CLINICAL DEVELOPMENT OF [redacted]

Clinical Trial Protocol: CLR_16_31

Protocol Title:	A Randomized, Double-Masked, Parallel Group, Multicenter, Study To Evaluate Efficacy And Safety of SPARC's SDN-037 Twice Daily Compared With Vehicle For The Treatment Of Inflammation And Pain Associated With Ocular Surgery.
Protocol Number	CLR_16_31
Version No.	01
Amendment No.	Amendment 02
Date	02 Aug 2019
Study Phase:	3
Investigational Product Name:	[redacted]
IND Number:	[redacted]
Indication:	Inflammation and pain associated with ocular surgery
Investigators:	Multi-center
Sponsor:	Sun Pharma Advanced Research Company, Ltd. (SPARC) 17 B Mahal Industrial Estate, Mahakali Caves Rd Andheri (E), Mumbai - 400 093 India

SPONSOR APPROVAL SIGNATURE

[redacted]

Sponsor's Medical Expert for the Study

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.0 SYNOPSIS

Title of the Study	A Randomized, Double-Masked, Parallel Group, Multicenter, Study To Evaluate Efficacy And Safety of SPARC's SDN - 037 Twice Daily Compared With Vehicle For The Treatment Of Inflammation And Pain Associated With Ocular Surgery.
Protocol Number	CLR_16_31
Investigational Product:	[redacted]
Study Phase:	3
Primary Objective(s):	To evaluate the efficacy and safety of topical administration of [redacted] compared with [redacted] when dosed [redacted] post cataract surgery.
Secondary Objective(s):	N/A
Overall Study Design Structure	Multi-center, double-masked, parallel group, randomization.
Duration:	Total duration: [redacted]
Vehicle:	Vehicle of [redacted]
Estimated Duration of Trial	Approximately [redacted]
Dosage/Dose Regimen/ Instillation/Application/Use:	1 drop of either: [redacted]
Summary of Visit	[redacted]

	[redacted]
Study Population Characteristics:	Subjects of all ages with inflammation and pain associated with cataract surgery
Number of Subjects:	[redacted]
Condition/Disease:	Inflammation and pain associated with ocular surgery.
Inclusion Criteria:	**Following criteria during screening visit:** 1. Be male or female, of all ages [redacted] 5. Able to self-instill the IP or have a caregiver available to instill all doses of the IP, as instructed. 6. Females of childbearing potential must not be pregnant (as confirmed by a negative urine pregnancy test [redacted]

	7. Be able and willing to follow study instructions and complete all required visits.
Exclusion Criteria:	1. Any known allergy or hypersensitivity to difluprednate [redacted] 7. An acute ocular infection (bacterial, viral or fungal) or active ocular inflammation in the study eye 11. Any active corneal pathology noted in the study eye [redacted]

	[redacted]
Evaluation Criteria :	**Primary Efficacy Endpoint** The primary efficacy endpoint is the proportion of subjects with an anterior chamber cell (ACC) grade of 0 at Day 15 [redacted] **Secondary Efficacy Endpoint** The key secondary efficacy endpoint is the proportion of subjects who achieve a pain score of 0 [redacted] at day 15 [redacted]
Safety Measures:	[redacted]
Efficacy Analysis:	[redacted]

	[redacted]
Safety Analyses:	[redacted]

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[redacted]

[redacted]

LIST OF ABBREVIATIONS

ACC	Anterior Chamber Cell
ACF	Anterior Chamber Flare
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BID	Twice a day (*bis in die*)
BSCVA	Best-Spectacle Corrected Visual Acuity
CI	Confidence Interval
CRO	Contract Research Organization
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IOL	Intra Ocular Lens
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
mITT	Modified Intent-To-Treat
LAR	Legally Acceptable Representative
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary of Regulatory Affairs

MRHD	Maximum Recommended Human Dose
NDA	New Drug Application
NOAEL	No Observed Adverse Effect Level
OPD	(in-)Office Physician Dispensing
PP	Per Protocol
PT	Preferred Term
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPARC	Sun Pharma Advanced Research Company, Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
VAS	Visual analog scale
WHO-DD	World Health Organisation Drug Dictionary

