

**Division of Anti-Infective and Ophthalmology Products
Advisory Committee Meeting
Briefing Package**

for

**Difluprednate ophthalmic emulsion for the treatment of
inflammation and pain associated with cataract surgery**

Sponsor: Sirion Therapeutics
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Tampa, FL 33619

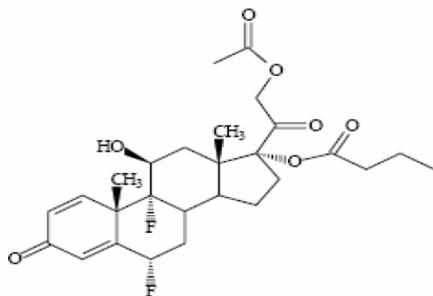
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Introduction and Background

ST-601 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 synthetic, glucocorticoid receptor agonist, a difluorinated derivative of prednisolone that has anti-inflammatory activity.



Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication, Dose, Regimens

Proposed Proprietary Name: Durezol
Established name: difluprednate ophthalmic emulsion
Sponsor: Sirion Therapeutics
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

NDA Drug Classification: P
Pharmacologic Category: Steroid
Proposed Indication: Topical corticosteroid indicated for the treatment of inflammation and pain associated with ocular surgery.

Dosage Form and Route of Administration: topical ophthalmic emulsion

State of Armamentarium for Indication

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

Chemical Composition

ST-601 Quantitative Composition

Component	Quantity (% w/w)	Function	Quality Standard
Difluprednate	0.05%	Active ingredient	In-house specification
Glycerin	2.20%	Tonicity agent	USP
Sodium acetate	0.05%	Buffer	USP
Boric acid	0.10%	Buffer	USP
Castor oil	5.00%	Oil phase	USP
Polysorbate 80	4.00%	Emulsifier	USP
Sodium edetate	0.02%	Stabilizer	USP
Sorbic acid	0.10%	Preservative	USP
Sodium hydroxide	As needed	pH adjustment	USP
Water for injection	qs	Water phase	USP

qs, as much as will suffice

Human Pharmacokinetics

Difluprednate is structurally similar to other corticosteroids and is a potent glucocorticoid in the “strong steroid” class. Examination of cortisol levels following 7 days of ocular instillation 4 times daily of difluprednate (0.05%) found no changes in blood cortisol levels. Difluprednate is rapidly metabolized in vivo to 6 α ,9-difluoroprednisolone 17-butyrate DFB, an active metabolite of difluprednate.

Clinical pharmacokinetic studies of difluprednate after repeat ocular instillation of 2 drops of difluprednate (0.01% or 0.05%) QID for 7 days showed that DFB levels in blood were below the quantification limit (50 ng/mL) at all time points for all subjects, indicating the systemic absorption of difluprednate after ocular instillation of difluprednate is limited.

Description of Clinical Data Sources

Clinical Studies with Ophthalmic Administration of Difluprednate

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product	No. of Subjects	Healthy Subject of Diagnosis of Patients	Duration of Treatment	Study Status
Safety and Efficacy	<i>Study 1</i> -A Phase 3 multi-center, randomized, double-masked, placebo-controlled study of the safety and efficacy of Difluprednate in the treatment of inflammation following ocular surgery (ST-601A-002a)	Safety and efficacy of ST-601 BID or QID vs. placebo for treatment of inflammation following ocular surgery	Randomized, double-masked, parallel-group, placebo controlled	ST-601: 1 drop BID or QID Placebo (vehicle): 1 drop BID or QID Tapering after Day 14 Ocular instillation	220 subjects ST-601 BID: 58 ST-601 QID: 55 Placebo: 107	Post-ocular surgery US males and females	Up to 14 days	Completed; Full report
Safety and efficacy	<i>Study 2</i> -A Phase 3 multi-center, randomized, double-masked, placebo controlled study of the safety and efficacy of difluprednate in the treatment of inflammation following ocular surgery (ST- 601A-002b) Jan 2007– Aug 2007	Safety and efficacy of ST-601 BID or QID vs. placebo for treatment of inflammation following ocular surgery	Randomized, double-masked, parallel-group, placebo controlled	ST-601: 1 drop BID or QID Placebo (vehicle): 1 drop BID or QID Tapering after Day 14 Ocular instillation	220 subjects ST-601 BID: 54 ST-601 QID: 52 Placebo: 114	Post-ocular surgery; US males and females	Up to 14 days	Completed; Full report

