

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-212

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Discipline Team Leader Memorandum

Date	June 9, 2008
From	Charles R. Bonapace, Pharm.D.
Subject	Clinical Pharmacology Team Leader Review
NDA/BLA #	22-212
Product	Difluprednate (Durezol)
Formulation	Ophthalmic emulsion, 0.05%
Sponsor	Sirion Therapeutics, Inc.
Proposed Indication	Treatment of inflammation and pain following ocular surgery

1. Background

Difluprednate (ST-601), a difluorinated derivative of prednisolone, is a glucocorticoid receptor agonist originally developed as a dermatologic product and first marketed as a cream and ointment in Europe and later in Japan. The successful development of difluprednate to treat inflammation in a dermatologic formulation subsequently led to its reformulation as an ophthalmic product by Senju Pharmaceutical Co. In Japan, Senju conducted nonclinical and clinical ophthalmic studies demonstrating the ability of difluprednate to reduce ocular inflammation resulting from ocular surgery or from uveitis. Sirion Therapeutics acquired the US rights to difluprednate and conducted two randomized, double-masked, placebo-controlled Phase 3 clinical trials examining its safety and effectiveness in the treatment of postsurgical inflammation to support product approval.

Difluprednate ophthalmic emulsion is an ~~oil-in-water~~ emulsion in which difluprednate is dissolved in the ~~oil phase~~. Difluprednate ophthalmic emulsion, 0.05% for ocular instillation is proposed for the treatment of inflammation and pain associated with ocular surgery. The proposed dosage and route of administration for difluprednate ophthalmic emulsion is instillation of one drop into the conjunctival sac of the affected eye(s) BID beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

2. Clinical Pharmacology Findings

The sponsor evaluated the systemic exposure of 6 α ,9-difluoroprednisolone 17-butyrate (DFB, the active metabolite of difluprednate) following repeated ocular instillation of two drops of difluprednate ophthalmic emulsion, 0.05% QID for 7 days to 12 healthy Japanese subjects in a single clinical pharmacology study. A pharmacodynamic assessment of the same subjects examining the effect of repeated ocular instillation on serum cortisol levels (HPA axis suppression) was also performed.

The concentrations of DFB in whole blood were below the lower limit of quantitation (50 ng/mL) in all 12 subjects at all time points (pre-dose and 0.5, 1, 2, 4, 8, 12, and 24 hours post-instillation) on day 7, indicating that multiple ocular instillation of difluprednate ophthalmic emulsion, 0.05% for 7 days has negligible systemic absorption. In addition, the mean serum

cortisol concentration was not significantly altered on day 7 compared to baseline following ocular instillation of difluprednate ophthalmic emulsion, 0.05% QID for 7 days.

3. Safety and Efficacy Findings

In support of the application, the sponsor submitted data from two efficacy studies conducted by Sirion Therapeutics in the US (Studies 1 and 2) and two studies conducted by Senju in Japan (Studies 3 and 4). Studies 1 and 2 evaluated the clinical safety and efficacy of difluprednate ophthalmic emulsion, 0.05% BID and QID versus placebo (vehicle) for postsurgical inflammation; Studies 3 and 4 evaluated the clinical safety and efficacy of difluprednate ophthalmic emulsion, 0.05% QID versus betamethasone ophthalmic solution, 0.1% QID in subjects who presented with inflammation after undergoing intraocular surgery. Studies 1 and 2 were double-masked, randomized, placebo-controlled clinical trials conducted under identical protocols. In these two studies, subjects were randomly assigned (1:1:1:1) to receive difluprednate ophthalmic emulsion, 0.05% administered either BID or QID or placebo, administered either BID or QID for up to 14 days.

The proportion of subjects with an anterior chamber cell grade of "0" (defined as ≤ 1 cell) on Day 8 was significantly greater with difluprednate ophthalmic emulsion, 0.05% QID or BID compared to placebo for Studies 1 and 2 (primary endpoint). However, the proportion of subjects with clearing (count=0) of the anterior chamber on Day 8 was significantly greater with the difluprednate ophthalmic emulsion, 0.05% QID compared to placebo in Studies 1 and 2 and difluprednate ophthalmic emulsion, 0.05% QID or BID compared to placebo in only Study 2. In addition, the percent of subjects pain/discomfort free on Day 3 was significantly greater with difluprednate ophthalmic emulsion, 0.05% QID compared to placebo in Studies 1 and 2. The percent of subjects pain/discomfort free on Day 3 was not significantly different with difluprednate ophthalmic emulsion, 0.05% BID compared to placebo in either study, suggesting a dose-response relationship between the BID and QID dose groups.

Adverse events were reported more frequently in subjects receiving placebo than among subjects receiving either difluprednate ophthalmic emulsion, 0.05% BID or QID. There were fewer adverse events reported in the difluprednate QID group versus the BID group and there were no marked differences between the difluprednate BID and QID treatment groups in the frequency or type of adverse events.

3. Advisory Committee Meeting

Difluprednate ophthalmic emulsion, 0.05% was discussed at the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting on May 29, 2008. When asked "Do you think difluprednate ophthalmic emulsion should be approved for the treatment of ocular inflammation and pain following cataract surgery", the four voting member of the advisory committee voted as follows: Yes (n=3), No (n=0), Abstain (n=1).

The primary issues raised during the advisory committee meeting consisted of whether the product should be labeled for BID or QID administration, risk of developing cataracts and increased intraocular pressures (IOP) with BID or QID administration, and whether the product should be labeled for inflammation and pain following ocular surgery or specifically following

cataract surgery. The advisory committee agreed that both dosing regimens (BID and QID) were shown to be effective for pain or inflammation and recommended that the labeling state difluprednate ophthalmic emulsion, 0.05% BID or QID for 14 days.

4. Conclusions

Based on the suggested dose-response for the primary and secondary efficacy endpoints in the Phase 3 trials conducted in the US by Sirion Therapeutics, difluprednate ophthalmic emulsion, 0.05% administered QID appears more effective than the BID regimen. Both regimens were well tolerated and there were no differences in the frequency or type of adverse events between the difluprednate BID and QID treatment groups.

