

Dermatologic and Ophthalmic Drugs Advisory Committee Briefing Document

Title: Difluprednate Ophthalmic Emulsion, 0.05% for the Treatment of Inflammation and Pain Associated With Ocular Surgery

NDA Number: 22-212

Product Name: Difluprednate ophthalmic emulsion, 0.05%; ST-601

Drug Substance: Difluprednate

Indication: Treatment of inflammation and pain associated with ocular surgery

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Confidentiality Statement

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best-corrected visual acuity
BID	Twice daily
BM	Betamethasone
cc	Cubic centimeter
CCS	Container closure system
DFB	Difluprednate metabolite
FDA	Food and Drug Administration
IND	Investigational new drug
ITT	Intent-to-treat
IOP	Intraocular pressure
LDPE	Low-density polyethylene
LOCF	Last observed carried forward
PP	Per protocol
NDA	New drug application
NSAID	Nonsteroidal antiinflammatory drug
QID	Four times daily
SAE	Serious adverse event
ST-601	Difluprednate ophthalmic emulsion, 0.05%
US	United States

EXECUTIVE SUMMARY

The data presented in this briefing document demonstrate that difluprednate ophthalmic emulsion, 0.05% (ST-601), has a favorable benefit–risk profile to support the following proposed indication:

- Difluprednate ophthalmic emulsion, 0.05% is indicated for the treatment of inflammation and pain associated with ocular surgery.

The proposed dosing regimen is:

- Difluprednate ophthalmic emulsion, 0.05% administered at a dosage of 1 drop in the affected eye(s) twice a day (BID) for 14 days.

Background

Difluprednate was first developed as a dermatological preparation (marketed in Japan by Senju Pharmaceuticals under the product name Myser[®]) and was subsequently developed as a topical ophthalmic emulsion by Senju Pharmaceutical Co., Ltd. of Japan. Sirion Therapeutics acquired from Senju the rights to develop and market difluprednate as an ophthalmic emulsion.

The potential for harm from ocular inflammation necessitates a rapid and effective clinical intervention. Topical corticosteroids are the mainstay therapy for ocular inflammation. Difluprednate has a potency similar to betamethasone, a strong steroid in frequent use outside the United States, and greater potency at the glucocorticoid receptor than prednisolone, the topical steroid typically used in the US (Wyatt, 2001). The potency of difluprednate allows for dosing 4 times a day (QID) for uveitis (as shown by Senju in 3 clinical studies) and allows for less frequent dosing (BID) in the treatment of postsurgical inflammation. In addition, the emulsion formulation of difluprednate enables consistent dosing without the need for shaking (as is the case with the ophthalmic prednisolone acetate suspension).

Clinical Development Program

A total of 10 clinical studies were conducted by Sirion Therapeutics and Senju Pharmaceuticals, evaluating the safety and efficacy of difluprednate ophthalmic emulsion, 0.05%.

Senju conducted 8 clinical efficacy and safety studies in Japan (6 Phase 1, 2, and 3 studies were positive-controlled; 1 Phase 2 study evaluated 2 concentrations of difluprednate; and 1 open-label study investigated treatment of severe uveitis). In these studies, 207 subjects were treated with difluprednate QID for up to 14 days. In the controlled studies difluprednate was compared to betamethasone sodium phosphate 0.1% ophthalmic solution (Rinderon[®]), a standard reference drug approved for use in Europe and Japan for the symptomatic treatment of inflammatory disease of the external and anterior segment of the eye.

Based on Senju's data, Sirion initiated a Phase 3 clinical program consisting of 2 replicative, placebo-controlled trials evaluating difluprednate dosed either BID or QID in the treatment of inflammation following ocular surgery. Eligible subjects had undergone unilateral ocular surgery and had a postsurgical anterior chamber cell grade of at least "2" (see Section 7.1.1.5 for AC grading). The treatment period was 14 days, followed by a tapering period of 14 days, during which the frequency of the dosage was reduced and then stopped. The primary efficacy endpoint was the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 for subjects in the difluprednate group treated QID compared with the placebo groups. Additional efficacy endpoints evaluated in both dose groups at all time points were clearing of inflammation (chamber cell grade of "0" and cell count of 0) and clearing of pain (pain/discomfort score of 0).

Safety evaluations were performed in subjects who were receiving at least 1 study treatment and who had at least 1 postbaseline safety assessment. The first postbaseline safety assessment occurred at Day 1, when the subjects were observed after investigator-directed instillation of the study drug. The last assessment for adverse events (AEs) occurred 1 week after cessation of the study drug, on about Day 35, if a normal tapering schedule was followed.

Sirion has also initiated 2 clinical trials evaluating the use of difluprednate administered BID or QID compared to placebo (vehicle) for the treatment of inflammation and pain following ocular surgery. Subjects will start treatment 1 day prior to surgery and continue for 16 days, followed by 14 days of graduated tapering. These trials will employ similar efficacy and safety analyses to the previous Sirion Phase 3 trials, although subjects in these ongoing trials were not required to demonstrate active inflammation prior to treatment with study drug.

Efficacy Results

The results from 4 clinical trials (2 Sirion Phase 3 studies, 1 Senju Phase 2 study, and 1 Senju Phase 3 study [Table 1]) evaluated difluprednate for the treatment of postsurgical ocular inflammation and demonstrated that difluprednate administered QID was noninferior to the strong steroid, betamethasone; difluprednate administered BID or QID was superior to placebo; and the Sirion Phase 3 studies established that there was no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID (Sirion Phase 3 studies).

The 2 Sirion Phase 3 studies, presented in this document as Study 1 and Study 2, were identical, randomized, double-masked, placebo controlled studies. All results presented in this briefing document were conducted on the intent to treat (ITT) population data set, using last observed carried forward (LOCF) for missing values. The primary efficacy endpoint in both studies was the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 for difluprednate QID compared with placebo. In both studies, subjects treated with difluprednate QID or BID showed significant clearing of inflammation (anterior chamber cell grade of "0") on Day 8 compared with subjects treated with placebo. In Study 1, 29.8% and 34.5% of subjects who received difluprednate BID and QID, respectively, achieved clearing

(anterior chamber cell grade of “0”) on Day 8 compared with 12.4% of subjects who received placebo (difluprednate BID, $P = 0.0066$; difluprednate QID, $P = 0.0014$). In Study 2, 30.2% and 34.6% of subjects who received difluprednate BID and QID, respectively, achieved clearing (anterior chamber cell grade of “0”) on Day 8 compared with 6.2% of subjects treated with placebo (difluprednate BID and QID, $P < 0.0001$). This effect continued, and by Day 15 in Study 1, 61.4% of subjects in the difluprednate BID group and 65.5% of subjects in the difluprednate QID group achieved clearing of inflammation compared to 17.1% of subjects in the placebo group (difluprednate BID and QID, $P < 0.0001$). By Day 15 in Study 2, 49.1% of subjects in the difluprednate BID group and 59.6% of subjects in the difluprednate QID group achieved clearing of inflammation compared with 15.0% of subjects in the placebo group (difluprednate BID and QID, $P < 0.0001$)

Another measure of the efficacy of difluprednate in the treatment of postsurgical inflammation is the reduction in the level of pain. The endpoint used was the proportion of subjects who were free of pain (a score of 0 on the Visual Analogue Scale). By Day 3, 40.4% of subjects in Study 1 treated with difluprednate BID were pain free, as were 50.0% of subjects in the difluprednate QID group, compared with 27.6% in the placebo group (difluprednate BID, $P = 0.0772$; difluprednate QID, $P = 0.0026$). In Study 2 on Day 3, 35.8% of subjects in the difluprednate BID group were pain free, as were 40.4% of subjects in the difluprednate QID group, compared to 22.1% of subjects in the placebo group (difluprednate BID, $P = 0.0800$; difluprednate QID, $P = 0.0116$). By Day 8, 40.4% of subjects in Study 1 treated with difluprednate BID were pain free, as were 69.1% of subjects in the difluprednate QID group compared with 30.5% in the placebo group (BID, $P = 0.2250$; QID, $P < 0.0001$). In Study 2 on Day 8, 43.4% of subjects treated with difluprednate BID were pain free, as were 46.2% of subjects treated with difluprednate QID (BID, $P = 0.0121$; QID, $P = 0.0027$). By Day 15, 63.2% of subjects in Study 1 treated with difluprednate BID and 76.4% of subjects treated with difluprednate QID were pain free compared with 44.8% in the placebo group (BID, $P = 0.0209$; QID, $P = 0.0001$). By Day 15, 43.4% of subjects treated with difluprednate BID and 48.1% of subjects treated with difluprednate QID were pain free (BID, $P = 0.0150$; QID, $P = 0.0021$)

Subjects treated with difluprednate BID and QID experienced meaningful reductions in mean anterior chamber cell counts from baseline, beginning at Day 3 and continuing through Day 15. At baseline, subjects in both studies had cell counts ranging from 20.5 cells to 27.6 cells. Subjects in both studies treated with difluprednate BID demonstrated a reduction in cell count ranging from 11.6 cells at Day 3 to 24.1 cells at Day 15. Subjects in both studies treated with difluprednate QID demonstrated a reduction in cell count ranging from 11.8 cells at Day 3 to 22.5 cells at Day 15. In comparison, subjects treated with placebo demonstrated a reduction in cell count ranging from 2.0 cells at Day 3 to 9.1 cells at Day 15.

Subjects treated with placebo were more likely to be withdrawn from the study due to lack of efficacy than those treated with difluprednate either BID or QID. The withdrawal rate resulting from lack of efficacy in both studies ranged from 1.8% to 9.3% for subjects treated with difluprednate BID or QID. In contrast, the withdrawal rate resulting from a lack of treatment effect for the subjects treated with placebo ranged from 30.8% to 47.8% ($P < 0.0001$ for difluprednate BID and QID vs placebo).

The 2 Sirion Phase 3 studies and the additional supportive data from Senju's Phase 2 and Phase 3 studies demonstrate the consistency of the efficacy of difluprednate in the treatment of inflammation and pain following ocular surgery. In addition, the Sirion Phase 3 studies did not show a clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID.

Safety Results

Overall, a total of 425 subjects in the 4 postsurgical inflammation and 3 uveitis studies were exposed to difluprednate for 14 days. Difluprednate was well tolerated when dosed either BID or QID. During the Sirion Phase 3 studies few subjects withdrew from treatment due to adverse events.

The ocular AEs reported were typical of the study population (ie, subjects with ocular inflammation related to ocular surgery or endogenous anterior uveitis) and were generally mild in severity and transient in nature. Overall, subjects treated in the placebo group experienced a much higher incidence of ocular AEs compared with those treated with difluprednate, and most of the ocular AEs reported by the investigators were associated with ocular surgery.

Increased intraocular pressure (IOP) is a common treatment-related AE resulting from the use of topical ophthalmic steroids. Overall, the incidence of a clinically significant IOP increase was low, occurring in 5.4% of subjects (23/425) treated with difluprednate across all studies. It is important to note that in all subjects, IOP rise was either controlled with medication or did not require treatment.

There were no marked differences observed between the difluprednate BID and QID treatment groups in the frequency or type of AEs, and both of the difluprednate dosing regimens (BID and QID) were well tolerated.

Conclusions

Difluprednate has a very favorable safety profile and is an effective treatment for postsurgical inflammation and pain. Results from 2 replicative randomized, placebo-controlled, double-masked clinical trials demonstrate a treatment benefit for the management of inflammation and pain following ocular surgery. Results from these two studies also demonstrate that difluprednate is efficacious whether dosed BID or QID. However, as no additional clinical benefit was apparent with QID dosing, the lowest effective dose, BID dosing, is therefore recommended.

