.5%, <.0001, (18.3, 48.7)
Visit 6 - Follow up	n	57	51	95		
	No	29(50.9%)	19(37.3%)	59(62.1%)		
	Yes	28(49.1%)	32(62.7%)	36(37.9%)	11.2%, 0.1747, (-5.0, 27.5)	24.9%, 0.0041, (8.4, 41.3)

(1) Difference in percent (difluprednate - placebo, positive values favor difluprednate), P-value (Chi-square unadjusted) and 95%"; confidence limits on the difference (P-value is 2-sided; significance level is 0.05).
N = number of subjects in the ITT Population

Proportion of Subjects with Clearing (Count of "0") of Anterior Chamber Cells and Pain VAS 0 (ITT Population) Protocol ST-601A-002b

Visit		Difluprednate 0.05% BID (N=54)	Difluprednate 0.05% QID (N=52)	Placebo (N=113)	BID Regimen (1)	QID Regimen (1)
Visit 2 - Day 3/4	n	52	52	112		
	No	51(98.1%)	51(98.1%)	111(99.1%)		
	Yes	1(1.9%)	1(1.9%)	1(0.9%)	1.0%, 0.5759, (-3.1, 5.1)	1.0%, 0.5759, (-3.1, 5.1)
Visit 3 - Day 8	n	51	50	91		
	No	44(86.3%)	45(90.0%)	88(96.7%)		
	Yes	7(13.7%)	5(10.0%)	3(3.3%)	10.4%, 0.0198, (0.3, 20.6)	6.7%, 0.0998, (-2.4, 15.8)
Visit 3 - Day 8 (LOCF)	n	53	52	113		
	No	46(86.8%)	47(90.4%)	110(97.3%)		
	Yes	7(13.2%)	5(9.6%)	3(2.7%)	10.6%, 0.0077, (1.0, 20.1)	7.0%, 0.0531, (-1.6, 15.5)
Visit 4 - Day 15	n	48	50	68		
	No	35(72.9%)	37(74.0%)	63(92.6%)		
	Yes	13(27.1%)	13(26.0%)	5(7.4%)	19.7%, 0.0038, (5.7, 33.7)	18.6%, 0.0054, (5.0, 32.3)
Visit 4 - Day 15 (LOCF)	n	53	52	113		
	No	40(75.5%)	39(75.0%)	108(95.6%)		
	Yes	13(24.5%)	13(25.0%)	5(4.4%)	20.1%, 0.0001, (7.9, 32.3)	20.6%, <.0001, (8.2, 32.9)
Visit 5 - Day 29	n	47	47	56		
	No	28(59.6%)	25(53.2%)	43(76.8%)		
	Yes	19(40.4%)	22(46.8%)	13(23.2%)	17.2%, 0.0601, (-0.7, 35.1)	23.6%, 0.0118, (5.5, 41.6)
Visit 5 - Day 29 (LOCF)	n	53	52	113		
	No	34(64.2%)	30(57.7%)	100(88.5%)		
	Yes	19(35.8%)	22(42.3%)	13(11.5%)	24.3%, 0.0002, (10.2, 38.5)	30.8%, <.0001, (16.1, 45.5)
Visit 6 - Follow up	n	52	51	111		
	No	32(61.5%)	27(52.9%)	82(73.9%)		
	Yes	20(38.5%)	24(47.1%)	29(26.1%)	12.3%, 0.1094, (-3.2, 27.9)	20.9%, 0.0084, (5.0, 36.9)

(1) Difference in percent (difluprednate - placebo, positive values favor difluprednate), P-value (Chi-square unadjusted) and 95%"; confidence limits on the difference (P-value is 2-sided; significance level is 0.05).
N = number of subjects in the ITT Population

8. Safety

Seven clinical trials were used to support safety of difluprednate. Studies 1, 2, 3, and 4 were in patients following cataract 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.

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.

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

See the following tables from the Medical Officer's review, Section 7.3.3

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

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

Ocular adverse reactions occurring in 5–20% of subjects in clinical studies with Durezol included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1–5% of subjects possibly related to Durezol administration included visual acuity reduced, punctate keratitis, eye inflammation, and iritis. Ocular adverse events occurring in < 1% of subjects included corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, scleral hyperemia, uveitis, application site discomfort and irritation, herpes zoster, superficial eye injury, ecchymosis and pruritis.

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.

See the Medical Officer's original review, Section 7.2.1.

9. Advisory Committee Meeting

An advisory committee meeting was held on May 29, 2008, because difluprednate is a NME.