5. Recommendations

I concur with the Dr. Kim Bergman's recommendations that the information provided by the sponsor is acceptable from a clinical pharmacology point of view. The clinical relevance of the observed differences in effectiveness between difluprednate ophthalmic emulsion, 0.05% administered BID and QID should be considered when deciding on the approvability and labeling for this submission.

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/s/

Charles Bonapace
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BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-212
Submission Date(s):	21DEC2007
Brand Name	Durezol
Generic Name	Difluprednate 0.05% (ST-601)
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Sirion Therapeutics, Inc.
Relevant IND(s)	IND 75,713
Submission Type; Code	Original NDA (NME); 505(b)(1) application
Formulation; Strength(s)	Difluprednate ophthalmic emulsion 0.05%
Indication	Treatment of inflammation and pain following ocular surgery

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1. EXECUTIVE SUMMARY

Difluprednate (ST-601), a difluorinated derivative of prednisolone, is a glucocorticoid receptor agonist. Difluprednate ophthalmic emulsion 0.05% for ocular instillation is proposed for the treatment of inflammation and pain associated with ocular surgery. The proposed dosage and route of administration for difluprednate ophthalmic emulsion is as follows: instill one drop into the conjunctival sac of the affected eye(s) 2 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

Difluprednate was originally developed as a dermatologic product and first marketed as a cream and ointment in Europe, and later in Japan. Difluprednate is currently marketed in Europe as Epitopic® cream, 0.02% and 0.05%, and Epitopic® gel, 0.05%, by Laboratoire Gerda of France and in Japan as Myser® cream and ointment, 0.05%, by Mitsubishi Pharma Corporation. These products are used for treating allergic dermatitis, eczema, psoriasis, prurigo, etc., in the same manner as other dermatologic corticosteroids. The successful development of difluprednate to combat inflammation in a dermatologic formulation subsequently led to its reformulation as an ophthalmic product by Senju Pharmaceutical Co. In Japan, Senju has conducted nonclinical and clinical ophthalmic studies (through Phase 3) demonstrating the ability of difluprednate to reduce ocular inflammation resulting from ocular surgery or from uveitis. Sirion Therapeutics has acquired the US rights to ST-601, and has conducted two randomized, double-masked, placebo-controlled Phase 3 studies examining its safety and effectiveness in the treatment of postsurgical inflammation to support product approval.

Two clinical pharmacology investigations of ST-601 were conducted as sub-studies of a single Phase 1 trial (Study 9): a pharmacokinetic study evaluating systemic exposure following repeated ocular instillation, and a pharmacodynamic study of the examining the effect of repeated ocular instillation on serum cortisol levels in the same subjects. Based on the assessment of systemic exposure information from Study 9 in the current submission, the regulatory requirement for submission of in vivo bioavailability data has been addressed.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Difluprednate (ST-601), a difluorinated derivative of prednisolone, is a glucocorticoid receptor agonist formulated for ocular instillation and proposed for the treatment of inflammation and pain associated with ocular surgery. To support product approval, the Applicant conducted two randomized, double-masked, placebo-controlled Phase 3 studies examining its safety and effectiveness in the treatment of postsurgical inflammation. In addition, two clinical pharmacology studies of ST-601 were conducted as sub-studies of a single Phase 1 trial (Study 9): a pharmacokinetic study evaluating systemic exposure following repeated ocular instillation, and a pharmacodynamic study examining the effect of repeated ocular instillation on serum cortisol levels in the same subjects.

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

The proposed dosing regimen for difluprednate 0.05% for the treatment of inflammation following ocular surgery is one drop into the affected eye(s) administered BID throughout the first two weeks of the postoperative period. In studies evaluating the efficacy and safety of difluprednate 0.05% administered either BID or QID for up to 14 days, a dose-response relationship was suggested between the BID and QID dose groups for the primary efficacy endpoint of the proportion of subjects in the ST-601 group with an anterior chamber cell grade of "0" on Day 8 compared with the placebo (vehicle) group and the secondary endpoints of 1) the proportion of subjects with clearing (count of 0) of anterior chamber cells, and 2) proportion of patients pain free and change from baseline in pain/discomfort, and 3) the percent of patients that were photophobia free (statistically significant). No dose-response relationship was observed between the BID and QID dose groups for safety. Based on the suggested dose-response for the primary and secondary efficacy endpoints in the Phase 3 trials conducted in the US, the QID regimen of difluprednate 0.05% ophthalmic emulsion appears more effective than the BID regimen. The clinical relevance of these differences in effectiveness between the BID and QID regimens should be considered when deciding on the approvability and labeling for difluprednate.

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Division File: NDA 22-212
HFD-520 (CSO/Dean)
HFD-520 (MO/Wadhwa)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1. General Attributes of the Drug

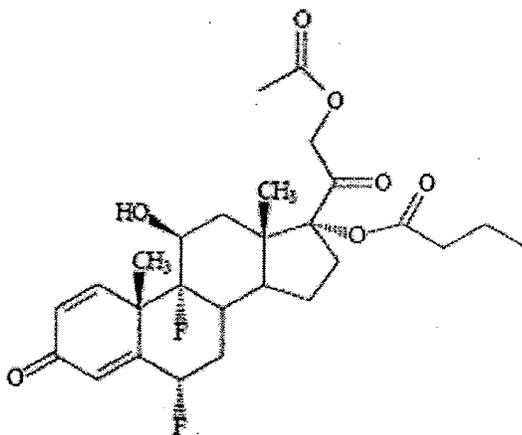
2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Difluprednate ophthalmic emulsion, 0.05% (ST-601) is a topical ophthalmic emulsion of difluprednate in a _____, solution. For the ST-601 drug product formulation,

The chemical structure and physical-chemical properties of difluprednate are as follows:

Structural Formula: $C_{27}H_{34}F_2O_7$

Chemical Structure:



Chemical Name: 6 α , 9-Difluoro-11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate

Compendial Name: NA

International Nonproprietary Name (INN): Difluprednate

Company Laboratory Code: Difluprednate (DFBA), ST-601

Chemical Abstract Service (CAS) Registry Number: 23674-86-4

Molecular Weight: 508.56

Difluprednate ophthalmic emulsion is an oil-in-water emulsion in which difluprednate is solution. The quantitative composition of the proposed difluprednate ophthalmic emulsion drug product is shown in Table 2.2-1.