1 PURPOSE OF THE DOCUMENT

This document, prepared for the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting of May 29, 2008, presents an overview of the efficacy and safety data from the clinical development program with difluprednate ophthalmic emulsion, 0.05% (ST-601) in subjects with postsurgical ocular inflammation and pain.

2 DIFLUPREDNATE OPHTHALMIC EMULSION, 0.05% OVERVIEW

2.1 Chemical Name and Structure

Difluprednate ophthalmic emulsion, 0.05% is a topical formulation of difluprednate that is an ophthalmic emulsion for ocular instillation. Difluprednate (6 α , 9-difluoro-11 β ,17,21,-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate) is a glucocorticoid receptor agonist, a difluorinated derivative of prednisolone that has anti-inflammatory activity. The structure of difluprednate (molecular weight 508.6) is shown in Figure 1.

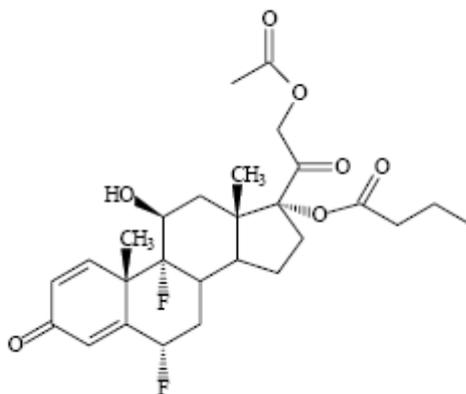


Figure 1. Difluprednate structure

2.2 Proposed Indication

Difluprednate is indicated for the treatment of inflammation and pain following ocular surgery.

2.3 Dosage and Administration

The recommended dose of difluprednate for the treatment of inflammation and pain following ocular surgery is 1 drop BID, beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

3 DEVELOPMENT RATIONALE

3.1 Disease Background

The indication being sought for difluprednate is for the treatment of inflammation and pain following ocular surgery.

Ocular inflammation can be subdivided into extraocular inflammation, such as conjunctivitis, keratitis, etc, and intraocular inflammation, which is usually a form of uveitis. There are 3 general causes of uveitis: reaction to trauma, including ocular surgery; response to infection (either localized or systemic); and autoimmune reaction (Pararajasegaram, 2004).

Intraocular inflammation from any cause has the potential to result in widespread damage to ocular tissues. The inflammatory process stimulates cellular infiltration and fibroblast proliferation, adhesions (peripheral anterior synechiae) between the iris and the angle can interfere with drainage of aqueous humor and lead to elevated IOP and glaucoma, posterior synechiae can cover the lens with pigment, and cataract may result. Keratic precipitates can result in permanent damage to corneal endothelial cells and result in corneal edema (Pavesio, 1999). In particular, postsurgical inflammation can also result in cystoid macular edema, which can result in blindness (Foster, 2007; Heier, 2000).

3.2 Unmet Medical Need

There is no Food and Drug Administration (FDA)–approved steroidal therapy for the treatment of both inflammation and pain following ocular surgery. Because of their ability to inhibit arachidonic acid synthesis, using steroids to treat of inflammation and pain can be more effective than treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). The potential for great harm resulting from ocular inflammation necessitates a quick and effective response.

Topical corticosteroids are the mainstay therapy for ocular inflammation. A more potent ophthalmic corticosteroid solution could provide benefits of working faster, and thus reduce the amount of damage done to the eye from the sequelae of inflammation or a reduced dosing frequency. The efficacy of a BID dosing regimen was shown in the US Phase 3 studies of difluprednate. In addition, the emulsion formulation of difluprednate enables consistent dosing without the need for shaking (as is the case with the marketed ophthalmic prednisolone suspensions), while providing better bioavailability than a suspension.

3.3 Scientific Background

Difluprednate (difluoroprednisolone butyrate acetate [DFBA]) is a derivative of prednisolone. In its dermatological formulation, difluprednate 0.05% is over 4 times more potent than prednisolone valerate acetate 0.3%, and 3200 times stronger than prednisolone 0.5%, as measured by peripheral vasoconstriction (Takeda et al, 1988).

Difluprednate was designed to be an antedrug (Takeda et al, 1988), which is to say that it was designed to act at the site of initial application and to be metabolized and inactivated at that

site before reaching the systemic circulation or other tissues. In this way, the topical drug has potent efficacy, but with fewer AEs. DFBA is quickly deacetylated to difluprednate, which also has good corticosteroid receptor agonist activity, but which is not believed to penetrate as well into tissues. Difluprednate, in turn, is quickly metabolized in the eye to difluoroprednisolone and other inactive metabolites, which are cleared from the body. This drug design is ideal for dermatologic and ophthalmic applications, where activity is desired only at the point of contact.

In the current model of difluprednate pharmacodynamics, difluprednate penetrates the epithelium, where it is converted to difluprednate metabolite (DFB). DFB saturates the corticosteroid receptors in the iris-ciliary body, quickly and efficiently activating them. Any unbound drug is converted to DF, the breakdown product of DFB, which is inactive and is carried away in the blood. The cellular cascade initiated by corticosteroid receptor activation continues on for several hours, however (Wyatt et al, 2001). The result is that difluprednate shows remarkable potency without a demonstrated proportionate increase in undesirable AEs. The greater potency of difluprednate may result in a more rapid control of inflammation and the activation of the cellular cascade at the corticosteroid receptor provides for less frequent dosing than prednisolone.

4 NONCLINICAL PROGRAM

Pharmacodynamic studies with difluprednate 0.05% have examined its action in several models of uveitis. Difluprednate, once instilled, is rapidly transferred to the anterior chamber and binds to the iris and ciliary body in a concentration-dependent fashion. In a rat endotoxin-induced acute uveitis model, difluprednate showed a dose-dependent ability to inhibit inflammation within 24 hours over the dose range 0.002%, 0.01%, and 0.05%, with the 0.05% dose found to be the most effective (and more effective than 0.1% betamethasone). Rat experimental melanin-protein-induced uveitis is the only animal model of uveitis that involves the anterior ocular segment, and its onset site (ie, iris, ciliary body, choroid) and symptoms are similar to human anterior uveitis. In this model, instillation of difluprednate QID for 20 days at concentrations of 0.002%, 0.01%, and 0.05% showed a dose-dependent ability to inhibit endotoxin-induced uveitis and was most effective at 0.05%. Difluprednate 0.05% was more effective than betamethasone 0.1%. In the rabbit experimental uveitis model, induced by injection of bovine serum albumin into the vitreous body, difluprednate at concentrations of 0.002%, 0.01%, and 0.05% inhibited uveitis in a concentration-dependent manner. In a rabbit postsurgical acute inflammation model, difluprednate was evaluated at 0.002%, 0.01%, and 0.05% and was found to be most effective at a concentration of 0.05%. Other pharmacodynamic studies examined difluprednate binding to the glucocorticoid receptor in the rat liver and in rabbit ocular tissues. These studies confirmed the optimum dosage of difluprednate for the treatment of ocular inflammation to be 0.05%.

The effect of formulation and particle size on difluprednate absorption and ocular bioavailability were evaluated in pharmacokinetic studies of 2 different ophthalmic formulations (emulsion and suspension). Difluprednate as an emulsion had a 40% higher bioavailability than difluprednate administered as a suspension, and when the particle size of

that emulsion was within the range of 90.3 nm to 129.3 nm, then particle size did not seem to interfere with drug absorption and bioavailability.

Ocular toxicity studies have found that instillation of difluprednate 0.05% in dogs and rabbits was well tolerated after 4 weeks, with no ocular toxicity noted and no corneal changes typical of glucocorticoid instillation. In vitro studies found no induction of aberrations in mammalian chromosomes, nor any mutagenesis in bacteria, as a result of exposure to difluprednate metabolites.

5 CLINICAL PHARMACOLOGY

The pharmacology program was primarily conducted in the Dutch rabbit model. The rabbit is a well-accepted animal model for ophthalmic studies in general. Other than pharmacokinetics, no additional clinical pharmacology studies were conducted.

5.1 Pharmacokinetics

Characterization of difluprednate ophthalmic emulsion, 0.05% pharmacokinetics in humans was performed during a Phase 1 clinical study. After repeated ophthalmic administration, the serum assay for the active DFB, after ocular administration QID for up to 7 days, failed to detect any DFB in the blood at any time. A subcomponent of this Phase 1 study looked at the degree of serum cortisol suppression as the result of ocular instillation of difluprednate QID for 7 days. No suppression was seen. Together these results indicate that ocular instillation of difluprednate has negligible systemic absorption and no detectible systemic effects on endogenous cortisol regulation.

To further elucidate the pharmacokinetics of difluprednate, the Dutch rabbit strain was used, as it is highly relevant to human pharmacokinetics and distribution. These nonclinical studies reveal pertinent information about the absorption, distribution, metabolism, and excretion of difluprednate that helped establish and validate the clinical dosing regimen.

When difluprednate is instilled into the eye, the active molecule difluprednate is known to be quickly metabolized into several major metabolites: DFB, DF (which is the breakdown product of DFB), and DF21C. DFB was the most prevalent metabolite and was considered a useful analytical surrogate for difluprednate absorption and distribution.

Single-dose and multiple-dose studies of difluprednate in Dutch rabbits demonstrated that difluprednate was rapidly metabolized and distributed to the main ocular target tissues that are affected by inflammation (iris, ciliary body, choroids, and aqueous humor in the anterior chamber), rather than accumulating in the blood. Difluprednate seems to have a low affinity for melanin, which indicates that difluprednate should work effectively in subjects regardless of their race and eye color (ie, differing levels of melanin in the eye, with brown eyes having higher levels of melanin than blue eyes). Single-dose studies also showed that 99.5% of difluprednate and its metabolites were cumulatively excreted via the feces and urine, and after repeated doses, difluprednate levels increased without affecting the maximum plasma concentration (C_{max}), with clearance from most ocular tissues within 168 hours.

On the basis of nonclinical studies, it is anticipated that difluprednate instilled in the eye will be metabolized within the ocular tissues, with little accumulation of metabolites over the time course of the proposed treatment regimen and no detectable amounts of DFB or its metabolites in the blood. Excretion of DFB and metabolites is via urine and feces.

6 CLINICAL PROGRAM

Data from 4 clinical studies are presented to show the efficacy of difluprednate in subjects with inflammation following ocular surgery. Two Phase 3 studies were conducted in the US by Sirion Therapeutics and evaluated the clinical efficacy and safety of difluprednate versus placebo (vehicle). The efficacy demonstrated in the Sirion studies is supported and confirmed by 2 studies (1 Phase 2 study and 1 Phase 3 study) conducted in Japan by Senju, which evaluated the clinical efficacy and safety of difluprednate versus betamethasone.

Seven clinical studies form the basis of the safety profile that will be reflected in the labeling (includes data from studies in another indication); these consist of 5 Phase 3 trials (Sirion Studies 1 and 2; Senju Studies 3, 6, and 11), 1 Phase 2a trial (Study 7), and 1 Phase 2b trial (Study 4).

An overview of these studies is given in Table 1.