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product	No. of Subjects	Healthy Subject of Diagnosis of Patients	Duration of Treatment	Study Status
Safety and efficacy	Study 3 -Difluprednate Phase 3 clinical study—A confirmatory study on post-operative inflammation (SJE2079/3-03) April 2004– March 2005	Safety and efficacy for post-surgical inflammation	Randomized, double-masked, parallel group, comparative	ST-601: 1 drop QID BM (betamethasone) ophthalmic solution 0.1%: 1 drop QID	200 subjects ST-601: 100 BM: 100	Post-ocular surgery; Japanese adult males & females	14 days	Completed; Legacy abbreviated report
Safety and efficacy	Study 4 -Phase 2 exploratory study of difluprednate ophthalmic emulsion in the treatment of post-operative inflammation (SJE2079/2-03- PC) April 2003– July 2003	Safety and efficacy for post-operative inflammation	Randomized, double-masked, parallel-group, comparative	ST-601: 1 drop QID BM ophthalmic solution 0.1%: 1 drop QID	24 subjects ST-601: 11 BM: 13	Post-ocular surgery; Japanese adult males and females	14 days	Completed; Legacy abbreviated report
Safety and efficacy	Study 6 -Phase 3 confirmatory study of difluprednate ophthalmic emulsion in the treatment of uveitis (SJE2079/3-01-PC) August 2002– November 2003	Safety and efficacy for anterior uveitis	Randomized, double-masked, parallel-group, comparative	ST-601: 1 drop QID BM ophthalmic solution 0.1%: 1 drop QID	137 subjects ST-601: 69 BM: 68	Uveitis; Japanese adult males and females	14 days	Completed; Legacy abbreviated report
Safety and Efficacy	Phase 7 -Phase 2a study of difluprednate ophthalmic emulsion in the treatment of anterior uveitis (SJE2079/2- 02-PC) March 2000– April 2001	Safety and efficacy for anterior uveitis	Randomized, double-masked, parallel-group, comparative	ST-601: 1 drop QID BM ophthalmic solution 0.1%: 1 drop QID	15 subjects ST-601: 8 BM: 7	Uveitis; Japanese adult males and females	14 days	Completed; Legacy abbreviated report

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product	No. of Subjects	Healthy Subject of Diagnosis of Patients	Duration of Treatment	Study Status
Safety	Study 8 -Phase 1 clinical study of difluprednate ophthalmic emulsion - single instillation study (SJE2079/1-01- PC-5); May 1998– June 1998	Safety evaluation	Randomized, single-masked, placebo-controlled	Difluprednate 0.002%, 0.01%, or 0.05%: 2 drops single, ocular instillation	18 subjects Difluprednate 0.002%: 6 eyes Difluprednate 0.01%: 6 eyes Difluprednate 0.05%: 6 eyes Placebo: 18 eyes	Healthy adult male subjects	Single dose	Completed; Legacy abbreviated report
PD/PK	Study 9 -Phase 1 clinical study of difluprednate ophthalmic emulsion— repeated instillation study (SJE2079/1-02- PC-2) August 1998- October 1998	Safety evaluation, blood levels of difluprednate and cortisol following repeated ocular instillation	Double-masked, placebo-controlled	Difluprednate 0.01% or 0.05% 2 drops QID for 7 days in 1 eye, with placebo (vehicle) in contralateral eye	12 subjects Difluprednate 0.01%: 6 eyes Difluprednate 0.05%: 6 eyes	Healthy adult Japanese male subjects	7 days	Completed; Legacy abbreviated report
Safety and efficacy	Study 10 -Phase 2a exploratory study of difluprednate ophthalmic emulsion in the treatment of post-operative inflammation (SJE2079/2-01- PC) Dec 1999– Oct 2000	Safety and efficacy for post-operative inflammation	Randomized, double-masked, parallel-group, comparative group	Difluprednate 0.002% or 0.05%: 1 drop QID	Difluprednate 0.002%: 2 Difluprednate 0.05%: 4	Post-ocular surgery; Japanese adult males and females	7 days	Completed; Legacy abbreviated report