Table 2.2-1 Composition of Difluprednate Ophthalmic Emulsion

Components	Function	Weight (mg/mL)	% w/v
Difluprednate	Active ingredient		0.05%
Polysorbate 80	Emulsifier		4.0%
Glycerin	Tonicity		2.2%
Sorbic acid	Preservative		0.1%
Sodium acetate	Buffer		0.05%
Boric acid	Buffer		0.1%
Sodium EDTA	Stabilizer		0.02%
Castor oil	Oil phase		5.0%
Water for injection	Water phase		-
Sodium hydroxide	pH adjustment		-

qs, sufficient quantity

Source: Section 2.3.P.1

Difluprednate was originally developed by Senju Pharmaceuticals in Japan; the current Applicant licensed the product from Senju to market the product in the US. The composition of the difluprednate ophthalmic emulsion as presented in Table 2.2-1 represents the formulation used in the US clinical studies, the Senju ophthalmic clinical studies and the nonclinical ophthalmic safety studies, and is the product intended for commercialization.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

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

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

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for difluprednate ophthalmic emulsion is as follows: instill one drop into the conjunctival sac of the affected eye(s) 2 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

2.2. General Clinical Pharmacology

2.2.1. *What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?*

Two (2) clinical pharmacology studies of ST-601 were conducted as sub-studies of a single Phase 1 trial (Study 9): a pharmacokinetic study evaluating systemic exposure following repeated ocular instillation and a pharmacodynamic study of the same subjects examining the effect of repeated ocular instillation on serum cortisol levels. In this Phase 1 repeated-dosing study conducted with ST-601 in healthy male Japanese subjects, the concentration of 6 α ,9-difluoroprednisolone 17-butyrate (DFB; the active metabolite of difluprednate) in whole blood was determined with high-performance liquid chromatography (HPLC) on Days 1, 4, and 7 following 4 times daily (QID) ocular instillation of 2 drops of difluprednate (0.01% or 0.05%) for 7 days. In addition to this Phase 1 trial, an in vitro assessment of protein binding characteristics of difluprednate was conducted, but a full study report was not included in this submission. This Office of Clinical Pharmacology review focuses on the Phase 1 clinical study (Study 9) and the proposed labeling.

To support product approval, the Applicant submitted efficacy data from four (4) randomized, controlled studies. Two studies were conducted by Sirion in the US (Study 1 and Study 2), and two were conducted by Senju in Japan (Study 3 and Study 4). Studies 1 and 2 evaluated the clinical efficacy and safety of ST-601 0.05% versus placebo (vehicle) for postsurgical inflammation; Studies 3 and 4 evaluated the clinical efficacy and safety of ST-601 0.05% administered QID versus betamethasone ophthalmic solution, 0.1% QID (a standard therapy used in Japan), in subjects who presented with inflammation after undergoing intraocular surgery. Studies 1, 2, and 3 were Phase 3 trials; Study 4 was a Phase 2 study. A total of 664 subjects were enrolled in these efficacy studies (329 of whom were treated with ST-601). Since betamethasone is not approved for ophthalmic use in the US, the application focused on Studies 1 and 2 conducted at US study sites.

Sirion's Studies 1 and 2 consisted of two double-masked, randomized, placebo-controlled clinical trials, concurrently conducted under identical protocols, as summarized in Table 2.2.1-1. The efficacy and safety of ST-601 was compared with placebo for the treatment of inflammation following ocular surgery. In these two studies, subjects were assigned (1:1:1:1) to receive ST-601, administered either BID or QID for up to 14 days, or placebo. For further discussion of these studies, refer to section 2.4.4 Exposure-Response and the Medical Officer's review of NDA 22-212.

Table 2.2.1-1 Clinical Efficacy and Safety Studies Conducted at US Sites for Difluprednate (ST-601)

# 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	# Subjects by Arm Entered/ Completed	Duration	Sex Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
<i>Study 1: 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-002a)</i>									
15 sites in the US	February 6, 2007– September 17, 2007 221 subjects	Randomized, Double-masked, parallel-group, placebo-controlled	ST-601: 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	ST-601: 57 BID: 57 QID: 55 Placebo: 109	Up to 14 days	Males and females Median age: 71.0 (Range: 29–96 yrs)	Postintraocular surgery AC cell grade \geq "2"	Proportion of subjects with an anterior chamber cell grade of "0" on Day 8 compared between ST-601 and vehicle groups
<i>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)</i>									
15 sites in the US	January 24, 2007– September 20, 2007 219 subjects	Randomized, Double-masked, parallel-group, placebo-controlled	ST-601: 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	ST-601: 55 BID: 52 QID: 52 Placebo: 112	Up to 14 days	Males and females Median age: 71.0 (Range: 24–88 yrs)	Postintraocular surgery AC cell grade \geq "2"	Proportion of subjects with an anterior chamber cell grade of "0" on Day 8 compared between ST-601 and vehicle groups

Source: 5.3.5.3.1 Integrated Summary of Efficacy

2.2.2. *What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The use of exogenously administered corticosteroids can be associated with dose- and duration-related hypothalamic-pituitary-adrenal (HPA) axis suppression. Cortisol suppression has been used previously as a marker of HPA axis suppression. Serum cortisol levels were measured in Study 9 by conventional clinical laboratory methods.

Difluprednate ophthalmic emulsion is indicated for the treatment of inflammation and pain associated with ocular surgery. Response endpoints included objective assessments of ocular inflammation, such as anterior chamber cell indices and flare (via slit lamp examination), as well as objective signs of inflammation (including chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates) in the Phase 3 trials conducted in the US. In addition, subjective symptoms of anterior chamber inflammation, eye pain/ discomfort and photophobia, were assessed via Visual Analog Scale (VAS).