2.0 BACKGROUND INFORMATION

Surgical technique in all fields of ophthalmology has evolved considerably over the years, from the transition to clear corneal incisions by anterior segment surgeons to the adoption of small-gauge minimally invasive pars plana vitrectomies by vitreoretinal specialists. Despite such technical advances, however, surgical manipulation of anterior segment structures triggers the release of arachidonic acid from cell membranes, leading to the production of prostaglandins and leukotrienes. These inflammatory mediators, in turn, lead to cellular reaction and protein leakage. Untreated inflammation can lead to complications such as pain/discomfort, photophobia, corneal edema, synechiae, glaucoma, and cystoid macular edema.[redacted]

In the immediate postoperative period, topical corticosteroids are employed to suppress the production of inflammatory mediators. By inhibiting the release of arachidonic acid from cell membrane phospholipids, corticosteroids prevent the formation of both leukotrienes and prostaglandins, disrupting the inflammatory cascade.[redacted] These agents are continued until the anterior chamber (AC) reaction has resolved and the blood–aqueous barrier has been reestablished.[redacted]

In June 2008, difluprednate ophthalmic emulsion 0.05% (Durezol™; Sirion Therapeutics, Tampa, FL) was approved by the US Food and Drug Administration (FDA) for the treatment of inflammation and pain associated with ocular surgery.

Sun Pharma Advanced Research Company Ltd. (SPARC) has developed a novel topical ophthalmic formulation of [redacted] for the treatment of inflammation and pain associated with ocular surgery. SPARC intends to develop the ophthalmic [redacted] product at a [redacted] dose [redacted] and with a [redacted] frequency, [redacted] compared to [redacted]

2.1 Summary of Findings from Nonclinical Studies

Safety and efficacy of Durezol [redacted] were extensively and adequately evaluated in nonclinical studies as described in Prescribing Information and Product Monograph.[redacted] The pharmacology studies in animal models of uveitis demonstrated that [redacted] was effective in a dose-dependent manner. SPARC plans to seek approval of [redacted] for the same indications as those for Durezol, and thus use Durezol as the reference listed drug (RLD). To support development of the novel ophthalmic formulation of [redacted]

[redacted]

[redacted]

2.1.1 Pharmacology

[redacted]

In the [redacted] model, [redacted] significantly reduced total clinical score, total cell count and total protein levels in aqueous humor compared to the disease control. [redacted] administration of [redacted] demonstrated comparable, significant effects on all these measurements, whereas [redacted] only had a significant effect on reducing total clinical score, but not on total cell count or total protein levels in aqueous humor.

In the [redacted] model, [redacted] treatment demonstrated comparable efficacy as [redacted] ocular instillation. Both treatments significantly reduced total clinical score, total cell count and total protein levels in aqueous humor. [redacted] dosed at a [redacted] dose of [redacted] had no significant effect on these measurements as compared to [redacted].

[redacted]

2.1.2 Pharmacokinetics:

Pharmacokinetic profile of Durezol, 0.05% w/v, is well established by ocular route. The systemic absorption of ocular administered difluprednate is very small. During the 7 days ocular instillation studies in rabbits of 0.05% ^{3}H-difluprednate, the Cmax in the plasma was not more than 10 ng/g dry weight. Difluprednate is rapidly metabolized by deacetylation (at 21- position) in the rabbit eye tissues to the metabolite 6 alpha-9-difluoroprednisolone 17- butyrate, active metabolite (DFB), which is in turn converted to 17-debutylated DFB , a breakdown product of DFB. Single-dose and multiple-dose studies of difluprednate in rabbits demonstrate that difluprednate is rapidly metabolized and distributed to the main ocular target tissues that are affected by inflammation (iris, ciliary body, choroids, and aqueous humor in the anterior chamber), difluprednate does not accumulate in the blood, and difluprednate seems to have a low affinity for melanin, which indicates that difluprednate should work effectively in patients regardless of their race and eye color (i.e., differing levels of melanin in the eye, brown eyes having higher levels of melanin than blue eyes). Single-dose studies also showed 99.5% of difluprednate and its metabolites were cumulatively excreted via the feces and urine, and after repeated doses, difluprednate levels increased without affecting the Cmax, with clearance from most ocular tissues within 168 hours [redacted]