Table 1. Description of Clinical Efficacy Studies

Study ID	No. of Study Centers (Location)	Study Start Enrollment Status, Date; Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Regimen, Route,	Study Objective	Number of Subjects by Group, Entered/ Completed	Duration	Sex, Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Study 1: A Phase 3 Multicenter, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Diffuprednate in the Treatment of Inflammation Following Ocular Surgery (ST-601A-002a)	13 sites in the US	February 6, 2007– September 17, 2007; 221 subjects	Randomized, double-masked, parallel-group, placebo-controlled	Diffuprednate: 1 drop BID or 1 drop QID Placebo: 1 drop BID or 1 drop QID Tapering at investigator discretion Topical instillation	Phase 3 safety and efficacy for postsurgical inflammation	Diffuprednate: BID: 57 QID: 55 Placebo: 109	Up to 14 days	Males and females Median age: 71.0 years (range: 29–96 years)	Postintraocular surgery anterior chamber cell grade \geq “2”	Proportion of subjects with an anterior chamber cell grade of “0” on Day 8 compared between diffuprednate and vehicle groups

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Study 2: A Phase 3 Multicenter, Randomized, Double- Masked, Placebo- Controlled Study of the Safety and Efficacy of Difluprednate in the Treatment of Inflammation Following Ocular Surgery (ST-601A- 002b)	11 sites in the US	January 24, 2007– September 20, 2007; 219 subjects	Randomized, double- masked, parallel group, placebo- controlled	Difluprednate: 1 drop, BID or 1 drop QID Placebo: 1 drop BID or 1 drop QID Tapering at investigator discretion Topical instillation	Phase 3 safety and efficacy for postsurgical inflammation	Difluprednate: BID: 55 QID: 52 Placebo: 112	Up to 14 days	Males and females Median age: 71.0 years (range: 24–88 years)	Postintraocular surgery anterior chamber cell grade \geq “2”	Proportion of subjects with and anterior chamber cell grade of “0” on Day 8 compared between difluprednate and vehicle groups

Table 1. Description of Clinical Efficacy Studies

Study ID	No. of Study Centers (Location)	Study Start Enrollment Status, Date; Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Regimen, Route,	Study Objective	Number of Subjects by Group, Entered/ Completed	Duration	Sex, Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Study 3 Diffuprednate Phase III – A Confirmatory Study on Postoperative Inflammation (SJE2079/3-03)	18 sites in Japan	April 16, 2004– March 1, 2005; 200 subjects	Randomized, double-masked, parallel group, comparative	Diffuprednate: 1 drop QID Betmethasone: 1 drop QID Topical instillation	Phase 2 safety and efficacy for postsurgical inflammation	200 subjects entered: Diffuprednate: 100 Betmethasone: 100 193 subjects completed: Diffuprednate: 93 Betmethasone: 99	14 days	Males and females Median age: 66 years (range: 48–86 years)	Postintraocular surgery	Change from baseline in mean anterior chamber cell score on Day 14 compared between diffuprednate and betamethasone groups
Study 4 Phase II Exploratory Study of Diffuprednate Ophthalmic Emulsion in the Treatment of Postoperative Inflammation (SJE2079/2-03-PC)	7 sites in Japan	April 9, 2003– July 22, 2003; 30 subjects	Randomized, double-masked, parallel-group, comparative	Diffuprednate: 1 drop QID Betmethasone: 1 drop QID Topical instillation	Phase 2 safety and efficacy for postsurgical inflammation	Diffuprednate: 11 BM: 13	14 days	Males and females Median age: 62 years (range: 53–78 years)	Postintraocular surgery	Change from baseline in mean anterior chamber cell score on Day 14 compared between diffuprednate and betamethasone groups

Table 1. Description of Clinical Efficacy Studies

Study ID	No. of Study Centers (Location)	Study Start Enrollment Status, Date; Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Regimen, Route,	Study Objective	Number of Subjects by Group, Entered/ Completed	Duration	Sex, Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Study 6 Phase 3 Confirmatory Study of Diffuprednate Ophthalmic Emulsion in the Treatment of Uveitis	18 sites in Japan	August 28, 2002– November 26, 2003; 136 subjects	Randomized, double- masked, comparative	Diffuprednate: 1 drop QID Betmethasone: 1 drop QID Topical instillation	Phase 3 safety and efficacy for uveitis	Diffuprednate: 69 Betmethasone: 67	14 days	Males and females Median age: 54 years (range: 13–83 years)	Diagnosed with endogenous anterior uveitis or panuveitis	Change from baseline in anterior chamber cell score on Day 14 compared between diffuprednate and betamethasone groups
Study 7 Phase 2a Study of Diffuprednate Ophthalmic Emulsion in the Treatment of Anterior Uveitis	7 sites in Japan	March 2, 2000–April 11, 2001; 15 subjects	Randomized, double- masked, parallel group, comparative	Diffuprednate: 1 drop QID Betmethasone: 1 drop QID Topical instillation	Phase 2 safety and efficacy for uveitis	Diffuprednate: 8 Betmethasone: 7	14 days	Males and females Median age: 46 years (range: 27–66 years)	Diagnosed with endogenous anterior uveitis (including panuveitis)	Change from baseline in anterior chamber cell score on Day 14 compared between diffuprednate and betamethasone groups

Table 1. Description of Clinical Efficacy Studies

Study ID	No. of Study Centers (Location)	Study Start Enrollment Status, Date; Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Regimen, Route,	Study Objective	Number of Subjects by Group, Entered/ Completed	Duration	Sex, Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Study 11 Phase 3 Open Label Study of Difluprednate Ophthalmic Emulsion in the Treatment of Severe Uveitis	18 sites in Japan	August 29, 2002–June 25, 2003; 19 subjects	Phase 3, open-label trial	Difluprednate: 1 drop QID Topical instillation	Phase 3 safety and efficacy for uveitis	Difluprednate: 19	14 days	Males and females Median age: 36 years (range: 23–66 years)	Diagnosed with endogenous anterior uveitis or panuveitis	The anterior chamber cell score was compared between baseline and Day 14

7 PHASE 3 STUDIES CONDUCTED BY SIRION AND SENJU

7.1 Sirion Study Design and Statistical Methodology

The 2 replicative Sirion Phase 3 postsurgical inflammation studies (Study 1 and Study 2) were conducted according to Good Clinical Practice (GCP) standards. These were multicenter, randomized, controlled, double-masked, parallel-group studies.

7.1.1 Study Design

7.1.1.1 Randomization

Subjects in the Sirion postsurgical inflammation studies were randomly assigned to 1 of 4 treatment groups—difluprednate BID, difluprednate QID, placebo BID, or placebo QID—in a 1:1:1:1 ratio.

7.1.1.2 Masking

In both Sirion Phase 3 studies, the vehicle of difluprednate was the placebo for the study trial and had an identical appearance to the active treatment. These studies were double-masked, and all participating parties were masked to treatment allocation. Masking to treatment allocation was ensured by randomly assigning the subjects to one of the investigational products that were indistinguishable from each other in packaging appearance. However, masking to the dosing regimen (BID vs QID) was not possible.

7.1.1.3 Choices of Control Treatment

In the 2 replicative Sirion Phase 3 postsurgical inflammation studies, placebo (vehicle of difluprednate) was selected as the control treatment.

7.1.1.4 Choice of Subject Population

Both of Sirion's Phase 3 studies were open to subjects aged 2 years or older on the day of consent. Subjects underwent unilateral ocular surgery the day before study enrollment and were required to present intraocular inflammation as evidenced by a minimum anterior chamber cell grade of "2."

7.1.1.5 Study Endpoints

The efficacy endpoints for the 2 Phase 3 studies supporting an indication for the treatment of inflammation and pain associated with ocular surgery were:

- The proportion of subjects with an anterior chamber cell grade of “0” for difluprednate QID and BID; AC 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
- The proportion of subjects with a pain/discomfort score of 0 for difluprednate QID and BID;
- The change from baseline in mean anterior chamber cell grade over time;
- The proportion of subjects with clearing of inflammation (cell count ≤ 5 and flare grade = “0”);
- The proportion of subjects withdrawn due to a lack of efficacy

7.1.1.6 Safety Endpoints

In each Sirion study, safety was assessed by corneal endothelial cell density, IOP, best-corrected visual acuity (BCVA), slit lamp examination, ophthalmoscopy, and the collection of AEs.

7.1.2 Statistical Methodology

Both Sirion Phase 3 studies were randomized, double-masked, and placebo-controlled trials, with 4 treatment groups comparing BID and QID dosing of difluprednate and placebo for the treatment of postsurgical anterior ocular inflammation.

Analyses of efficacy were conducted when all subjects completed the study in accordance with the Statistical Analysis Plan. The outcomes of the 2 placebo groups were examined, and because they were similar, the placebo groups were pooled for comparison with the difluprednate groups. Each difluprednate group was independently compared with placebo. Thus, there were 3 treatment groups in the analyses: difluprednate BID, difluprednate QID, and placebo.

The ITT population was defined as all randomized subjects who received at least 1 administration of the study drug. An ITT analysis with LOCF for missing data was conducted as a primary efficacy analysis for all efficacy endpoints.

The per protocol (PP) population consisted of those subjects in the ITT population who had no major 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). The PP population was used for an analysis of efficacy using only observed data.

No differences in efficacy were observed between the ITT and PP populations in each of the individual studies.

The safety analysis population was defined as all randomized subjects who received at least 1 dose of study drug.

The 2 Sirion Phase 3 studies were conducted in parallel under separate but identical protocols (Study 1, protocol ST-601A-002A, and Study 2, protocol ST-601A-002B). For the statistical analysis, sites were apportioned to each study strictly geographically, with sites located south of latitude 37 degrees being placed in Study ST-601A-002A and sites located north of latitude 37 degrees being placed in Study ST-601A-002B. In the efficacy analyses of each of Sirion's Phase 3 studies, treatments (active vs placebo) were compared in a pairwise 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 prespecified order with a 2-sided alpha of 0.05. Testing continued until a *P* value greater than 0.05 was obtained.

7.2 Senju Study Design and Statistical Methodology

7.2.1 Study Design

- Two studies were conducted in postsurgical inflammation
 - Conducted according to GCP standards
 - Multicenter, randomized, controlled, double-masked, parallel-group design
 - Used the strong steroid betamethasone as the comparator drug
 - Subjects randomized in a 1:1 fashion to receive either difluprednate or betamethasone
- Key inclusion characteristics
 - 20 years of age or older
 - Have undergone ocular surgery, either cataract or vitreous surgery or both
 - Anterior chamber cell score ≥ 2 the day after surgery
- Primary endpoint
 - The change from baseline in anterior chamber cell score on Day 14 compared between the treatment groups (ie, between difluprednate and betamethasone)
- Safety endpoints
 - AEs
 - BCVA
 - IOP
 - Slit lamp examination
 - Ophthalmoscopy
 - Clinical laboratory values

7.2.2 Statistical Methodology

- Phase 2 study
 - Primary efficacy analyses were conducted using a 1-sample or 2-sample *t*-test, as appropriate

- Between-group comparison of the number of subjects with an anterior chamber cell score of 0 was calculated using Fisher's exact test.
- Secondary analyses of between-group comparisons were reported using a 2-sample *t*-test and include changes from baseline on Days 3, 7, and 14 in the anterior chamber cell score and anterior chamber cell flare score
- Phase 3 study
 - Noninferiority hypothesis that the changes from baseline in mean anterior chamber cell grade for subjects in the difluprednate group would not be less than that for subjects in the betamethasone group was tested by setting a significance level on 1 side to 2.5%, with a noninferiority margin value of 0.21.
 - Secondary analyses were compared using the chi-square test or Fisher's exact test, as appropriate and include changes from baseline on Days 3, 7, and 14 in the anterior chamber cell score and anterior chamber cell flare score

8 SUBJECT POPULATIONS AND DEMOGRAPHICS ACROSS CONTROLLED STUDIES IN POSTSURGICAL INFLAMMATION

8.1 Disease Characteristics and Prior Treatment

In each of the 2 Sirion studies, all subjects had undergone unilateral intraocular surgery on the day before study enrollment. In Senju's Phase 2 and Phase 3 studies, this was specified as cataract surgery, vitreous surgery, or both. In both of Sirion's Phase 3 studies, the type of ocular surgery was not restricted but consisted of cataract surgery, iridoplasty, vitrectomy, wound modification, Kelman phacoemulsification, and extracapsular cataract extraction. All studies required an anterior chamber cell grade of "2" or greater on Day 1 after surgery.