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

DFB is the active metabolite of difluprednate formed when the parent is rapidly deacetylated in ocular tissues. This active moiety was appropriately identified and measured in whole blood for purposes of assessment of systemic exposure following ocular administration. Refer to Section 2.3 for further details regarding analytical methodology and performance.

2.2.4. *Exposure-Response*

2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

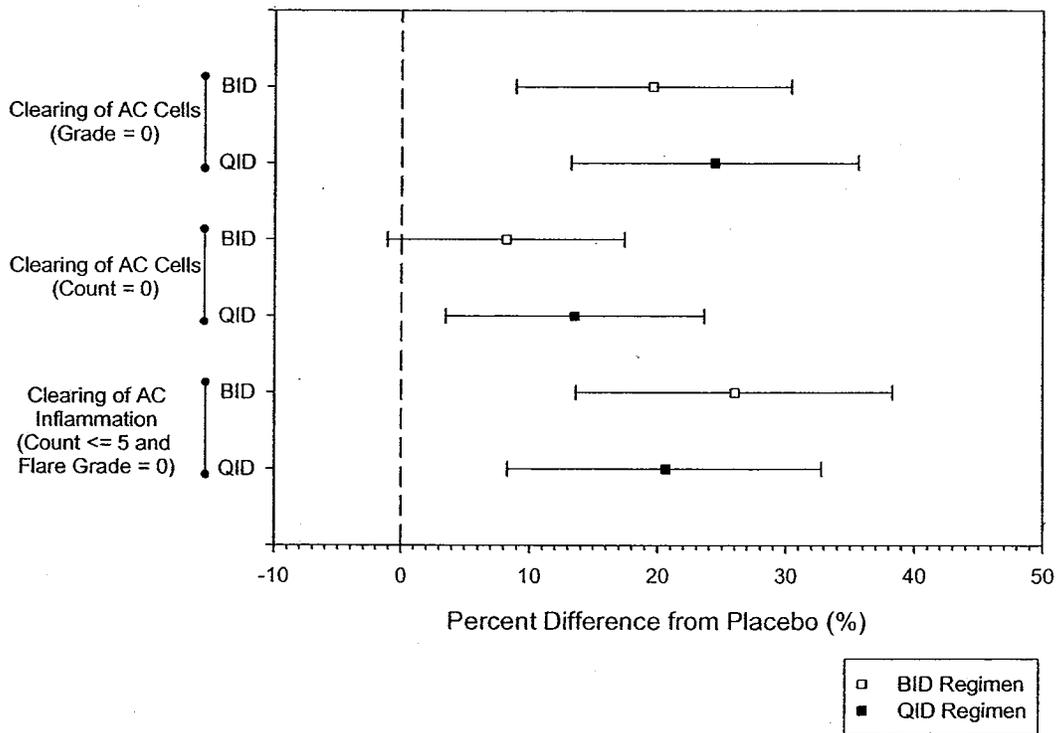
The proposed dosing regimen for difluprednate 0.05% for the treatment of inflammation following ocular surgery is one drop into the affected eye(s) administered BID. In the replicate placebo-controlled studies conducted in the US (Studies 1 and 2), the primary efficacy endpoint was the proportion of subjects in the ST-601 QID group with an anterior chamber cell grade of "0" on Day 8 compared with the placebo (vehicle) group. The Applicant's proposal for BID dosing is based on analysis of multiple secondary endpoints and establishing the lowest effective dose from these data. Secondary endpoints included the following:

- Proportion of subjects with clearing (count of 0) of anterior chamber cells
- Proportion of subjects with clearing of anterior chamber inflammation (cell count ≤ 5 and flare grade = "0")
- Observed and change from baseline in anterior chamber cell grade
- Observed and change from baseline in anterior chamber cell count
- Proportion of subjects who were pain/discomfort free
- Proportion of subjects who were photophobia free

For the primary efficacy endpoint of the proportion of subjects in the ST-601 group with an anterior chamber cell grade of "0" on Day 8 compared with the placebo (vehicle) group and the

secondary endpoint of the proportion of subjects with clearing (count of 0) of anterior chamber cells, a dose-response relationship was suggested between the BID and QID dose groups, as displayed in Figure 2.2.4.1-1. Conversely, a lack of dose-response was observed in the proportion of subjects with clearing of anterior chamber inflammation (cell count ≤ 5 and flare grade = "0"). In addition, only slight differences in the changes from baseline in anterior chamber cell grade and count were observed between the two dose regimens, BID versus QID, as displayed in Figures 2.2.4.1-2 and 2.2.4.1-3.

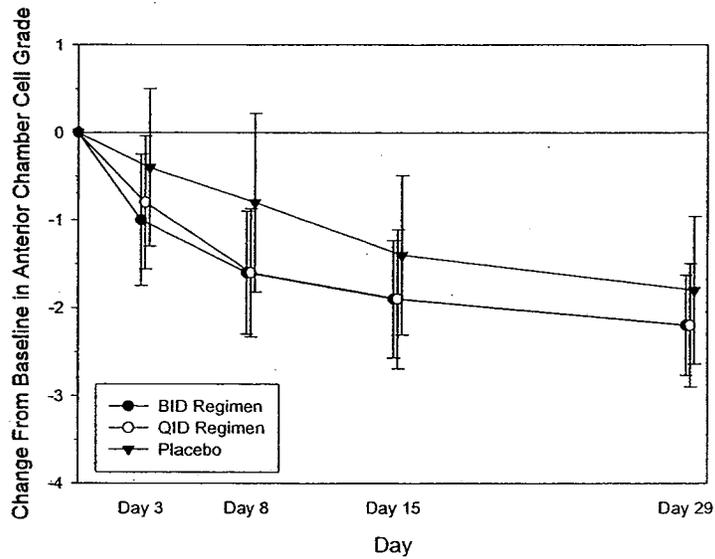
Figure 2.2.4.1-1. Proportion of Patients with Clearing of Anterior Chamber Cells and Inflammation (Expressed in Relation to Placebo) on Day 8