[redacted]

2.1.3 Toxicology

[redacted]. The NOAELs in the [redacted] were [redacted]. Neither deaths nor serious toxicological findings were noted in the studies. Many changes at higher doses were those generally observed in glucocorticoid (GC) treated animals. Ocular

[redacted]

administration of [redacted] for up to [redacted]

[redacted] difluprednate and difluprednate metabolites were negative. Reproductive toxicity tests were performed with difluprednate in rats and rabbits. Fetal death and malformations such as cleft palate (commonly associated with high-dose administration of GCs) were observed during the organogenesis in rabbits. The effects of difluprednate on rat fetuses were weak; fetal death and/or malformed fetuses were not found. Long-term studies have not been conducted to evaluate the carcinogenic potential of difluprednate. [redacted]

[redacted]

same ratio of dosing frequency of the reference drug and the test drug as in the clinical situation. Repeated ocular administration of difluprednate resulted in adverse findings including significant alteration in organ weights and histopathological changes in organs like liver and thymus accompanied by clinical pathology changes in the study. The systemic NOAEL was not obtained. However, based on minimal/less incidence of local effect, the local (ocular) NOAEL was obtained at [redacted] of [redacted]. No marked drug accumulation in systemic exposure was observed following repeated dosing for 30 days. No significant difference was observed in the toxicokinetic profiles of [redacted].

2.2 Summary of the Known and Potential Risks and Benefits to Human Subjects

Difluprednate was approved in US as Durezol® in 2008 in the form of difluprednate ophthalmic emulsion 0.05%. Difluprednate is used for the treatment of inflammation and pain associated with ocular surgery.

Class warnings for corticosteroids such as difluprednate are well known and state that prolonged use may result in glaucoma with damage of optic nerve, defect in visual acuity and field of vision, posterior subcapsular cataract formation. It is recommended that if corticosteroids are used for 10 days or longer, IOP should be routinely monitored. Prolonged use may also suppress the host response and thus increase the hazard of secondary ocular infections. Use of corticosteroids after cataract surgery may delay healing and increase the incidence of bleb formation. In diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. Use of difluprednate is also contraindicated in epithelial herpes simplex, and other viral diseases of the cornea and conjunctiva and fungal disease of ocular structures.

According to Durezol package insert, ocular adverse reactions occurring in 5-15% of subjects in clinical studies with Durezol included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis.

2.3 Summary of Clinical Data

There have been no specific clinical studies conducted with SPARC's [redacted]

2.4 Compliance Statement for Study Conduct in Accordance with Protocol, GCP and Applicable Regulatory Requirements

The study protocol, amendments to the protocol (if applicable), IB, subject recruitment procedures (e.g. advertisements) and the subject's information and informed consent form and assent forms(as applicable) as well as consent and assent (as applicable) form updates (if applicable) will be submitted to the IRB, which is constituted according to local law to obtain approval before initiation of the study and as applicable thereafter.

The study will only be initiated after receipt of the approval from the IRB. The investigator will report promptly to the IRB new information that may adversely affect the safety of the subjects or the conduct of the study.

The investigator will carry out the protocol in conformity with Good Clinical Practice (GCP) described in Guideline E6 of the ICH and applicable regulatory requirements. Before admission into the study, the written informed consent form and assent form(as applicable) must be personally signed and dated by the subject and /or guardian and by the investigator or designee who conducted the informed consent discussion.

In obtaining and documenting informed consent and assent (as applicable) the investigator must comply with the applicable regulatory requirement(s), and must adhere to GCP. The investigator must inform the subject of all pertinent aspects of the study including the written information approved/favorably assessed by the IRB.