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product	No. of Subjects	Healthy Subject of Diagnosis of Patients	Duration of Treatment	Study Status
Safety and Efficacy	Study 11 -Phase 3 open-label clinical study of difluprednate ophthalmic emulsion in the treatment of severe uveitis (SJE2079/3- 02-PC) August 2002– June 2003	Phase 2 safety and efficacy study for anterior uveitis	Open-label	ST-601: 1 drop QID Ocular instillation	19 subjects	Refractory uveitis; Japanese adult males and females	14 days	Completed; Legacy abbreviated report

Discussion of Individual Trials

Two Phase 3 clinical trials were reviewed to support efficacy (Studies ST-601A-002a and ST-601A-002b) and seven studies in total were analyzed to support safety. The efficacy studies (Studies 002a and 002b) were double-masked, randomized, placebo-controlled clinical trials evaluating ST-601 in the treatment of inflammation and pain following ocular surgery. Each study was conducted under an identical but separate protocol. In each study, the efficacy and safety of ST-601, dosed either BID or QID for 14 days, was compared with vehicle in subjects who had undergone unilateral ocular surgery. On Day 15, after completion of the planned treatment course, subjects who had an anterior chamber cell grade of “0” or who had responded satisfactorily to treatment as judged by the investigator began graduated tapering of the study drug, which successively halved the number of doses per day at each step. Beginning at Day 15, the subjects who were initially assigned to the QID dosing group instilled study medication BID from Days 15 to 21, and QD from Days 22 to 28. If further tapering was required after Day 28, the investigator discontinued study drug and prescribed a suitable drug, as deemed appropriate. Beginning at Day 15, the subjects who were initially assigned to the BID dosing group instilled study medication QD from Days 15 to 28. If further tapering was required after Day 28, the investigator discontinued study drug and prescribed a suitable drug, as deemed appropriate.

Tapering Schedule

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

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

In Studies 002a and 002b the total number of subjects included in the intent-to-treat (ITT)/safety population was 438. Of these, 111 subjects were assigned to receive treatment with ST-601 BID, 107 were assigned to receive ST-601 QID treatment, and 220 were assigned to the vehicle group.

Study Schedule for ST-601A-002a and 002b

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

AE, adverse event; BCVA, best-corrected visual acuity; IOP, intraocular pressure; VAS, Visual Analogue Scale

(1) May be done prior to surgery or on Day 1, at investigator's option.

(2) May be done on Day 0 or Day 1.

(3) Anterior chamber cell count and grade.

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

Dosing for ST-601A-002a and 002b

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

ST-601A-002a: List of Investigators

Site No.	Principal Investigator	Location	Total Randomized
0021	Carlos Buznego, MD	Miami, FL	29
0032	G. Richard Cohen, MD	Boca Raton, FL	9
0050	George Fournier, MD	Ft. Lauderdale, FL	2
0054	Robert DaVanzo, MD	High Point, NC	34
0049	Harvey B. DuBiner, MD	Morrow, GA	9
0039	Ronald E.P. Frenkel, MD	Stuart, FL	2
0033	Charles A. Garcia, MD	Houston, TX	11
0031	Barrett R. Ginsberg, MD	Ft. Meyers FL	0
0024	Richard E. Hector, MD	Bradenton, FL	1
0025	Gregory L. Henderson, MD	Brandon, FL	18
0019	Charles A. Kirby, MD	Chattanooga, TN	36
0029	Bernard R. Perez, MD	Tampa, FL	27
0012	Michael H. Rotberg, MD	Charlotte, NC	28
0048	Kenneth N. Sall, MD	Artesia, CA	14

ST-601A-002b: List of Investigators

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

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

Inclusion/Exclusion Criteria for ST-601A-002a and 002b

Inclusion Criteria:

- Unilateral ocular surgery on the day prior to study enrollment
- Anterior chamber cell grade \geq “2” on the day after surgery (Day 1)
- Age 2 years or older on the day of consent
- Negative urine pregnancy test on Day 1 for post-menarchal subjects; negative urine pregnancy test for pre-menarchal subjects at the investigator’s discretion
- Provide signed written consent prior to entering the study or signed written consent from parent or legal guardian if subject is a minor and signed assent from minor subject

Exclusion Criteria:

- Systemic administration of any corticosteroid in the 2 weeks prior to study enrollment
- Periocular injection in the study eye of any corticosteroid solution within 4 weeks prior to instillation of the study drug, or of any corticosteroid depot within 2 months prior to instillation of the study drug
- Instillation of any topical ocular corticosteroid or NSAID within 24 hours prior to instillation of the study drug or during the course of the study, with the exception of pre-surgical administration of a topical NSAID to prevent miosis
- Any history of glaucoma or ocular hypertension in the study eye
- History or presence of endogenous uveitis
- Any current corneal abrasion or ulceration
- Any confirmed or suspected active viral, bacterial, or fungal keratoconjunctival disease
- Allergy to similar drugs, such as other corticosteroids
- History of steroid-related IOP increase
- Scheduled surgery on the contralateral eye during the treatment period
- Unwilling to discontinue use of contact lenses during the study period
- Pregnancy or lactation
- Participation in any study of an investigational topical or systemic new drug or device within 30 days prior to screening, or at any time during the study
- Prior participation in the study described in this protocol
- Unable or unwilling to give signed informed consent prior to participation in any study-related procedures
- Ocular hemorrhage which interferes with evaluation of post-surgery inflammation
- Injection of gas into the vitreous body during surgery
- Presence of IOP \geq 24 mmHg on Day 1 after surgery

Integrated Review of Efficacy

Demographics

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

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

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

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

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

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

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

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

Protocol Defined Analysis Populations

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

Subjects in the Analysis Populations by Treatment Group: ST-601A-002a

	ST-601 BID (N=58)	ST-601 QID (n=55)	Vehicle (N=107)
Randomized	58	55	107
ITT Population	57	55	107
PP Population	57	52	105
Safety Population	57	55	107

Subjects in the Analysis Populations by Treatment Group: ST-601A-002b

	ST-601 BID (N=54)	ST-601 QID (N=52)	Vehicle BID (N=57)	Vehicle QID (N=57)
Randomized	54	52	57	57
ITT Population	54	52	56	57
PP Population	54	51	56	57
Safety Population	54	52	56	57

Primary Efficacy Endpoint

The primary efficacy endpoint for Studies 002a and 002b was the proportion of subjects with an anterior chamber cell grade of “0” on Day 8 as compared between the ST-601 QID and placebo groups.

Efficacy endpoints were calculated from the following assessments:

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

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

Complete Clearing of Anterior Chamber Cell (ITT and PP)

Study 002a: Proportion of Subjects with Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	3	4	0	0.0180	0.0075
Day 8 (LOCF)	9 (16%)	13 (24%)	11 (10%)	0.3584	0.0302
Day 15 (LOCF)	25	25	15	<0.0001	<0.001
Day 29 (LOCF)	35	32	26	<0.0001	<0.001
Follow-up	35	36	51	0.2200	0.0148

Study 002a: Proportion of Subjects with Clearing (Count=0) of Anterior Chamber Cells by Visit: PP Population

Subjects Cleared	ST-601 BID (N=57)	ST-601 QID (n=52)	Vehicle (N=105)	ST-601 BID P value	ST-601 QID P value
Day 3	3	3	0	0.0168	0.0169
Day 8	9 (16%)	13 (27%)	11 (14%)	0.9535	0.1652
Day 15	24 (46%)	23 (49%)	15 (21%)	0.0074	0.0020
Day 29	34	28	25	0.0003	0.0060
Follow-up	35	34	50	0.1969	0.0138

Study 002b: Proportion of Subjects with Clearing (Count=0) of Anterior Chamber Cells by Visit: ITT Population