Data set presented: ITT population

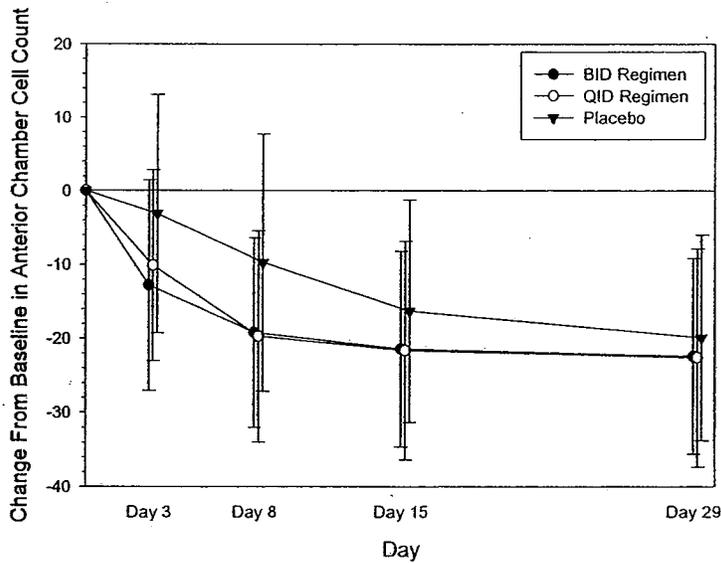
Source: Integrated Summary of Efficacy, Tables 14.2.1.1, 14.2.1.3, and 14.2.1.5

Figure 2.2.4.1-2. Change from Baseline in Anterior Chamber Cell Grade (ITT Population)



Source: Integrated Summary of Efficacy, Table 14.2.2.1

Figure 2.2.4.1-3. Change from Baseline in Anterior Chamber Cell Count (ITT Population)

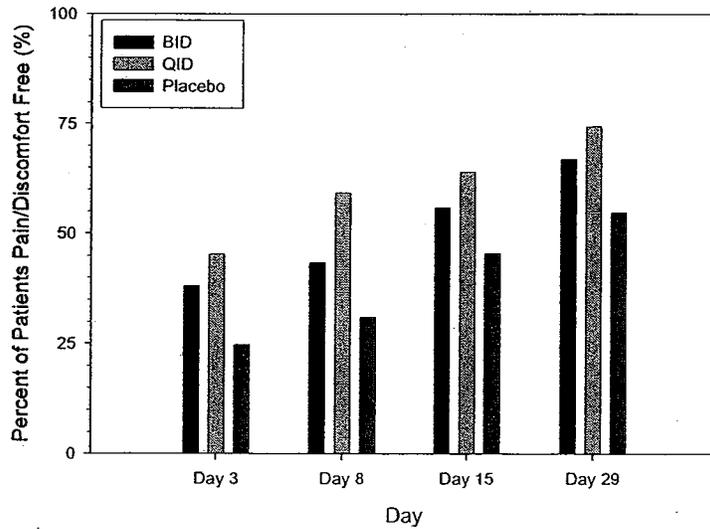


Source: Integrated Summary of Efficacy, Table 14.2.2.3

The proportion of patients that were pain/discomfort free was consistently higher following QID dosing of difluprednate ophthalmic emulsion 0.05% for up to 14 days versus BID dosing, as depicted in Figure 2.2.4.1-4. Changes from baseline in pain/discomfort demonstrated a

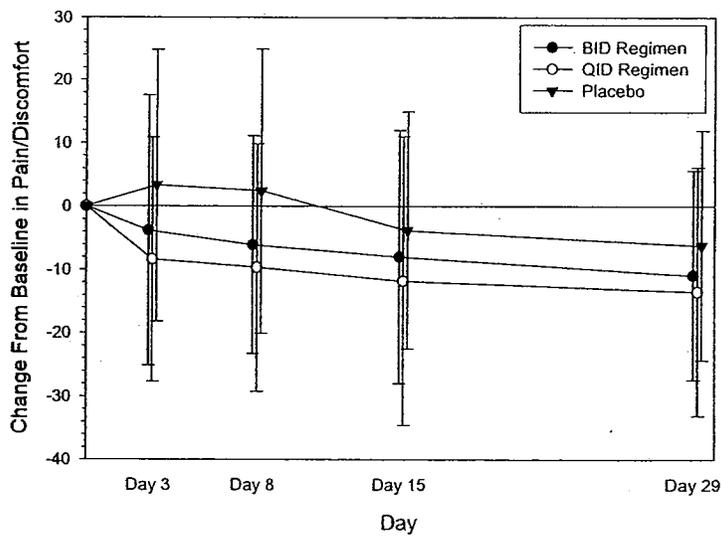
relationship to the frequency of dosing, as illustrated in Figure 2.2.4.1-5; QID dosing yielded greater mean changes from baseline versus BID dosing and placebo.

Figure 2.2.4.1-4. Percent of Patients Pain/Discomfort Free (ITT Population)



Source: Integrated Summary of Efficacy, Table 14.2.3.1

Figure 2.2.4.1-5. Change from Baseline in Pain/Discomfort (ITT Population)

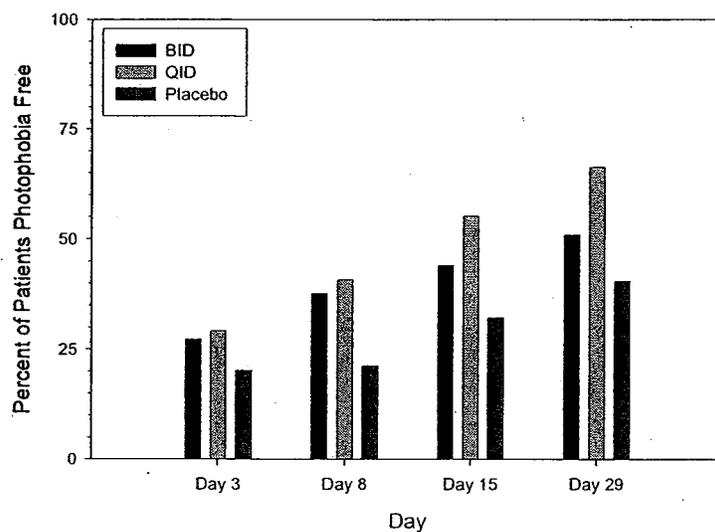


Source: Integrated Summary of Efficacy, Table 14.2.3.2

The proportion of patients that were photophobia free was significantly higher post-treatment (> 14 days) following QID dosing of difluprednate ophthalmic emulsion 0.05% for up to 14 days