3.0 STUDY OBJECTIVES

To evaluate the efficacy and safety of topical administration of [redacted] compared with [redacted] dose in the [redacted] surgery followed by [redacted].

4.0 OVERALL STUDY DESIGN

This study is a phase 3, randomized, multicenter, double-masked, vehicle-controlled, parallel-group clinical study. Subjects of all ages scheduled to undergo uncomplicated unilateral cataract surgery and

who meet all study entry criteria will be enrolled. [redacted]

[redacted]

Prior to enrollment, the study will be discussed with prospective subjects and/or LAR/parent/gaurdian and those who are willing to enter the study will be asked to give written informed consent.

Once informed consent and assent (as applicable) has been obtained, the subjects and/or LAR/parent/gaurdian will be questioned regarding their medical history to determine whether or not they are in satisfactory health to enter the study and to determine if they meet the specific entry criteria.

[redacted]

4.1 Measures taken to avoid bias

4.1.1 Subject number

[redacted]

4.1.2 [redacted]

[redacted]

4.1.3 [redacted]

[redacted]

[redacted].

[redacted]

4.2.1 Inclusion Criteria

Inclusion criteria during the screening visit are:

1. Be male or female, of all ages

[redacted]

5. Able to self-instill the IP or have a caregiver available to instill all doses of the IP, as instructed.
6. Females of childbearing potential must not be pregnant (as confirmed by a negative urine pregnancy test [redacted]

[redacted]

[redacted]

7. Be able and willing to follow study instructions and complete all required visits.

4.2.2 Exclusion Criteria

1. Any known allergy or hypersensitivity to difluprednate [redacted]

[redacted]

7. An acute ocular infection (bacterial, viral or fungal) or active ocular inflammation in the study eye.

[redacted]

11. Any active corneal pathology noted in the study eye.

[redacted]

14. Currently suffering from alcohol and/or drug abuse.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] to exclude subject based on clinical judgment, even if other eligibility criteria are satisfied.

[redacted]

[redacted]

4.2.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.0 STUDY PARAMETERS

5.1 Efficacy Measures

5.1.1 Primary Efficacy Variable(s)

The primary efficacy endpoint is the proportion of subjects with an anterior chamber cell (ACC) grade of 0 at Day 15 [redacted]

5.1.2 Secondary Efficacy Variable(s)

The key secondary efficacy endpoints are the proportion of subjects who achieve a pain score of 0 [redacted] at day 15([redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.0 STUDY MATERIALS

6.1 Study Treatment(s)

6.1.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.1.3 Study medication labeling

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.1.4 [redacted]

The IP is to only be prescribed by the principal investigator or his/her delegated sub investigator(s), and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. IP accountability includes the amount of IP dispensed to the subjects, amount of IP returned by the subjects, and the amount returned or disposed upon the completion of the study.

6.1.5 Return or Disposal of Investigational Product

All used study drugs will be returned to the sponsor or their designee or destroyed at the study site. The return or disposal of study drug will be specified in writing.

7.0 STUDY METHODS AND PROCEDURES

7.1 Subject Entry Procedures

7.1.1 Overview

Subjects as defined by the criteria in [redacted], will be considered for entry into this study.

7.1.2 Informed Consent and Assent (as applicable)

Prior to a subject's participation in the study (i.e, changes in a subject's medical treatment and/or study specific procedures), the study will be discussed with the subject and/or LARparent/guardian. Subjects wishing to participate the study must give written informed consent and assent form (as applicable) using an informed consent form (ICF) and assent form(as applicable) The ICF form and the assent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board.

7.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3.1.7 Unscheduled Visits

Additional exams may be scheduled as necessary to ensure the safety and well-being of subjects who experience adverse effects during the course of the study. Any additional examinations during the study will be fully documented in the source documents and on Unscheduled Visit eCRFs.

7.4 Compliance with Protocol

Site personal shall contact subjects/ caregivers at least once between the visits during the treatment period via phone or email and remind them to instill IP and to complete the pain and dosing diary. A call log has to be completed by study personnel after the call.