Subjects Cleared	ST-601 BID (N=54)	ST-601 QID (n=52)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	1	1	2	0.8706	1.0000
Day 8 (LOCF)	10 (19%)	11 (21%)	6 (5%)	0.0075	0.0012
Day 15 (LOCF)	20	19	10	<0.0001	<0.0001
Day 29 (LOCF)	29	33	20	<0.0001	<0.0001
Follow-up	33	32	48	0.0209	0.0101

Study 002b: Proportion of Subjects with Clearing (Count=0) of Anterior Chamber Cells by Visit: PP Population

Subjects Cleared	ST-601 BID (N=54)	ST-601 QID (n=51)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	1	1	2	0.9101	0.9029
Day 8	10 (20%)	11 (22%)	6 (7%)	0.0283	0.0042
Day 15	18 (39%)	19 (39%)	10 (15%)	0.0214	0.0164
Day 29	26	31	19	0.0404	0.0081
Follow-up	33	31	48	0.0209	0.0165

Grade “0” Anterior Chamber Cell where Grade “0” represents “0” ≤1 cell.

Study 002a: Proportion of Subjects with Clearing (Grade “0”) of Anterior Chamber Cells by Visit: ITT Population

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

Study 002b: Proportion of Subjects with Clearing (Grade “0”) of Anterior Chamber Cells by Visit: ITT Population

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

Analysis of Secondary Endpoints(s)

Hierarchical Testing of Endpoints

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

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

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

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

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

1. The proportion of subjects with an anterior chamber cell grade of “0” on Day 8 for ST-601 BID
2. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 QID
3. The proportion of subjects with a pain/discomfort score of 0 on Day 3 for ST-601 BID
4. The proportion of subjects with an anterior chamber cell grade of “0” on Day 15 for ST-601 QID
5. The proportion of subjects with an anterior chamber cell grade of “0” on Day 15 for ST-601 BID

Study 002a: Proportion of Patients with a Pain/Discomfort Score of 0 (ITT Population)

	ST-601 BID (N=57)	ST-601 QID (N=55)	Vehicle (N=107)	ST-601 BID P value	ST-601 QID P value
Day 3	23 (40.4%)	27 (50%)	29 (27.6%)	0.0772	0.0026
Day 8 (LOCF)	23 (40.4%)	38 (69.1%)	32 (30.5%)	0.2250	<0.0001
Day 15 (LOCF)	36 (63.2%)	42 (76.4%)	47 (44.8%)	0.0209	0.0001
Follow-up	41 (71.9%)	44 (86.3%)	75 (78.9%)	0.3961	0.2516

Study 002b: Proportion of Patients with a Pain/Discomfort Score of 0 (ITT Population)

	ST-601 BID (N=54)	ST-601 QID (N=52)	Vehicle (N=113)	ST-601 BID P value	ST-601 QID P value
Day 3	19 (35.8%)	21 (40.4%)	25 (22.1%)	0.0800	0.0116
Day 8 (LOCF)	23 (43.4%)	24 (46.2%)	27 (23.9%)	0.0121	0.0027
Day 15 (LOCF)	23 (43.4%)	25 (48.1%)	29 (25.7%)	0.0150	0.0021
Follow-up	30 (57.7%)	36 (70.6%)	56 (50.5%)	0.4282	0.0088

Other Endpoints

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

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

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

Subpopulations

The primary endpoint was analyzed for the following subgroups: age (≤ 65 years vs. > 65 years), sex (male vs. female), race (white vs. non-white), and iris color (light vs. dark). Subject baseline demographics were comparable between treatment groups in Studies 1 and 2. There were no marked differences between treatment groups on ethnic or physical characteristics, including eye color.

Study 002a: The study population was largely elderly (median age, 71 years, range 29–96 years), and there were slightly more women (51.4%) than men (48.6%). The subjects were mostly non-Hispanic white. Light eye color (blue, grey, green) was seen in 35% of the subjects, and dark eye color (hazel, brown) in 65% of the subjects. Cataract surgery was the type of ocular surgery performed in nearly all subjects (96.8%).