8.2 Subject Demographics

A comparison of demographic characteristics for the ITT population (full analysis set) for both Sirion studies is shown in Table 2. In both Sirion Phase 3 studies, there was a balance in the overall distribution of males (45%) and females (55%), the mean age across treatment groups (68.2–70.8 years), and the proportion of subjects whose race was white (82.4%–91.6%). Although subjects older than 2 years of age were eligible, the overall age range was 24 to 96 years.

Both Senju postsurgical inflammation studies were composed of subjects with a similar balance for gender. The proportion of male subjects in these 2 studies ranged from 42.0% to 64.0%. Ages ranged from 45 to 89 years. Only the component of race could be considered to be different from the Sirion studies, as the subjects in both Senju studies were Asian.

In the Sirion Phase 3 studies, the predominant iris color was brown, followed by blue, hazel, green, and gray. Iris color was not recorded in the case report forms for either Senju study.

Table 2. Demographic Profile of Subjects in Sirion’s Phase 3 Controlled Trials

Parameter	Sirion Study 1			Sirion Study 2		
	Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 107)	Difluprednate BID (N = 54)	Difluprednate QID (N = 52)	Placebo (N = 113)
Gender (n)	57	55	107	54	52	113
Male (n, %)	27 (47.4%)	24 (43.6%)	56 (52.3%)	24(44.4%)	23 (44.2%)	43 (38.1%)
Female (n, %)	30 (52.6%)	31 (56.4%)	51 (47.7%)	30(55.6%)	29 (55.8%)	70 (61.9%)
Age, years (n)	57	55	107	54	52	113
Mean	70.8	68.1	69.1	70.7	68.4	69.9
Standard deviation	10.67	10.17	11.59	9.36	12.31	9.67
Median	73.0	69.0	69.1	71.0	72.5	71.0
Range	29–87	39–86	32–96	49–88	24–87	41–88
Race (n)	57	55	107	54	52	113
White	46 (80.7%)	48 (87.3%)	96 (89.7%)	43 (79.6%)	47 (90.4%)	100 (88.5%)
Black/African-American	9 (15.8%)	7 (12.7%)	8 (7.5%)	7(13.0%)	4 (7.7%)	6 (5.3%)
American Indian/Alaskan Native	0	0	0	1 (1.9%)	0	0
Asian	1 (1.8%)	0	2 (1.9%)	1(1.9%)	0	2 (1.8%)
Other race	1 (1.8%)	0	1 (0.9%)	2(3.7%)	1 (1.9%)	5 (4.4%)
Ethnicity (n)	57	55	107	54	52	113
Hispanic/Latino	10 (17.5%)	12 (21.8%)	28 (26.2%)	0	1 (1.9%)	2 (1.8%)
Iris color (n)	57	55	107	54	52	113
Blue	18 (31.6%)	9 (16.4%)	27 (25.2%)	20 (37.0%)	22 (42.3%)	44 (38.9%)
Brown	24 (42.1%)	33 (60.0%)	50 (46.7%)	22 (40.7%)	10 (19.2%)	33 (29.2%)
Green	6 (10.5%)	3 (5.5%)	8 (7.5%)	8 (14.8%)	7 (13.5%)	11 (9.7%)
Hazel	6 (10.5%)	8 (14.5%)	17 (15.9%)	3 (5.6%)	10 (19.2%)	20 (17.7%)
Gray	0	0	2 (1.9%)	1 (1.9%)	2 (3.8%)	5 (4.4%)
Unknown	3 (5.3%)	2 (3.6%)	3 (2.8%)	0	1 (1.9%)	0

8.3 Subject Disposition: Withdrawals from Study Treatment

In the integration of efficacy for both Sirion Phase 3 studies, the percentage of subjects who completed the study in the combined difluprednate BID and QID groups was 91.3%, and the percentage of subjects in the placebo group who completed the study was 56.4%—a statistically significant difference ($P < 0.0001$).

Table 3 shows the withdrawals from study treatment for all subjects who were randomly assigned to receive treatment in the Sirion Phase 3 studies. In Study 1, 4 subjects in the difluprednate BID group and 1 subject in the QID group were withdrawn due to a lack of treatment effect. In contrast, 33 subjects in the placebo group were withdrawn due to a lack of treatment effect. Study 2 showed similar withdrawal results, with 5 subjects in the difluprednate BID group and 2 in the QID group being withdrawn early due to a lack of treatment effect. In contrast, 54 subjects in the placebo group were withdrawn.

Table 3. Subject Withdrawals by Study: Controlled Trials

Studies and Treatment Regimen		Total Withdrawals	Reason for Withdrawal		
		Total (%)	Adverse Events n (%)	Lack of Efficacy n (%)	Other n (%)
Study 1	Difluprednate BID (N = 57)	5 (8.8%)	0	4 (7.0%)	1 (1.8%)
	Difluprednate QID (N = 55)	4 (7.3%)	2 (3.6%)	1 (1.8%)	1 (1.8%)
	Placebo (N = 107)	39 (36.4%)	3 (2.8%)	33 (30.8%)	3 (2.8%)
Study 2	Difluprednate BID (N = 54)	6 (11.1%)	0	5 (9.3%)	1 (1.9%)
	Difluprednate QID (N = 52)	4 (7.7%)	0	2 (3.8%)	2 (3.8%)
	Placebo (N = 113)	57 (50.4%)	1 (0.9%)	54 (47.8%)	2 (1.8%)

9 EFFICACY DATA

9.1 Summary of Efficacy

The 2 clinical trials conducted by Sirion demonstrated that difluprednate instilled BID or QID is superior to placebo and that there is no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID.

The proposed indication for difluprednate is for the treatment of inflammation and pain following ocular surgery, and the proposed dosing regimen is 1 drop in the affected eye(s) BID for 14 days. The data from the 2 Phase 3 studies demonstrate that with BID dosing of difluprednate, clinical efficacy is maintained. In addition to improving compliance, this dosing schedule also reduces the exposure of the eye and the subject to corticosteroids, potentially limiting the side effects typically seen with steroids.

Efficacy results from Sirion Study 1 showed that 29.8% and 34.5% of subjects who received difluprednate BID and QID, respectively, achieved clearing of ocular inflammation (anterior chamber cell grade = “0”) on Day 8 compared with 12.4% of subjects who received placebo (BID, $P = 0.0066$; QID, $P = 0.0014$). Efficacy results from Sirion Study 2 demonstrated similar results, with 30.2% and 34.6% of subjects who received difluprednate BID and QID, respectively, achieving clearing of ocular inflammation on Day 8 compared with 6.2% of subjects who received placebo (BID and QID, $P < 0.0001$) (Table 4).

Table 4. Comparative Efficacy Results: Effect of Difluprednate on Ocular Inflammation in the Sirion Studies

Sirion Study 1			Sirion Study 2		
Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Clearing: Anterior Chamber Cell Grade = "0" on Day 8 (LOCF)					
29.8% <i>P</i> =0.0066	34.5% <i>P</i> <0.0001	12.4%	30.2% <i>P</i> <0.0001	34.6% <i>P</i> <0.0001	6.2%
Clearing: Anterior Chamber Cell Count = 0 on Day 8 (LOCF)					
15.8% <i>P</i> =0.3584	23.6% <i>P</i> =0.0302	10.5%	18.9% <i>P</i> =0.0075	21.2% <i>P</i> =0.0012	5.3%
Clearing of inflammation: Anterior Chamber Cells ≤ 5 and Flare = 0 on Day 8 (LOCF)					
49.1% <i>P</i> <0.0001	50.9% <i>P</i> <0.0001	21.0%	43.4% <i>P</i> =0.0001	32.7% <i>P</i> =0.0118	17.0%

LOCF, last observation carried forward

Efficacy was also assessed by a more stringent criterion—the proportion of subjects who had clearing of ocular inflammation, as evidenced by an anterior chamber cell count equal to 0 by Day 8. In this analysis, 15.8% and 23.6% of subjects in Study 1 in the difluprednate BID and QID groups, respectively, reached an anterior chamber cell count of 0, compared with 10.5% of subjects in the placebo group. In Study 2, 18.9% and 21.2% of subjects in the difluprednate BID and QID groups, respectively, reached an anterior chamber cell count of 0, compared with 5.3% of subjects in the placebo group. These results were comparable to the results achieved in Senju Studies 3 and 4, in which 11.8% and 18.2% of subjects, respectively, met this endpoint when dosed with difluprednate QID.

Additional parameters evaluated by Sirion confirmed the efficacy of difluprednate. In particular, the change from baseline in the mean anterior chamber cell grade following approximately 8 days of treatment shows that in both Sirion studies, the change was significant when compared with placebo. In Studies 1 and 2, subjects displayed a reduction in anterior chamber cell grade ranging from -1.5 grade units for difluprednate BID dosing to -1.5 (Study 1) to -1.6 grade units (Study 2) for QID dosing (BID and QID, *P* < 0.0001). In contrast, subjects treated with placebo experienced a decrease in mean anterior chamber cell grade that ranged from -0.5 to -0.7 grade units (Table 5).

Similar efficacy results were seen for both studies in the change from baseline for the mean anterior chamber cell count. Subjects in Study 1 treated with difluprednate BID and QID demonstrated a reduction of 16.7 units and 17.2 units, respectively, in the mean anterior chamber cell count from baseline to treatment Day 8 compared with subjects on placebo who demonstrated a 6.5 unit reduction in the mean anterior chamber cell count (BID and QID, *P* < 0.0001). Subjects in Study 2 treated with difluprednate BID and QID demonstrated a reduction of 21.1 units and 20.6 units, respectively, in the mean anterior chamber cell count from baseline to treatment Day 8 compared with subjects on placebo who demonstrated a 6.0 unit reduction in the mean anterior chamber cell count (BID and QID, *P* < 0.0001).

Another important indication of the efficacy of difluprednate in the treatment of postsurgical inflammation is the proportion of subjects who were free of pain. Study 1 showed that as early as Day 3, 40.4% of subjects treated with difluprednate BID were pain free, as were 50.0% of subjects treated with difluprednate QID compared with 27.6% of subjects treated with placebo (BID, $P = 0.0772$; QID, $P = 0.0026$). By Day 8, 40.4% of the subjects in the difluprednate BID group and 69.1% of subjects in the QID group were pain free, compared with 30.5% of those in the placebo group (BID, $P = 0.2250$; QID, $P < 0.0001$). Study 2 also showed that as early as Day 3, 35.8% of subjects treated with difluprednate BID were pain free, as were 40.4% of subjects treated with difluprednate QID, compared with 22.1% of subjects treated with placebo (BID, $P = 0.0800$; QID, $P = 0.0116$). Study 2 further showed that by Day 8, 43.4% of subjects in the difluprednate BID group and 46.2% of those in the QID group were pain free compared with only 23.9% of subjects treated with placebo (BID, $P = 0.0121$; QID, $P = 0.0027$) (Table 10).

In summary, the 2 replicative studies conducted by Sirion show that difluprednate instilled BID or QID is superior to placebo and that there is no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID, for the treatment of inflammation and pain following ocular surgery.