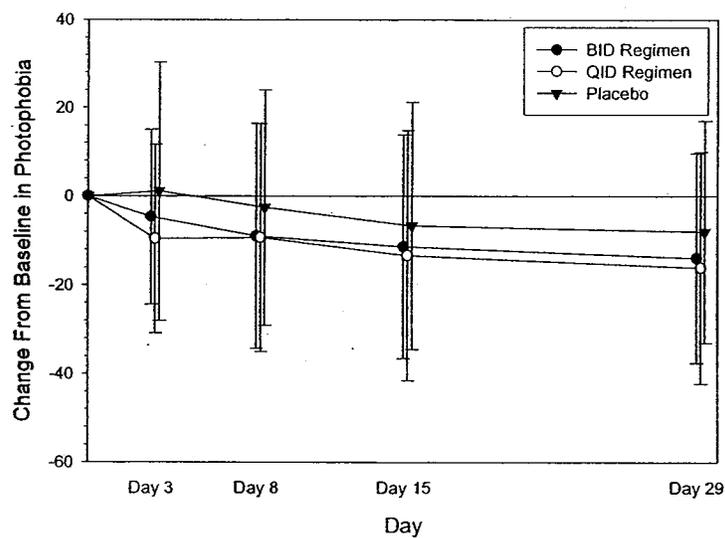
versus BID dosing, as depicted in Figure 2.2.4.1-6. In contrast, change from baseline in photophobia showed no discernible relationship to dose regimen, as illustrated in Figure 2.2.4.1-7.

Figure 2.2.4.1-6. Percent of Patients Photophobia Free (ITT Population)



Source: Integrated Summary of Efficacy, Table 14.2.4.1

Figure 2.2.4.1-7. Change from Baseline in Photophobia (ITT Population)



Source: Integrated Summary of Efficacy, Table 14.2.4.2

In summary, a dose-response relationship was suggested between the BID and QID dose groups for the primary efficacy endpoint of the proportion of subjects in the ST-601 group with an anterior chamber cell grade of "0" on Day 8 compared with the placebo (vehicle) group and the secondary endpoints of 1) the proportion of subjects with clearing (count of 0) of anterior chamber cells, and 2) proportion of patients pain free and change from baseline in pain/discomfort, and 3) the percent of patients that were photophobia free (statistically significant). Based on the suggested dose-response for the primary and secondary efficacy endpoints in the Phase 3 trials conducted in the US, the QID regimen of difluprednate 0.05% ophthalmic emulsion appears more effective than the BID regimen. The clinical relevance of these differences in effectiveness between the BID and QID regimens should be considered when deciding on the approvability and labeling for difluprednate. For further discussion of the efficacy comparison of the difluprednate BID and QID regimens, refer to the Medical Officer's review of NDA 22-212.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In addition to the efficacy findings, the Applicant's proposed dosing regimen for difluprednate 0.05% for the treatment of inflammation following ocular surgery, one drop into the affected eye(s) administered BID, is based on a comparison of safety profiles between the QID and BID regimens of difluprednate and placebo in the post-surgical Phase 3 studies conducted in the US (Studies 1 and 2). In an integrated assessment of safety for these studies, adverse events occurred consistently more frequently in the placebo group than in either of the difluprednate groups, as summarized in Table 2.2.4.2-1. There were fewer adverse events reported in the ST-601 QID group versus the BID group. There were no marked differences between the ST-601 BID and QID treatment groups in the frequency or type of adverse events. In these Phase 3 studies, 1 of 111 subjects (<1%) receiving the BID regimen experienced 1 SAE (syncope secondary to atrial fibrillation), 4 of 107 subjects (37%) receiving the QID regimen had 1 SAE each (syncope secondary to dehydration resulting from vomiting and diarrhea, urinary tract infection, headache, and pneumonia), and 2 of 220 subjects (<1%) in the placebo group had 1 SAE (cerebrovascular accident and respiratory distress). These SAEs were considered not related to study drug. Overall, both of the dosing regimens of difluprednate were well tolerated.

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Table 2.2.4.2-1. Most Frequently Occurring Adverse Events Following BID and QID Dosing of Difluprednate Ophthalmic Emulsion 0.5% for 14 Days

Preferred Term	ST-601 BID	ST-601 QID	ST-601 BID/QID	Placebo
Posterior capsule opacification	17 (15.3%)	12 (11.2%)	29 (13.3%)	32 (14.5%)
Corneal edema	12 (10.8%)	5 (4.7%)	17 (7.8%)	56 (25.5%)
Eye pain	12 (10.8%)	5 (4.7%)	17 (7.8%)	44 (20.0%)
Photophobia	11 (9.9%)	10 (9.3%)	21 (9.6%)	43 (20.5%)
Conjunctival hyperaemia	11 (9.9%)	16 (15.0%)	27 (12.4%)	76 (34.5%)
Punctate keratitis	8 (7.2%)	6 (5.6%)	14 (6.4%)	8 (3.6%)
Conjunctival edema	7 (6.3%)	5 (4.7%)	12 (5.5%)	27 (12.3%)
Ciliary hyperemia	6 (5.4%)	10 (9.3%)	16 (7.3%)	62 (28.2%)
Visual acuity reduced	6 (5.4%)	2 (1.9%)	18 (3.7%)	37 (16.8%)
Anterior chamber cells	5 (4.5%)	4 (3.7%)	9 (4.1%)	40 (18.2%)
Anterior chamber flare	3 (2.7%)	11 (10.9%)	4 (1.8%)	31 (14.1%)
Eye inflammation	3 (2.7%)	5 (4.7%)	8 (3.7%)	17 (7.7%)

Source: Integrated Summary of Safety, Table 18

In summary, no dose-response relationship was observed between the BID and QID dose groups for safety. For further discussion of the safety comparison of the difluprednate BID and QID regimens, refer to the Medical Officer's review of NDA 22-212.