Study 002a: Subpopulation Analysis

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

Study 002b: The study population was largely elderly (mean age, 71 years; range, 24–88 years), mostly women (59%), and mostly non-Hispanic white. Light eye color (blue, grey, green) was seen in 55% of subjects, and dark eye color (hazel, brown) in 45%. Cataract surgery was the type of ocular surgery performed in nearly all subjects (98.2%).

Study 002b: Subpopulation Analysis

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

Vitrectomy	1	1	0	2
Wound Modification	0	0	1	1

Over 95% of the patients in 002a and 002b underwent cataract surgery versus another ocular surgery.

Integrated Review of Safety

Seven clinical trials were used to evaluate safety of difluprednate (see Clinical Studies with Ophthalmic Administration of Difluprednate, page 6). Studies 1, 2, 3, and 4 were in patients following intraocular surgery with moderate inflammation. Studies 6, 7, and 11 were conducted in patients with a diagnosis of endogenous anterior uveitis or panuveitis.

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

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

Studies Used to Evaluate Safety

Sirion Post-surgical Studies	Study 1: ST-601A-002a	US	55
	Study 2: ST-601A-002b	US	52
Senju Post-surgical Studies	Study 3: SJE2079/3-03	Japan	100
	Study 4: SJE2079/2-03-PC	Japan	11
Senju Uveitis Studies	Study 6: SJE2079/3-01-PC	Japan	69
	Study 7: SJE2079/2-02-PC	Japan	8
	Study 11: SJE2079/3-02-PC	Japan	19
Total No. of Patients Treated with ST-601 QID for at least 14 days			314

Overall Exposure

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

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

Study 002a: Mean Duration of Exposure to Study Drug (ITT/Safety Population)

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

Study 002a: Distribution of Exposure Durations to Study Drug (ITT/Safety Population)

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

Study 002b: Mean Duration of Exposure to Study Drug (ITT/Safety Population)

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

Study 002b: Distribution of Exposure Durations to Study Drug (ITT/Safety Population)

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

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

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

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

Deaths

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

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

Nonfatal Serious Adverse Events

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

In the Sirion post-surgical studies (Studies 002a and 002b), 1 of 111 subjects (<1%) treated with ST-601 BID experienced 1 SAE (syncope), 4 of 107 subjects (37%) treated with ST-601 QID had 1 SAE each, and 2 of 220 subjects (<1%) in the placebo group had 1 SAE. The narratives for these 6 events are listed below:

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

On Day 14 of the study, the subject was admitted to the hospital after experiencing syncope secondary to atrial fibrillation. The subject had a history of atrial fibrillation, hypertension, stroke, triple heart bypass, and carotid endarterectomy. Hospital physicians also suspected an internal bleed from an unknown origin because the subject's fecal matter was dark. Esophageal endoscopy and colonoscopy were inconclusive in regard to the suspected bleed. The subject received 6 units of fresh frozen plasma and 2 units of packed red blood cells due to progressive anemia, coagulopathy, and intermittent black stools. Concomitant medications were: vitamin K, Lasix, Benadryl, Labetalol, Lisinopril, Pepcid, levothyroxine sodium, Lisinopril, Coumadin, hydralazine HCL, and Nexium. This AE was considered resolved with sequelae of atrial fibrillation and anemia, and the subject was discharged from the hospital on Day 18. The subject did not interrupt study drug, he completed the study.

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

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

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

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

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

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

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

dismissed 2 days later, and prescribed Paxil once again. The subject did not interrupt treatment with the study drug. The event was considered resolved when the subject was discharged from the hospital.

6. Headache (ST-601A-002B-0048009 [REDACTED]; Age: 66, Female), ST-601 QID

On Day 16 of the study, the subject went into the hospital with the chief complaint of pain in the neck that had been intractable for 3 days, resulting in a severe headache. She was given morphine sulfate in the emergency room with no relief, and was admitted to the hospital for a magnetic resonance imaging (MRI) and a neurological consultation. The MRI showed a severely degenerated C4-C5 disk, which was causing encroachment upon the spinal canal, and a discectomy and fusion surgery of the C3-C4 and C4-C5 was performed. While admitted, the subject received Zofran and Vicodin. The subject was discharged from the hospital on Day 33 of treatment with difluprednate. The subject did not interrupt study drug and she completed the study.