9.2 Efficacy Endpoints

Proportion of subjects with clearing on Day 8 of anterior chamber cells (anterior chamber cell grade of “0”)

Both Sirion Phase 3 studies evaluated the proportion of subjects in the difluprednate QID treatment group with clearing on Day 8, defined as a grade of “0” for anterior chamber cells (ie, cells ≤ 1). By Day 8, 34.5% (19/55) of the subjects treated with difluprednate QID in Study 1 achieved clearing of inflammation compared with 12.4% (13/105) of subjects in the placebo group ($P < 0.0001$). Similarly, in Study 2, 34.6% (18/52) of the subjects treated with difluprednate QID achieved clearing of inflammation by Day 8 compared with 6.2% (7/113) of subjects in the placebo group ($P < 0.0001$) (Table 5).

An analysis of the proportion of subjects who achieved clearing of grade of “0” in the difluprednate BID group also showed a statistically significant difference when compared with the placebo group. By Day 8, 29.8% (17/57) of subjects in Study 1 treated with difluprednate BID had a grade equal to “0” compared with 12.4% (13/105) in the placebo group ($P < 0.0001$). In Study 2, 30.2% (16/53) of subjects treated with difluprednate BID had a grade equal to “0” on Day 8 compared with 6.2% (7/113) in the placebo group ($P < 0.0001$) (Table 5).

Table 5. Comparative Efficacy Results: Effect of Difluprednate on Ocular Inflammation (Anterior Chamber Cell Grade = “0”) on Day 8

Sirion Study 1			Sirion Study 2		
Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
29.8% <i>P</i> = 0.0066	34.5% <i>P</i> < 0.0001	12.4%	30.2% <i>P</i> < 0.0001	34.6% <i>P</i> < 0.0001	6.2%

The efficacy of a therapeutic agent for the management of inflammation following ocular surgery can be demonstrated in multiple analyses. Following are presented additional efficacy analyses that support the conclusion that difluprednate is effective in the treatment of postsurgical ocular inflammation.

Proportion of subjects with clearing (anterior chamber cell grade of “0”) of anterior chamber cells (ITT population)

Both Study 1 and Study 2 demonstrated clearing of anterior chamber cell inflammation, as defined by the proportion of subjects with an anterior chamber cell grade of “0.” Subjects in both Sirion Phase 3 studies achieved significant clearing of inflammation by Day 8 in both dosage regimens, and this clearing effect was observed throughout the remainder of treatment on Day 29. Clearing of inflammation was observed to increase even after tapering of study medication began on Day 15. Results from both studies are presented in Table 6.

Table 6. Comparative Efficacy Results: Effect of Difluprednate on Anterior Chamber Cell Grade

Sirion Study 1			Sirion Study 2		
Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 107)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Clearing: Anterior Chamber Cell Grade = "0" on Day 3 (LOCF)					
7.0% <i>P</i> = 0.1126	9.3% <i>P</i> = 0.0540	1.9%	1.9% <i>P</i> = 0.8706	3.8% <i>P</i> = 0.4093	1.8%
Clearing: Anterior Chamber Cell Grade = "0" on Day 8 (LOCF)					
29.8% <i>P</i> = 0.0066	34.5% <i>P</i> = 0.0014	12.4%	30.2% <i>P</i> < 0.0001	34.6% <i>P</i> < 0.0001	6.2%
Clearing: Anterior Chamber Cell Grade = "0" on Day 15 (LOCF)					
61.4% <i>P</i> < 0.0001	65.5% <i>P</i> < 0.0001	17.1%	49.1% <i>P</i> < 0.0001	59.6% <i>P</i> < 0.0001	15.0%
Clearing: Anterior Chamber Cell Grade = "0" on Day 29 (LOCF)					
78.9% <i>P</i> < 0.0001	81.8% <i>P</i> < 0.0001	34.3%	69.8% <i>P</i> < 0.0001	78.8% <i>P</i> < 0.0001	24.8%

LOCF, last observation carried forward

Proportion of subjects with clearing (count of 0) of anterior chamber cells (ITT population)

Individual study results for the clearing of anterior chamber cells are shown in Table 7 and demonstrate that difluprednate achieved significant clearing of anterior chamber cell inflammation, beginning at Day 8 and continuing through the remainder of the study period (Day 29). These results are similar to those achieved in the Senju Phase 2 and Phase 3 studies, in which difluprednate dosed QID was compared with betamethasone. In the Senju Phase 3 study, the proportion of subjects with clearing of anterior chamber cells on Day 7 was 11.8% for the difluprednate group and 16.5% for the betamethasone group, a difference that was not statistically different (*P* = 0.3571), supporting a conclusion of noninferiority.

Table 7. Comparative Efficacy Results: Effect of Difluprednate on Anterior Chamber Cell Count

Sirion Study 1			Sirion Study 2		
Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Clearing: Anterior Chamber Cell Count = 0 on Day 8 (LOCF)					
15.8% <i>P</i> = 0.3584	23.6% <i>P</i> = 0.0302	10.5%	18.9% <i>P</i> = 0.0075	21.2% <i>P</i> = 0.0012	5.3%
Clearing: Anterior Chamber Cell Count = 0 on Day 15 (LOCF)					
43.9% <i>P</i> < 0.0001	45.5% <i>P</i> < 0.0001	14.3%	37.7% <i>P</i> < 0.0001	36.5% <i>P</i> < 0.0001	8.8%
Clearing: Anterior Chamber Cell Count = 0 on Day 29 (LOCF)					
61.4% <i>P</i> < 0.0001	58.2% <i>P</i> < 0.0001	24.8%	54.7% <i>P</i> < 0.0001	63.5% <i>P</i> < 0.0001	17.7%

LOCF, last observation carried forward

Change from baseline in anterior chamber cell count (ITT population)

The results presented in Table 7 for the clearing of anterior chamber cells are confirmed by the analysis of the change from baseline in anterior chamber cell count. This analysis determines the change in absolute cell count over time. The details of the observed and change from baseline in anterior chamber cell count are presented in Table 8.

Table 8. Comparative Efficacy Results: Observed and Change from Baseline in Anterior Chamber Cell Count

Sirion Study 1			Sirion Study 2		
Difluprednate BID (N = 57)	Difluprednate QID (N = 54)	Placebo (N = 102)	Difluprednate BID (N = 54)	Difluprednate QID (N = 52)	Placebo (N = 113)
Observed and Change From Baseline In Anterior Chamber Cell Count on Day 8					
4.0 -16.7 <i>P</i> < 0.0001	3.6 -17.2 <i>P</i> < 0.0001	13.9 -6.5	6.7 -21.1 <i>P</i> < 0.0001	6.7 -20.6 <i>P</i> < 0.0001	18.4 -6.0
Observed and Change From Baseline In Anterior Chamber Cell Count on Day 15					
2.9 -17.9 <i>P</i> < 0.0001	1.6 -19.3 <i>P</i> < 0.0001	11.7 -8.7	3.8 -24.1 <i>P</i> < 0.0001	4.8 -22.5 <i>P</i> < 0.0001	15.4 -9.1
Observed and Change From Baseline In Anterior Chamber Cell Count on Day 29					
2.3 -18.5 <i>P</i> < 0.0001	1.1 -19.7 <i>P</i> < 0.0001	9.6 -10.8	3.0 -24.8 <i>P</i> < 0.0001	3.7 -23.6 <i>P</i> < 0.0001	13.9 -10.6

Proportion of subjects with clearing of anterior chamber inflammation (cell count ≤ 5 and flare grade = “0”)

The analysis presented here is similar to that conducted for other antiinflammatory drugs that have received approval from the FDA for this indication (Donnenfeld et al, 2007). This analysis determines the effectiveness of difluprednate in clearing anterior chamber inflammation (ie, anterior chamber cell count of ≤ 5 plus flare grade of “0”). In Study 1, the proportion of subjects with clearing of inflammation on Day 8 in the difluprednate BID and QID groups, respectively, were 49.1% and 50.9% compared with 21.0% in the placebo group ($P < 0.0001$ for each comparison with placebo). The proportion of subjects who achieved this level of clearance continued to increase over time, and on Day 15, 73.7% and 70.9% in the difluprednate BID and QID groups, respectively, had achieved clearing of inflammation compared with 31.4% in the placebo group ($P < 0.0001$ for difluprednate BID and QID vs placebo). This effect was sustained through Day 29, even though tapering of study medication began on Day 15. Study 2 displayed similar and significant results. The proportion of subjects with clearing of inflammation on Day 8 in the difluprednate BID and QID groups, respectively, were 43.4% and 32.7% compared with 17.0% in the placebo group (BID, $P = 0.0001$; QID, $P = 0.0118$). The proportion of subjects who achieved this level of clearance continued to increase over time, and on Day 15, 71.7% and 71.2% in the difluprednate BID and QID groups, respectively, had achieved clearing of inflammation compared with 23.0% in the placebo group ($P < 0.0001$ for difluprednate BID and QID vs placebo). This effect was also sustained through Day 29. These data are summarized in Table 9.

Table 9. Comparative Efficacy Results: Effect of Difluprednate on Anterior Chamber Cells and Flare

Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Sirion Study 1			Sirion Study 2		
Clearing of Inflammation: Anterior Chamber Cells ≤ 5 and Flare = “0” on Day 8 (LOCF)					
49.1% $P < 0.0001$	50.9% $P < 0.0001$	21.0%	43.4% $P = 0.0001$	32.7% $P = 0.0118$	17.0%
Clearing of inflammation: Anterior Chamber Cells ≤ 5 and Flare = “0” on Day 15 (LOCF)					
73.7% $P < 0.0001$	70.9% $P < 0.0001$	31.4%	71.7% $P < 0.0001$	71.2% $P < 0.0001$	23.0%
Clearing of Inflammation: Anterior Chamber Cells ≤ 5 and Flare = “0” on Day 29 (LOCF)					
80.7% $P < 0.0001$	83.6% $P < 0.0001$	46.7%	77.4% $P < 0.0001$	80.8% $P < 0.0001$	32.7%

LOCF, last observation carried forward

Observed and change from baseline in anterior chamber cell grade (ITT population)

In both Sirion Phase 3 studies, an analysis of the change from baseline in mean anterior chamber cell grade demonstrated that there was a clinically significant improvement in postsurgical inflammation following treatment with difluprednate. This response was achieved as early as Day 3 after surgery and was sustained through Days 8, 15, and 29. By Day 8, both the difluprednate BID and QID dosing regimens in both studies had achieved a clinically significant mean change from baseline of 1.5 and 1.6 cell grade steps (LOCF) in Studies 1 and 2, respectively, in mean anterior chamber cell grade, compared with a reduction of 0.6 for the placebo group ($P < 0.0001$ for both comparisons with placebo). These results are summarized in Table 10.

Table 10. Observed and Change From Baseline in Anterior Chamber Cell Grade

Time Point	Sirion Study 1			Sirion Study 2		
	Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Day 8	0.8	0.7	1.5	1.0	0.9	1.9
	-1.5 $P < 0.0001$	-1.5 $P < 0.0001$	-0.7	-1.5 $P < 0.0001$	-1.6 $P < 0.0001$	-0.5
Day 15	0.5	0.4	1.3	0.6	0.6	1.6
	-1.8 $P < 0.0001$	-1.9 $P < 0.0001$	-0.9	-1.9 $P < 0.0001$	-1.9 $P < 0.0001$	-0.8
Day 29	0.3	0.2	1.1	0.4	0.4	1.4
	-1.9 $P < 0.0001$	-2.0 $P < 0.0001$	-1.2	-2.1 $P < 0.0001$	-2.1 $P < 0.0001$	-1.0

Proportion of subjects who were pain/discomfort free

Another indication of the efficacy of difluprednate in the treatment of postsurgical inflammation is the proportion of subjects who are free of postsurgical pain or discomfort, as measured using the Visual Analogue Scale (VAS). A significant number of subjects enrolled in both Sirion Phase 3 studies were pain free by Day 3. This effect continued throughout the study period. The proportion of subjects with a pain score of 0 can be found in Table 11. A significant reduction in pain was observed as early as Day 3 of treatment, and a significant reduction in pain continued to increase over time within both treatment groups throughout the study.