Study 9 investigated the degree of serum cortisol suppression as the result of multiple ocular instillation of difluprednate. A summary of mean cortisol levels in subjects receiving multiple ocular doses of difluprednate ophthalmic emulsion 0.01% and 0.05% QID for 7 days is presented in Table 2.2.4.2-2.

Table 2.2.4.2-2. Mean Cortisol Levels ($\mu\text{g}/\text{dL}$) Following QID Ocular Administration of Difluprednate Ophthalmic Emulsion in Healthy, Male Japanese Subjects

Treatment Group	N	Day 1 Pre	Day 4 Pre	Paired T-Test vs. Day 1	Day 7 Pre	Paired T-Test vs. Day 1	Day 7 24 hours Post	Paired T-Test vs. Day 1
0.01%	6	15.67 (4.97)	20.08 (5.36)	NS	18.57 (3.65)	NS	19.30 (1.22)	NS
0.05%	6	17.20 (5.98)	17.57 (3.91)	NS	23.42 (3.74)	$p < 0.05$	17.25 (3.32)	NS

Data presented as mean (SD).

NS, not significant

Source: Clinical Study Report 9, Table 13.

No significant changes in mean serum cortisol levels were noted following multiple ocular instillation of difluprednate 0.01% and 0.05% for 7 days.

2.2.5. *What are the PK characteristics of the drug and its major metabolite?*

2.2.5.1. *Systemic Exposure Following Ocular Administration*

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

2.3. Analytical Section

2.3.1. *How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?*

The active moiety DFB was identified and measured in whole blood by a high performance liquid chromatography (HPLC) method with ultraviolet (UV) detection.

2.3.2. *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total DFB concentrations were measured in whole blood of subjects receiving treatment in Study 9. The measurement of total concentrations of DFB for purposes of determining systemic exposure following ocular administration is appropriate.

2.3.3. *What bioanalytical methods are used to assess concentrations?*

In the pharmacokinetic study conducted by the Applicant (Study 9), whole blood concentrations of DFB were measured by HPLC following ocular administration of following 4 times daily (QID) ocular instillation of 1 to 2 drops of difluprednate (0.01% or 0.05%) for 7 days.

2.3.3.1. *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The range of the standard curve is 50 to 1000 ng/mL for DFB in human whole blood. Reported DFB concentrations in whole blood following ocular administration of following 4 times daily (QID) ocular instillation of 1 to 2 drops of difluprednate (0.01% or 0.05%) for 7 days were below the quantifiable limit in Study 9. Standard curves were obtained by linear regression analysis, with (1/x) weighting. The range of the assay was sufficient to measure DFB concentrations in whole blood for the intended purpose.

2.3.3.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The lower limit of quantitation (LLOQ) of DFB in whole blood was 50 ng/mL, and the upper limit of quantitation (ULOQ) was 1000 ng/mL. Prior to validation of the assay, a preliminary study to confirm separation was performed using human blank whole blood. Although various separation conditions were attempted in this preliminary study, interfering peaks for DFB were observed. Thus, the lower limit of quantitation of 10 ng/mL used in the nonclinical studies was raised to 50 ng/mL for the assay in human whole blood.

2.3.3.3. *What are the accuracy, precision, and selectivity at these limits?*

A summary of accuracy and precision for the DFB assay are presented in Table 2.3.3.3-1. The procedure was fully validated for the working range of 50 to 1000 ng/mL for DFB in human whole blood.

Table 2.3.3.3-1 Accuracy and Precision for DFB in Whole Blood

	Accuracy	Precision
Intra-day	99.63 – 102.69%	1.76 – 5.72%
Inter-day	99.97 – 101.19%	0.64 – 4.63%

Source:

Six samples of human blank whole blood obtained from different individuals were pretreated and measured. The presence or absence of peaks interfering with quantification and the effects of individual differences on quantification were verified from the resultant chromatograms. There were two cases of blanks where the ratio of the DFB equivalent peak height to the peak height for the 30 ng/mL addition exceeded 30%. The maximum was 25.15% for the peak height for the 50 ng/mL addition.

The accuracy, precision and selectivity of the bioanalytical method are acceptable for the intended purpose.

2.3.3.4. *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Stability of DFB in whole blood in frozen storage was demonstrated using two concentrations (400 and 800 ng/mL) for verification of analysis precision. The results satisfied the determination criteria (target residual ratio of $100 \pm 15\%$) at both concentrations for up to 3.5 months, with residual ratios at 1 month, 2 months, and 3.5 months at 400 ng/mL were 98.5%, 92.2%, and 97.8% respectively, and at 800 ng/mL, the ratios were 97.5%, 98.6% and 98.4% respectively.

2.3.3.5. *What is the QC sample plan?*

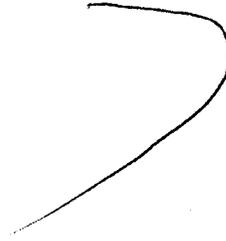
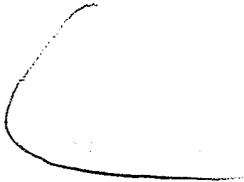
QC samples at three concentrations (80, 400, and 800 ng/mL; $n = 5$ at each concentration) within the calibration curve concentration range were measured. For run acceptance, samples had to assay within $\pm 15\%$ of nominal concentration. All QCs met acceptance criteria.

3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in **bold italicized underlined type**).

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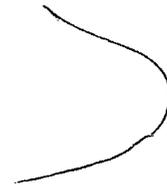
12.1 Mechanism of Action



12.2 Pharmacodynamics



12.3 Pharmacokinetics



4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study 9

TITLE:

Phase 1 Clinical Study of Difluprednate Ophthalmic Emulsion 0.05% and 0.01% - Repeated Instillation Study (SJE2079/1-02-PC-2)

Principal Investigator: _____

OBJECTIVES:

- To investigate the safety and pharmacokinetics of difluprednate ophthalmic emulsion 0.05% and 0.01% given by repeated instillation in healthy adult male Japanese volunteers.
- To observe any systemic effects of repeated instillation of difluprednate ophthalmic emulsion 0.05% and 0.01%.