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

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

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

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

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

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

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

3. Iris Adhesions (Study 3, Subject #53-1; Age: 69 years, Male)

Although iris adhesions manifested at Day 2 of the study, administration of difluprednate was continued until Day 12. Thereafter, the iris adhesions progressed; and the subject underwent posterior synechiotomy 5 days after termination of treatment, with a prolonged hospitalization period. The iris adhesions were resolved by the surgery.

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

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

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

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

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

3. Monoarthritis (Study 11, Subject #10-1; Age: 25 years, Female)

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

Overall Listing of Serious Adverse Events

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

Adverse Events That Led To Discontinuation of Study Drug

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

Integrated Summary of Treatment-Emergent Adverse Events Occurring in $\geq 2\%$ of Subjects

Organ Class	Sirion Post-Surgical Studies ST-601 BID N=111 Studies 1&2	Sirion Post-Surgical Studies ST-601 QID N=107 Studies 1&2	Senju Uveitis Studies ST-601 QID N=96 Studies 6, 7, 11	Senju Post-Surgical Studies ST-601 QID N=111 Studies 3&4	Sirion Post-Surgical Studies Placebo N=220 Studies 1&2
Eye disorders					
Posterior capsular opacification	17	12	0	0	32
Conjunctival hyperemia	11	16	0	1	76
Punctate keratitis	8	6	9	2	8
Eye pain	12	5	3	2	44
Photophobia	11	10	0	0	45
Corneal edema	12	5	0	0	56
Ciliary hyperemia	6	10	0	0	62
Conjunctival edema	7	5	0	0	27
Visual acuity reduced	6	2	2	0	37
Anterior chamber cell	5	4	0	0	40
Eye inflammation	3	5	0	0	17
Vitreous floaters	3	5	0	0	5
Iritis	5	2	0	0	3
Foreign body sensation	3	2	0	2	16
Vitreous detachment	3	2	0	0	4
Conjunctival hemorrhage	3	1	0	0	1
Anterior chamber flare	3	1	0	0	31
Macular edema	1	2	0	0	5
Blepharitis	1	2	0	0	12
Trichiasis	0	2	0	0	6
Vision blurred	1	0	0	0	4
Corneal deposits	0	0	0	0	5
Eyelid edema	0	0	0	0	5
IOP increased	3	2	9	9	2
Other					
Corneal dystrophy	1	0	0	0	6
Application site irritation	0	1	9	5	3
Application site pruritis	0	1	1	3	0
Application site pain	0	0	2	0	0
Constipation	0	0	0	9	0
Headache	0	2	1	5	2
Insomnia	0	0	1	5	0
Back pain	0	0	1	3	0

Laboratory Findings/Special Safety Studies

Laboratory Findings

No clinical laboratory evaluations were conducted in Sirion Studies 002a or 002b, except for urine pregnancy tests conducted at screening.

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

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

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

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

Vital Signs

Vital signs were not measured in these studies.

Electrocardiograms (ECGs)

ECGs were not performed in the studies.

Special Safety Studies

An increase in IOP is a common treatment-related AE resulting from corticosteroid use, especially with the use of topical ophthalmic steroids.

Integrated Summary of IOP Increases (Safety Population)

IOP Increase	Sirion Post-Surgical Studies ST-601 BID N=111 Studies 1&2	Sirion Post-Surgical Studies ST-601 QID N=107 Studies 1&2	Sirion Post-Surgical Studies Placebo N=220 Studies 1&2	Senju Post-Surgical Studies ST-601 QID N=111 Studies 3&4	Senju Uveitis Studies ST-601 QID N=96 Studies 6, 7, 11
No. of subjects with rise of ≥ 10 mmHg from baseline and observed IOP ≥ 21 mmHg	3	3	2	6	5

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

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

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

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

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

Post-marketing Experience

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

Potential Questions for the Advisory Committee

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