Table 11. Comparative Efficacy Results: Effect of Difluprednate on Pain

Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Sirion Study 1			Sirion Study 2		
Pain Free (Pain/Discomfort Score = 0) on Day 3					
40.4% <i>P</i> = 0.0772	50.0% <i>P</i> = 0.0026	27.6%	35.8% <i>P</i> = 0.0800	40.4% <i>P</i> = 0.0116	22.1%
Pain Free (Pain/Discomfort Score = 0) on Day 8					
40.4% <i>P</i> = 0.2250	69.1% <i>P</i> < 0.0001	30.5%	43.4% <i>P</i> = 0.0121	46.2% <i>P</i> = 0.0027	23.9%
Pain Free (Pain/Discomfort Score = 0) on Day 15					
63.2% <i>P</i> = 0.0209	76.4% <i>P</i> = 0.0001	44.8%	43.4% <i>P</i> = 0.0150	48.1% <i>P</i> = 0.0021	25.7%
Pain Free (Pain/Discomfort Score = 0) on Day 29					
70.2% <i>P</i> = 0.0116	85.5% <i>P</i> < 0.0001	50.5%	56.6% <i>P</i> = 0.0007	57.7% <i>P</i> = 0.0002	30.1%

Proportion of subjects who were withdrawn due to a lack of efficacy

The majority of subjects withdrawing from either of Sirion’s Phase 3 studies did so due to the lack of efficacy of the study drug. A significantly higher proportion of subjects in the placebo group withdrew than in either difluprednate treatment group. This withdrawal rate further underscores the efficacy of difluprednate. Table 12 presents this withdrawal rate across both studies and for all treatment groups. Clearly, those subjects treated with placebo were much more frequently withdrawn from the study, which is to be expected due to the lack of treatment effect of the placebo medication.

Table 12. Comparative Efficacy Results: Withdrawals Resulting From a Lack of Treatment Effect

Difluprednate BID (N = 57)	Difluprednate QID (N = 55)	Placebo (N = 105)	Difluprednate BID (N = 53)	Difluprednate QID (N = 52)	Placebo (N = 113)
Sirion Study 1			Sirion Study 2		
7.0% <i>P</i> = 0.0001	1.8% <i>P</i> < 0.0001	30.8%	9.3% <i>P</i> < 0.0001	3.8% <i>P</i> < 0.0001	47.8%

9.3 Analysis of Clinical Information Relevant to Dosing Recommendations

Difluprednate ophthalmic emulsion, 0.05% is a strong topical corticosteroid that has been investigated in Japan by Senju and in the US by Sirion for the treatment of inflammation following ocular surgery. The 4 clinical trials evaluating its safety and efficacy in postsurgical inflammation show that difluprednate instilled QID was statistically noninferior to the strong steroid betamethasone and was superior to placebo. In addition, the 2 replicative Sirion Phase 3 studies showed that there was no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID.

The proposed indication for difluprednate is for the treatment of inflammation and pain following ocular surgery, and the proposed dosing regimen is 1 drop in the affected eye(s) BID for 14 days. With BID administration of difluprednate, patient compliance is expected to be enhanced while clinical efficacy is maintained. In addition to potentially improving compliance, this dosing schedule also reduces the exposure of the eye and the patient to corticosteroids, potentially limiting the side effects typically seen with other topical steroids.

The replicated efficacy results from Sirion Studies 1 and 2 showed that 29.8%–30.2% of subjects who received difluprednate BID and 34.5%–34.6% of subjects who received difluprednate QID achieved clearing of ocular inflammation as measured by a cell grade of “0” on Day 8 compared with only 6.2%–12.4% of subjects treated with placebo who experienced clearing ($P < 0.0001$) (Table 4).

Another important indication of the efficacy of difluprednate in the treatment of postsurgical inflammation is the proportion of subjects who were free of postsurgical pain or discomfort. Results from both of the Sirion Phase 3 studies showed that subjects treated with difluprednate were pain free as early as Day 3 and that this effect on pain elimination increased from Day 3 of treatment through to the end of treatment on Day 29. Subjects treated with difluprednate BID remained pain free even after tapering of study medication on Day 15.

In summary, the studies conducted by Senju consistently demonstrate the efficacy of difluprednate QID in the treatment of inflammation following ocular surgery. Furthermore, the Sirion Phase 3 studies both show that there is no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID, and show the efficacy of both doses for the treatment of pain. Current clinical practice would suggest that the lowest effective dose of a topical steroid would be chosen to reduce exposure to the steroid.

9.4 Efficacy Conclusions

- Four clinical trials (1 Phase 2 and 3 Phase 3 studies) conducted by Senju and Sirion show that difluprednate instilled QID is noninferior to the strong steroid betamethasone and is superior to placebo for the treatment of inflammation following ocular surgery. In addition, the 2 Sirion Phase 3 studies show that there is no clinically meaningful difference in the efficacy of difluprednate, whether dosed BID or QID.
- Difluprednate achieved statistical significance for a clinically meaningful efficacy endpoint (proportion of subjects in the difluprednate treatment group with clearing on Day 8, defined as a grade of “0”, for anterior chamber cells) in 2 replicate, well-controlled clinical trials (Sirion Studies 1 and 2). This effect continued and increased through Day 29, even after tapering of medication began on Day 15.
- Replicative results for the efficacy endpoints consistently supported the treatment benefit demonstrated by difluprednate in both studies.
- Efficacy results from both Sirion Phase 3 studies showed that subjects who received difluprednate BID and QID achieved significant clearing of ocular inflammation on Days 8, 15, and 29 compared with subjects who received placebo.
- The proportion of subjects with clearing of ocular inflammation, as evidenced by an anterior chamber cell count of 0, was significantly larger in the BID and QID treatment groups compared with subjects in the placebo groups.
- Efficacy was further confirmed by the change from baseline in mean anterior chamber cell grade following approximately 8 days of treatment, which shows that in all studies, the change ranged from -1.5 to -1.6 grade units.
- An indication of the efficacy of difluprednate is the proportion of subjects who were free of postsurgical pain or discomfort. Studies 1 and 2 both show that subjects were pain free as early as Day 3 and that this effect was observed throughout the treatment period even after tapering of study medication had begun on Day 15.

10 SAFETY DATA

10.1 Summary of Safety

There were 10 clinical studies conducted with difluprednate ophthalmic emulsion. Seven of these studies form the basis of the safety profile that will be reflected in the labeling; these consist of 5 Phase 3 trials (Sirion Studies 1 and 2; Senju Studies 3, 6, and 11), 1 Phase 2a trial (Study 7), and 1 Phase 2b trial (Study 4). Three studies (Studies 8, 9, and 10) are excluded from the integrated analysis of safety, because Senju Studies 8 and 9 were Phase 1 studies conducted in healthy volunteers, and Senju Study 10 treated subjects for only 7 days, rather than for 14 days, as was typical of the other studies.

The 7 trials that were integrated in the analysis of safety were randomized, multicenter, double-masked, parallel-group, and comparative, except for Study 11, which was an open-label trial. Four clinical studies (Studies 1, 2, 3, and 4) were conducted in subjects with inflammation following ocular surgery, whereas the remaining 3 studies were conducted in

subjects with anterior uveitis. Studies 3, 4, 6, 7, and 11 were conducted in Japan by Senju; the comparator drug in Studies 3, 4, 6, and 7 was betamethasone ophthalmic emulsion, 0.1%, which is widely used for the treatment of ocular inflammation in countries outside of the United States. Studies 1 and 2 were conducted in the US by Sirion Therapeutics and compared difluprednate with placebo.

All of these trials evaluated difluprednate at the dosing regimen of 1 drop of difluprednate QID for 14 days; in Studies 1 and 2, subjects also could be randomly assigned to receive 1 drop BID for 14 days. In addition, during both of Sirion's Phase 3 clinical studies, difluprednate was tapered during a 2-week period following the treatment period.

Safety measurements evaluated in these studies included corneal endothelial cell density, IOP, BCVA, slit lamp examination, ophthalmoscopy, and the collection of AEs. In addition, the Senju trials evaluated hematological changes.

AE data from the following sources were integrated: including 5 Phase 3 trials (Studies 1, 2, 3, 6, and 11) and 2 Phase 2 trials (Studies 4 and 7) conducted in subjects with ocular inflammation related to postsurgical inflammation or endogenous anterior uveitis.

As part of the ongoing difluprednate clinical program, Sirion has 3 Phase 3 studies currently enrolling: 1 study in endogenous anterior uveitis and 2 studies in postsurgical inflammation, in which dosing is initiated before surgery, as is commonly done in clinical practice.

10.2 Extent of Exposure

10.2.1 Enumeration of Subjects

The number of subjects exposed to difluprednate is shown by study in Table 13. Overall, a total of 425 subjects in the 4 postsurgical (Studies 1, 2, 3, and 4) and 3 uveitis (Studies 6, 7, and 11) studies have been exposed to difluprednate for 14 days, as defined in the individual study protocols. In the studies that investigated postsurgical inflammation (Sirion Studies 1 and 2; Senju Studies 3 and 4), treatment with the study drug was initiated 1 day following surgery. Total duration of exposure in both Sirion Phase 3 studies included both the 14-day treatment period and a tapering period of approximately 2 weeks. In Senju postsurgical Studies 3 and 4, subjects were treated with the study drug for 14 days without a tapering period. In the studies that investigated endogenous anterior uveitis (Senju 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.

Table 13. Number of Subjects Exposed to Difluprednate

	Study ID	Dose Regimen	No. Subjects Exposed
Sirion PostSurgical Studies	ST-601A-002a Study 1	1 drop of: Difluprednate BID for 14 days Difluprednate QID for 14 days	56 55
	ST-601A-002b Study 2	1 drop of: Difluprednate BID for 14 days Difluprednate QID for 14 days	55 52
Senju PostSurgical Studies	SJE2079/3-03-PC Study 3	1 drop of: Difluprednate QID for 14 days	100 ^a
	SJE2079/2-03-PC Study 4	1 drop of: Difluprednate QID for 14 days	11
Senju Uveitis Studies	SJE2079/3-01-PC Study 6	1 drop of: Difluprednate QID for 14 days	69
	SJE2079/2-02-PC Study 7	1 drop of: Difluprednate QID for 14 days	8
	SJE2079/3-02-PC Study 11	1 drop of: Difluprednate QID for 14 days	19
	TOTAL	Subjects treated with Difluprednate for 14 days	425
	TOTAL	Subjects treated with Difluprednate (including subjects treated in Studies 8, 9, and 10 for less than 14 days)	441

^aThis total includes 1 case of protocol violation related to the timing of consent obtainment.

10.2.2 Duration of Exposure

In the 7 controlled studies pooled for safety, 425 subjects were exposed to difluprednate at varying dosing regimens (BID or QID). Of these, 314 subjects were treated with difluprednate QID for approximately 14 days during the study treatment period. In the Sirion Phase 3 postsurgical studies (Studies 1 and 2), the mean duration of exposure was 27 days in both the difluprednate BID and QID treatment groups and 19 days in the placebo group. The shorter duration of exposure in the placebo group was attributed to the large number of subjects in this group who discontinued treatment early due to a lack of efficacy. Subjects in the Senju postsurgical and Senju uveitis studies received 1 drop difluprednate QID for 14 days. The mean duration of exposure to difluprednate was similar across the Senju postsurgical and uveitis studies at 13 days and 14 days, respectively. The vast majority of subjects in the Senju postsurgical and uveitis studies were treated for at least 12 days (94.6% and 99%, respectively). Duration of exposure in these studies is summarized in Table 14.