STUDY DESIGN:

In this double-masked, placebo-controlled study, difluprednate ophthalmic emulsion 0.01% (Step 1) and 0.05% (Step 2) were instilled into the eyes of 12 healthy, Japanese, male subjects (difluprednate ophthalmic emulsion to the test eye and placebo ophthalmic solution to the contralateral eye, 6 subjects per step) two (2) drops QID (at 4-hour intervals) for 7 days (only once, at 9:00 AM, on Day 7). Examinations included ocular findings, ophthalmic examination, subjective symptoms/objective findings, laboratory tests (including serum cortisol levels), physical examination, and metabolite blood drug concentration measurement (6 α ,9-difluoroprednisolone 17-butyrate, DFB). The higher concentration of difluprednate (0.05%; Step 2) was administered after confirmation of the safety of the lower concentration (0.01%; Step 1).

FORMULATIONS:

Study participants received multiple topical ocular doses of difluprednate ophthalmic emulsion 0.01% (0.1 mg/mL), 0.05% (0.5 mg/mL), and placebo ophthalmic solution from the same lot (Lot No. 98G60). The placebo ophthalmic solution was indistinguishable from the test product.

PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS:

Blood samples for the determination of serum drug concentrations of DFB were collected at the following time points, for a total of 10 time points per subject:

- Day 1: Before first instillation
- Day 4: Before first instillation
- Day 7: Before instillation and 0.5, 1, 2, 4, 8, 12, and 24 hours post-instillation.

Blood samples for the determination of serum cortisol levels were collected at the following time points: Days 1 and 4: before first instillation and Day 7: before instillation and 24 hours post-instillation.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Pharmacokinetic analysis of drug concentration data was not performed since concentrations of DFB were below quantifiable limits for all subjects in Steps 1 and 2.

RESULTS:

Study Population and Disposition

A total of thirty-two (32) subjects were screened, and twelve (12) healthy subjects (6 per step) were enrolled. All twelve subjects completed the study. There were two protocol deviations; one high blood glucose level and one subject with the post-study examination conducted 2 days behind schedule. These deviations were deemed to not affect the interpretation of study results.

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 4.1.1-1.

Table 4.1.2-1. Demographics and Baseline Characteristics – Study 9

Demographic Characteristic	Mean ± SD (Range)	
	Step 1 (n = 6)	Step 2 (n = 6)
Age (yr)	21.8 ± 1.5 (21 – 24)	24.3 ± 4.2 (22 – 31)
Height (cm)	169.7 ± 5.3 (164.4 – 176.7)	172.4 ± 6.4 (161.9 – 181.4)
Weight (kg)	60.0 ± 6.0 (50.1 – 65.9)	60.9 ± 4.8 (54.5 – 66.4)
Obesity Index (%)	96.1 ± 11.2 (81.8 – 111.5)	93.7 ± 7.9 (83.7 – 103.3)

Source: Clinical Study Report 9, Tables 5-1 and 5-2.

Pharmacokinetic Results

Following 7-day multiple ocular administration of difluprednate ophthalmic emulsion 0.01% and 0.05%, concentrations of DFB in whole blood were below the quantification limit (50.00 ng/mL) at all time points for all subjects.

Pharmacodynamic Results

A summary of mean cortisol levels in subjects receiving multiple ocular doses of difluprednate ophthalmic emulsion 0.01% and 0.05% for 7 days is presented in Table 4.1.2-2. Based on an assessment of mean cortisol levels following multiple dose administration of 0.01% and 0.05% difluprednate ophthalmic emulsion QID for 7 days, difluprednate administration did not result in cortisol suppression. One subject (Subject 9) experienced a change in cortisol level that was judged possibly related to difluprednate administration. This subject had a significant increase in the mean cortisol value before instillation on Day 7 (to 24.8 µg/dL from a baseline value of 16.0 µg/dL). However, the mean value returned to the baseline level at 24 hours post-instillation on Day 7. Although the effects of difluprednate could not be completely ruled out, the event was considered highly likely to be due to environmental factors since this parameter can be influenced by diurnal variation and stress.

Table 4.1.2-2.

Mean Cortisol Levels ($\mu\text{g/dL}$) Following QID Ocular Administration of Difluprednate Ophthalmic Emulsion in Healthy, Male Japanese Subjects

Treatment Group	N	Day 1 Pre	Day 4 Pre	Paired T-Test vs. Day 1	Day 7 Pre	Paired T-Test vs. Day 1	Day 7 24 hours Post	Paired T-Test vs. Day 1
0.01%	6	15.67 (4.97)	20.08 (5.36)	NS	18.57 (3.65)	NS	19.30 (1.22)	NS
0.05%	6	17.20 (5.98)	17.57 (3.91)	NS	23.42 (3.74)	$p < 0.05$	17.25 (3.32)	NS

Data presented as mean (SD).

NS, not significant

Source: Clinical Study Report 9, Table 13.

APPLICANT'S CONCLUSIONS:

One week of ocular administration of difluprednate ophthalmic emulsion 0.01% and 0.05% QID results in a negligible amount of the active metabolite of difluprednate (DFB) in the blood. In general, administration of corticosteroids causes negative hypothalamic-pituitary-adrenal (HPA) feedback, resulting in a decrease in serum cortisol level. In the present study, no such decreases were noted. In the 0.05% treatment group, a significant increase in cortisol in a single subject was considered likely due to environmental factors, although a relationship to treatment could not be completely ruled out.

REVIEWER ASSESSMENT:

Study 9 adequately evaluated the safety and pharmacokinetics of difluprednate ophthalmic emulsion 0.01% and 0.05% given by repeated instillation in healthy adult male Japanese volunteers. The Applicant's conclusions regarding systemic exposure to difluprednate and cortisol suppression following multiple ocular administration are acceptable from a Clinical Pharmacology perspective.

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