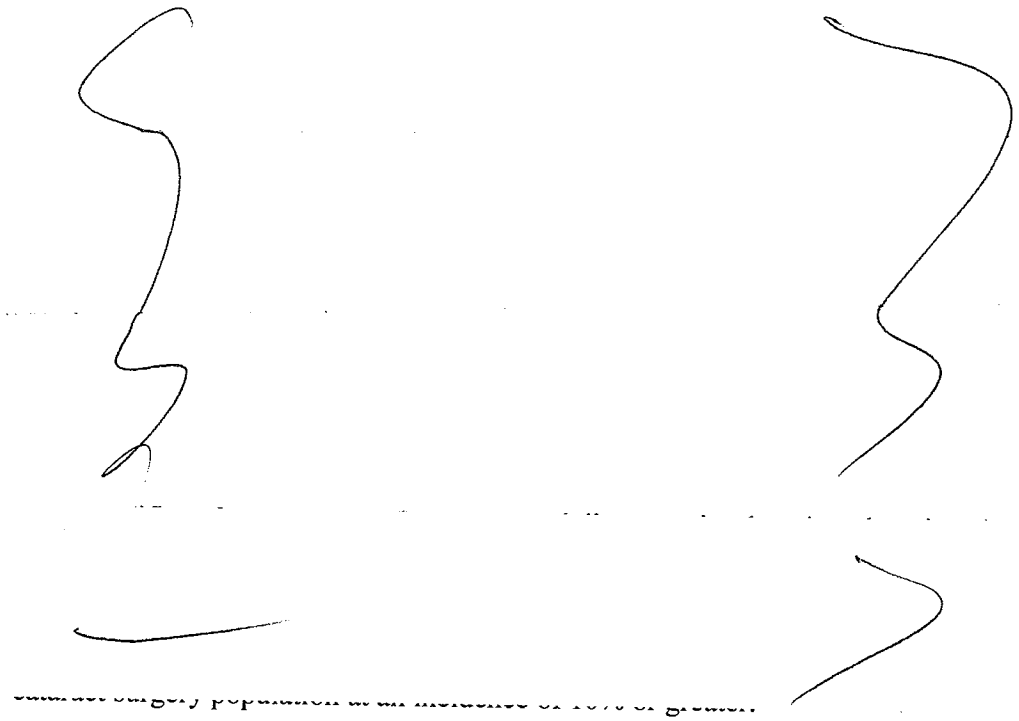
The following questions were posed:

- Do you think difluprednate ophthalmic emulsion should be approved for the treatment of ocular inflammation and pain following cataract surgery?
- If not, what additional studies should be performed?
- Do you have any suggestions concerning the labeling of the product?

The consensus of the advisory committee meeting was that difluprednate ophthalmic emulsion should be approved for the treatment of ocular inflammation and pain associated with ocular surgery.

10. Pediatrics

On June 5, 2008, Sirion has committed to conduct a post-marketing study of difluprednate in pediatric subjects as described below. A formal electronic NDA amendment will be submitted within the next few business days:



Protocol Submission Date: 10/26/2008
Study Start Date: 01/26/2009
Final Report Submission: 06/26/2011

11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. A total of three inspections were scheduled, two clinical sites plus the applicant. Per DSI, the preliminary results from the two clinical sites are NAI (no significant deviations, data appear reliable). The results of the applicant's inspection are pending. A summary of the inspections will be entered in DFS when competed.

Sirion Therapeutics has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the study were impacted by any financial payments.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "Durezol." The results of the Proprietary Name Risk Assessment found that the proposed name, Durezol, is vulnerable to name confusion that could

lead to medication errors with the name [redacted] (NDA [redacted]) is not approved and the action date for [redacted] is scheduled after the action date for Durezol.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed [redacted] proposed product labeling (PI) for this application submitted to the Agency on [redacted]

12. Labeling

NDA 22-212 is recommended for approval for the treatment of ocular inflammation and pain associated with ocular surgery with the labeling submitted by Sirion Therapeutics on 18 June 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-212 is recommended for approval for the treatment of ocular inflammation and pain associated with ocular surgery.

The labeling submitted by Sirion Therapeutics on 18 June 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

RISK BENEFIT ASSESSMENT:
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. 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.

The application supports the safety of Durezol (difluprednate ophthalmic emulsion) 0.05% for the treatment of ocular inflammation and pain associated with ocular surgery. Overall, Durezol was safe and well tolerated. Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, 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.

Clinical, CMC, Pharmacology/Toxicology, Product Quality Microbiology, Statistics, and Clinical Pharmacology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

5 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Wiley Chambers
6/23/2008 02:57:41 PM
MEDICAL OFFICER
For William Boyd, MD

Wiley Chambers
6/23/2008 03:31:50 PM
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