Table 14. Integrated Summary of Exposure: Safety Population

	Sirion Postsurgical Studies			Senju Postsurgical Studies	Senju Uveitis Studies
	Difluprednate BID (N = 111)	Difluprednate QID (N = 107)	Placebo (N = 220)	Difluprednate QID (N = 111) ^a	Difluprednate QID (N = 96)
Exposure (days)					
Mean	26.7	26.9	19.4	13.2	14.0
Median	28.0	28.0	27.0	14.0	14.0
Min, Max	2, 49	2, 34	1, 33	0, 16	12, 17
Duration of exposure, n (%)					
0–4 days	4 (3.6%)	2 (1.9%)	42 (19.1%)	6 (5.5%)	0
5–11 days ^b	4 (3.6%)	3 (2.8%)	35 (15.9%)	0	0
12–18 days ^c	2 (1.8%)	3 (2.8%)	14 (6.4%)	104 (94.6%)	95 (99.0%)
≥19 days ^d	101 (91.0%)	99 (92.5%)	129 (58.6%)	0	1 (1.0%)

^a One subject is excluded from the count because there is no information on duration of exposure.

^b Range = 5–9 days in the Sirion postsurgical studies.

^c Range = 10–16 days in the Sirion postsurgical studies.

^d Range ≥17 days in the Sirion postsurgical studies.

10.2.3 Adverse Events

The primary sources of AE data for difluprednate ophthalmic emulsion, 0.05% are from 5 Phase 3 trials (Studies 1, 2, 3, 6, and 11) and 2 Phase 2 trials (Studies 4 and 7) conducted in subjects with ocular inflammation related to postsurgical inflammation or endogenous anterior uveitis. Subjects who were 13 to 96 years of age received difluprednate, betamethasone 0.1%, or placebo in the affected eye(s) for 14 days. Studies 1 and 2 evaluated the safety of difluprednate BID or QID compared with placebo in subjects with postsurgical inflammation. The placebo in these studies was the difluprednate study drug vehicle. Studies 3 and 4 evaluated safety related to treatment with difluprednate or betamethasone 0.1% QID in subjects with postsurgical inflammation, whereas Studies 6 and 7 evaluated safety related to treatment with difluprednate or betamethasone 0.1% QID in subjects with endogenous anterior uveitis. Open-label Study 11 evaluated safety of difluprednate QID in subjects with endogenous anterior uveitis.

Of the 425 subjects in the safety population who were treated with difluprednate, 52.6% reported at least 1 AE compared with 82.7% of the 220 subjects treated with placebo. Of the subjects who received at least 1 dose of difluprednate, 2.6% experienced at least 1 serious AE (SAE), and 3.8% permanently discontinued treatment with study drug. One subject (0.2%) experienced a SAE that was considered by the investigators to be related to difluprednate.

Integrated data from 6 controlled studies (Sirion Studies 1 and 2; Senju postsurgical Studies 3 and 4; and Senju uveitis Studies 6 and 7) and narrative data from 3 additional studies (Studies 9, 10, and 11) were evaluated for treatment-emergent AEs (TEAEs). The TEAEs

were summarized by system organ class (SOC) and preferred term (PT), using MedDRA Version 10.0. For this summary, AE information from all studies, with the exception of the Sirion studies (Studies 1 and 2), was recoded to MedDRA Version 8.0 to provide uniformity of presentation across studies.

Table 15 presents an overall summary of the distribution of different types of TEAEs for the 4 postsurgical (Sirion Studies 1 and 2 and Senju Studies 3 and 4) and 3 uveitis (Senju Studies 6, 7, and 11) studies, respectively.

Table 15. Comparison of Treatment-Emergent Adverse Events Across Studies: Safety Population

Adverse Event Categories	Sirion Postsurgical Studies			Senju Postsurgical Studies				Senju Uveitis Studies				
	Studies 1 and 2			Study 3		Study 4		Study 6		Study 7		Study 11
	Diffuprednate BID (N = 111)	Diffuprednate QID (N = 107)	Placebo (N = 220)	Diffuprednate QID (N = 100)	BM 0.1% (N = 100)	Diffuprednate QID (N = 11)	BM 0.1% (N = 13)	Diffuprednate QID (N = 69)	BM 0.1% (N = 67)	Diffuprednate QID (N = 8)	BM 0.1% (N = 7)	Diffuprednate QID (N = 19)
Subjects reporting at least 1 TEAE	66 (59.5%)	62 (57.9%)	182 (82.7%)	44 (44.0%)	37 (37.0%)	7 (63.6%)	5 (38.5%)	28 (40.6%)	23 (34.3%)	6 (75.0%)	3 (42.9%)	8 (42.1%)
Subjects with treatment-related AEs	27 (24.3%)	23 (21.5%)	99 (45.0%)	15 (15.0%)	7 (7.0%)	2 (18.2%)	0	17 (24.6%)	15 (22.4%)	6 (75.0%)	3 (42.9%)	5 (26.3%)
Subjects with at least 1 AE in study eye ^a	65 (58.6%)	58 (54.2%)	179 (81.4%)	26 (26.0%)	—	5 (5.0%)	—	21 (30.4%)	—	6 (75.0%)	—	6 (31.6%)
Subjects with at least 1 AE in fellow eye (untreated) ^a	12 (10.8%)	13 (12.1%)	13 (5.9%)	0	0	0	0	0	0	0	0	0
Subjects permanently discontinued study drug due to AEs	9 (8.1%)	4 (3.7%)	58 (26.4%)	3 (3.0%)	0	0	0	0	0	0	1 (14.3%)	0
Subjects temporarily discontinued study drug due to AEs	1 (0.9%)	1 (0.9%)	5 (2.3%)	—	—	—	—	—	—	—	—	—
Subjects with at least 1 SAE	1 (0.9%)	4 (3.7%)	2 (0.9%)	3 (3.0%)	1 (1.0%)	0	0	2 (2.9%)	0	0	0	1 (5.3%)

Table 15. Comparison of Treatment-Emergent Adverse Events Across Studies: Safety Population

Adverse Event Categories	Sirion Postsurgical Studies			Senju Postsurgical Studies				Senju Uveitis Studies				
	Studies 1 and 2			Study 3		Study 4		Study 6		Study 7		Study 11
	Diffuprednate BID (N = 111)	Diffuprednate QID (N = 107)	Placebo (N = 220)	Diffuprednate QID (N = 100)	BM 0.1% (N = 100)	Diffuprednate QID (N = 11)	BM 0.1% (N = 13)	Diffuprednate QID (N = 69)	BM 0.1% (N = 67)	Diffuprednate QID (N = 8)	BM 0.1% (N = 7)	Diffuprednate QID (N = 19)
Subjects with treatment-related SAEs	0	0	0	1 (1.0%)	0	0	0	0	0	0	0	0
Deaths	0	0	1 (0.5%)	0	0	0	0	0	0	0	0	0
Overall Adverse Event Severity												
Mild	45 (40.5%)	35 (32.7%)	82 (37.3%)	39 (39.0%)	35 (35.0%)	7 (63.6%)	5 (38.5%)	24 (34.8%)	21 (31.3%)	4 (50.0%)	3 (42.9%)	5 (26.3%)
Moderate	18 (16.2%)	21 (19.6%)	76 (34.5%)	4 (4.0%)	4 (4.0%)	0	0	5 (7.6%)	0	3 (37.5%)	0	2 (10.5%)
Severe	3 (2.7%)	6 (5.6%)	24 (10.9%)	3 (3.0%)	0	0	0	1 (1.5%)	0	0	0	1 (5.3%)

AE, adverse event; BM, betamethasone ophthalmic solution, 0.1%; N, number of subjects in the safety population; SAE, serious adverse event; TEAE, treatment-emergent adverse event

^aBilateral ocular events are counted twice (ie, once for each eye).

Ocular events in the fellow eye are excluded from the AE summary tables.

10.2.4 Common Adverse Events

Typical of this study population (ie, subjects with ocular inflammation related to intraocular surgery or endogenous anterior uveitis) and class of drug, the most commonly reported AEs were ocular events that occurred in the study eye. In all studies, the severity of AEs reported was predominantly mild to moderate, as reported by the investigators. Overall, subjects treated in the placebo group experienced a much higher incidence of ocular AEs compared with those treated with difluprednate. Most of these AEs were associated with ocular surgery. The ocular events with the highest incidence in subjects treated with difluprednate were posterior capsule opacification, conjunctival hyperemia, and punctate keratitis. These events all occurred at a higher percentage in the placebo group than in the difluprednate groups.

The nonocular/systemic AEs reported in these studies for difluprednate and placebo did not differ, were as expected for this class of drug, and gave no indication of target organ toxicity.

10.2.5 Deaths

There was 1 death in 1 of the 2 Sirion Phase 3 trials, Study 1. A subject in the placebo group experienced a cerebrovascular accident, the outcome of which was death. This event was considered unrelated to study treatment. No deaths occurred in any of the other studies.

10.2.6 Other Serious Adverse Events

The overall incidence of SAEs in the 7 clinical studies was low, with SAEs reported for 11 of 425 subjects (3%) exposed to difluprednate. Of the 329 subjects who were treated with difluprednate in the combined Senju and Sirion postsurgical studies, SAEs were reported for 8 subjects (2.4%), 1 SAE per subject. Of the 8 SAEs reported, 7 were considered by the investigator to be unrelated to study drug, and 1 (iris adhesions: subject 53-1, Study 3) was considered possibly related to study drug. Of the 96 subjects in the Senju uveitis studies, SAEs were reported in 3 subjects (3%): 1 SAE in Study 11 and 2 SAEs in Study 6; none of these events was considered related to study drug.

In the Sirion postsurgical studies (Studies 1 and 2), 1 of 111 subjects (<1%) treated with difluprednate BID experienced 1 SAE, 4 of 107 subjects (3.7%) treated with difluprednate QID had 1 SAE each, and 2 of 220 subjects (<1%) in the placebo group had 1 SAE.

In the Senju postsurgical studies (Studies 3 and 4), 3 of 111 subjects (2.7%) treated with difluprednate QID reported 1 SAE each (maculopathy, retinal detachment, and iris adhesions). Of these events, only the iris adhesions event was judged to be possibly related to difluprednate. However, the subject who experienced this event recovered after 3 days and continued to participate in the study.

In the Senju uveitis studies (Studies 6, 7, and 11), 3 of 96 subjects (3%) treated with difluprednate QID reported 1 SAE each (monoarthritis, corneal perforation, and necrotizing retinitis).

10.2.7 Other Significant Adverse Events

ADVERSE EVENTS LEADING TO DISCONTINUATION

Discontinuations due to AEs did not suggest safety concerns associated with difluprednate and were consistent with events typically expected in subjects who have just had surgery or who are receiving treatment with a topical corticosteroid. Overall, the proportion of subjects withdrawing due to AEs was much higher in the placebo group than in the difluprednate group (26.4% [58/220 subjects] vs 3.8% [16/425 subjects]).

IOP INCREASE

An increase in IOP is a common treatment-related AE resulting from corticosteroid use, particularly in the use of topical ophthalmic steroids. Overall, the incidence of IOP increase was low, occurring in 5.4% of subjects (23/425) treated with difluprednate across Studies 1, 2, 3, 4, 6, 7, and 11. Comparatively, the incidence of IOP increase was 2.3% (5/218) in the Sirion postsurgical studies, 8.1% (9/111) in the Senju postsurgical studies, 9.4% (9/96) in the Senju uveitis studies, and 0.9% (2/220) in subjects treated with placebo.

An IOP increase of ≥ 21 mm Hg that was also ≥ 10 mm Hg higher than the baseline taken the day after surgery was considered a clinically significant increase. This criterion was adopted because in the context of a short study in which transient steroid induced IOP rises could be treated by observation, such an increase in IOP would be sufficient to consider treatment to lower the IOP. The incidence of clinically significant IOP increases in subjects treated with difluprednate was low, occurring at 4% (17/425) overall in Studies 1, 2, 3, 4, 6, 7, and 11, and at 2.8% (6*/218) in the Sirion postsurgical studies, 5.4% (6/111) in the Senju postsurgical studies, 5.2% (5/96) in the Senju uveitis studies, and 0.9% (2/220) treated with placebo. (*This numerator differs by 1 subject from the number of subjects with AEs reported in the paragraph above; the investigator did not report an increase in a subject treated with difluprednate as an AE, yet it met the criteria for a clinically significant IOP increase.) In all subjects, IOP elevation either was controlled with medication or did not require treatment.

10.3 Safety Conclusions

- A total of 425 subjects have been exposed to difluprednate for 14 days at varying dosing regimens (BID or QID). Of these individuals, 314 subjects were treated with difluprednate QID for approximately 14 days.
- In US placebo controlled studies, the mean duration of exposure was 27 days in both the difluprednate BID and QID treatment groups and 19 days in the placebo group. The shorter duration of exposure in the placebo group was attributed to the large number of subjects in this group who discontinued due to a lack of efficacy.
- Of the 425 subjects in the safety population who were treated with difluprednate, 52% reported at least 1 AE compared with 82.7% of the 220 subjects treated with placebo.
- Overall, the proportion of subjects withdrawing due to AEs was much higher in the placebo group than in the difluprednate group (26.4% for placebo vs 3.8% for difluprednate-treated subjects).

- Difluprednate is well tolerated at all doses studied, and few subjects withdrew from the studies for AEs.
- AEs were mostly ocular and considered mild to moderate in severity.
- A clinically significant rise in IOP was seen in less than 3% of subjects receiving difluprednate in the US postsurgical inflammation studies.
- In the US postsurgical inflammation studies, the majority of the ocular AEs seen in any of the treatment groups were events related to the outcome of ocular surgery. These AEs were more common in those receiving placebo, as might be expected because they were not benefiting from the anti-inflammatory effect of difluprednate.

11 DISCUSSION AND CONCLUSIONS

11.1 Discussion

The proposed indication for difluprednate is for the treatment of inflammation and pain following ocular surgery. Two Phase 3 studies in postsurgical inflammation were conducted by Sirion in the United States (Study 1 and Study 2), and 2 were conducted by Senju in Japan (Phase 3 Study 3 and Phase 2 Study 4). Sirion Studies 1 and 2 evaluated the clinical efficacy and safety of difluprednate versus placebo (vehicle); Senju Studies 3 and 4 evaluated the clinical efficacy and safety of difluprednate versus betamethasone ophthalmic solution, 0.1% (a standard therapy used in Japan). A total of 664 subjects were enrolled in these 4 efficacy studies (329 of whom were treated with difluprednate).

Sirion's Phase 3 clinical program consisted of 2 double-masked, randomized, placebo-controlled clinical trials, concurrently conducted under identical protocols. The efficacy and safety of difluprednate was compared with placebo for the treatment of inflammation following ocular surgery. In these 2 studies, a total of 438 subjects were randomized, and 218 subjects were assigned to receive difluprednate, administered either BID or QID.

Senju's Phase 2 and 3 clinical programs compared difluprednate QID to betamethasone in subjects who presented with inflammation after undergoing intraocular surgery. In these studies, a total of 111 subjects were randomly assigned to receive difluprednate, administered QID.

The chief efficacy data are those from the replicate Sirion Phase 3 studies (Studies 1 and 2); the data from Senju's Phase 2 and Phase 3 studies (Studies 3 and 4) are supplemental.

The primary efficacy endpoint for the 2 Phase 3 studies conducted in the United States (Study 1 and Study 2) was the proportion of subjects in the QID treatment group with clearing on Day 8, defined as a grade of "0" for anterior chamber cells (ie, ≤ 1 cell). Multiple other endpoints were examined, including the proportion of subjects in the BID treatment group with clearing on Day 8.

The primary efficacy endpoint for both of Senju's studies (Studies 3 and 4) was the change from baseline of anterior chamber cell grade on Day 14 for difluprednate QID compared with betamethasone.

The study population for the Sirion studies was generally representative of the US population as a whole, in terms of sex and of race/ethnicity. The studies conducted by Senju in Japan evaluated an Asian population. In all these studies, the subjects were geriatric, as is typical of the ocular surgery population. Although the type of surgery was not specified in any study, the majority of subjects had cataract surgery.

The 2 Sirion studies were conducted simultaneously and in parallel under separate but identical protocols (protocol ST-601A-002A and protocol ST-601A-002B). For the statistical analysis, sites were apportioned to each study strictly geographically, with sites located south of latitude 37 degrees in Study 1 (Study ST-601A-002A), and sites located north of latitude 37 degrees in Study 2 (Study ST-601A-002B). In the efficacy analyses of Studies 1 and 2, treatments (active vs placebo) were compared in a pairwise manner, using the chi-square test stratified by study site.

In the primary efficacy analyses of Senju's Study 3, the noninferiority hypothesis that the changes from baseline in mean anterior chamber cell grade for subjects in the difluprednate group would not be less than that for subjects in the betamethasone group was tested by setting a significance level on one side to 2.5%, with a noninferiority margin value of 0.21. Secondary analyses were compared using the chi-square test or Fisher's exact test, as appropriate.

In Study 4, the primary efficacy analyses were conducted using a 1-sample or 2-sample *t*-test, as appropriate, and between-group comparison of the number of subjects with an anterior chamber cell score of 0 was calculated using Fisher's exact test. Secondary analyses of between-group comparisons were reported using a 2-sample *t*-test.

In both Sirion Phase 3 studies, multiple endpoints were found to be significant:

- The proportion of subjects administered difluprednate QID with a cell grade of "0" compared with placebo on Day 8;
- The proportion of subjects administered difluprednate BID with a cell grade of "0" compared with placebo on Day 8; and
- The proportion of subjects administered difluprednate QID on Day 3/4 with a pain/discomfort score of 0 compared with placebo.
- The proportion of subjects administered difluprednate BID and QID on Day 8 with anterior chamber cells ≤ 5 and a flare grade = "0" on Day 8.
- The proportion of subjects administered difluprednate BID and QID on Days 15 and 29 with an anterior chamber cell count = 0.
- The proportion of subjects administered placebo who were withdrawn from the studies due to a lack of treatment effect compared with difluprednate BID and QID

Both Sirion Phase 3 studies independently replicated the demonstration of efficacy of difluprednate, dosed BID or QID.

11.2 Benefit and Risk Discussion

Intraocular inflammation—whether iatrogenic, in the case of postsurgical inflammation, or endogenous, in the case of iritis, cyclitis, pars planitis, or uveitis—has the potential to cause permanent changes within the eye as a result of the inflammatory process and the fibrosis and scarring that can result. These changes include fibrous adhesions of the iris to the lens (posterior synechiae), fibrous adhesions of the anterior periphery of the iris to the cornea (peripheral anterior synechiae), and obstruction of the anterior chamber angle, causing elevated IOP. For these reasons, and also due to the pain and discomfort associated with postsurgical inflammation, it is now standard clinical practice to treat these inflammatory conditions with topical anti-inflammatory agents to bring the inflammation under control as rapidly as possible. The speed of resolution of inflammation is associated with the limitation of its sequelae.

Steroids are the most effective pharmacological group of compounds for control of inflammation and are widely used and approved for this purpose. Benefits for the physician and for the patient that are expected to be offered by difluprednate are an excellent safety and efficacy profile and less frequent dosing.

The studies conducted by Senju demonstrated that difluprednate dosed QID was as effective in reduction of postsurgical inflammation as betamethasone, a reference ophthalmic steroid widely used in Europe and Japan and regarded as a strong steroid. In subjects with severe and refractory uveitis, as well as in subjects with postsurgical uveitis following cataract extraction, the Senju studies showed a rapid response of uveitis and postsurgical inflammation to difluprednate QID, with the majority of subjects exhibiting clearing of anterior chamber cells and flare within 14 days.

The Sirion studies additionally evaluated the efficacy of BID dosing for treatment of postsurgical inflammation and included a placebo (vehicle) control group. There was significantly earlier clearing of anterior chamber cells in the BID and QID difluprednate treatment groups compared with placebo, with approximately 30% of all subjects cleared in the BID treatment group and 35% of all subjects cleared in the QID group by Day 8, as demonstrated by the proportion of subjects with an anterior chamber cell grade of “0.” Using a broader definition of clearing of anterior chamber inflammation (≤ 5 cells and a flare grade of “0”), significantly more subjects administered difluprednate BID or QID were cleared at Day 3 compared with those on placebo, and over 40% of both BID- or QID-treated subjects were cleared by Day 8 compared with 19% of placebo-treated subjects.

These data, along with the supporting evidence of rapid resolution of pain and discomfort, photophobia, corneal edema, injection, and chemosis, demonstrate the benefit of using difluprednate either BID or QID for the treatment of inflammation and pain following ocular surgery.

The risks associated with topical ophthalmic steroid use have been shown to be IOP elevation, cataract formation, delayed wound healing, and decreased resistance to infection. All of these steroid class effects are known to be more likely to occur the longer dosing continues. This has led to the general consensus that steroids should be administered at the

lowest effective dose and reduced in dose (either concentration or frequency) as quickly as possible after initiation of treatment.

The most common ocular AEs in the Sirion difluprednate Phase 3 studies were posterior capsule opacification, conjunctival hyperemia, and punctate keratitis. These AEs are similar to those seen with other ophthalmic steroid products. There were nearly twice as many AEs in the placebo group as in the difluprednate groups. Most of these AEs were associated with ocular surgery, and thus the lower incidence seen in the difluprednate group indicates an amelioration of these sequelae.

In the Senju studies, a 5% incidence of IOP elevation was associated with difluprednate QID treatment, and in the US studies conducted by Sirion, only 2.7% of subjects treated with difluprednate (either BID or QID) exhibited a clinically significant IOP rise versus 1% of subjects in the placebo group. In comparison, treatment with prednisolone acetate 1.0% has been reported to be associated with an incidence of clinically significant IOP elevation of up to 17%. On the basis of these data gathered from studies evaluating the safety and efficacy of difluprednate for the treatment of inflammation following ocular surgery, the benefit-to-risk assessment supports the use of difluprednate dosed BID dosing for 14 days for this indication.

In summary, difluprednate has been shown to be safe and effective for the treatment of inflammation and pain following ocular surgery in adequate and well-controlled studies. It has the added benefit over currently marketed ophthalmic steroid products of BID dosing (versus QID dosing) for this indication, which should enhance patient convenience and may enhance patient compliance. The identified risks associated with difluprednate are no different than with any topical ophthalmic steroid, and the safety profile of difluprednate compares favorably with that of other similar products.

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13 SIGNATURE PAGE

Title: Difluprednate Ophthalmic Emulsion, 0.05% for the Treatment of Inflammation and Pain Associated With Ocular Surgery

NDA Number: 22-212

Product Name: Difluprednate ophthalmic emulsion, 0.05%; ST-601

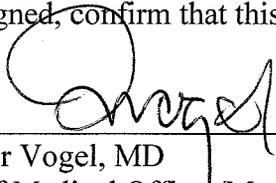
Drug Substance: Difluprednate

Indication: Treatment of inflammation and pain associated with ocular surgery

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Date: May 29, 2008

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