The specifications of the log will include

1. Date & Time of call
2. Site Staff able to make contact (Y/N)
3. If Yes, Point of Contact
4. A very short description of call

Subjects who are inappropriately enrolled will be discontinued from the study. The reason for such discontinuation will be recorded as “protocol violation” in the source document and on the appropriate

page in the eCRF. Notification of such protocol violations will be sent to IRB. Subjects will be provided with a pain and dosing diary to document their assigned dosing regimen. Subject compliance with dosing will be assured by in-office review of the pain and dosing diary.

[redacted]

7.5 Study Duration

[redacted]

7.6 Monitoring and Quality Assurance

During the course of the study CRO monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, quality assurance and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

8.0 [redacted]

[redacted]

8.1.1 Definitions

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Relationship to study drug, to be [redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

TERM	DEFINITION	CLARIFICATION
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
		[redacted]

Assessment of Expectedness

The most recent version of IB for [redacted] will be used for assessing expectedness of SAE for the subjects who have received [redacted]

Definition of the adverse event reporting period

The AE/ SAE reporting period for safety surveillance begins when the subject sign's ICF and/or assent form continues till end of study visit or early termination visit.

[redacted]

[redacted]

8.3 Procedures for Reporting Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR)

Serious Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's safety physician/ CRO to file a report, which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24-hours of his/ her awareness to the Sponsor's safety physician/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE Report Form and SAE report form in the eCRF and source documents.

The following minimum information must be included in the SAE form:

- Name, address and telephone number of the reporting Investigator
- IP details
- Subject identification number, initials, sex and date of birth
- Description of the SAE, measures taken and outcome

In the case of fatal or life-threatening events, please also immediately telephone the Sponsor's safety physician/CRO.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor's safety physician/CRO.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by e-mail to the Sponsor's safety physician/CRO.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor's safety physician/CRO may have on the AE. This is necessary to ensure prompt assessment of the event by the Sponsor's safety physician to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Sponsor's safety physician/CRO.

Suspected Unexpected Serious Adverse Reactions (SUSARs):

The applicable Regulatory Authorities shall be initially notified by Sponsor Safety Physician/ CRO of any SUSAR, no later than 15 calendar days from the "date learned" of the event. The applicable Regulatory Authorities will be initially notified as per regulation within 7 calendar days of any fatal or life-threatening SUSAR. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day 0 is not required.

[redacted]

[redacted]

[redacted]

8.4 [redacted]

[redacted]

[redacted]

[redacted]

8.5 Follow-Up

The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated. The Investigator should follow up on the outcome of any AE till end of study visit/ early termination visit. All SAEs will be followed until the event has resolved or stabilized as per medical judgement of the investigator.

Any AE/ SAE brought to the attention of the Investigator post end of study visit/ early termination visit requires notification to Sponsor and other stakeholders if it is considered related to study drug.

Any AE unresolved at the time of end of study/ early termination visit requires detailed evaluation and will be followed for outcome as per medical judgment of the investigator.

8.6 PREGNANCY

A pregnancy test will be performed at screening and at visits specified in the protocol. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test

[redacted]

9.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

[redacted]

9.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15 [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9.1.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the proportion of subjects who achieve a pain score of 0 [redacted] at Day 15 [redacted]

9.1.3 [redacted]

[redacted]

9.1.4 Analysis Populations

[redacted]

[redacted]

9.1.5 Baseline Variables

Age in years (7 to < 65, ≥ 65)

- Sex (male, female)
- Ethnicity (hispanic, nonhispanic)
- Race (white, black, other)

9.2 [redacted]

[redacted]

[redacted]								

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

9.3 Methods of Analysis

9.3.1 General Approach

The final analysis will be conducted when all subjects have either completed the [redacted] visit or have otherwise [redacted]. At that time, the database will be cleaned, processed, and locked. At this stage the study will be unblinded. Efficacy and safety endpoints will be analyzed based on this locked database.

Summary statistics for categorical variables will include frequency and percentage. For continuous variables, number of subjects with non-missing value (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) will be reported.

Subject disposition, demographics and baseline characteristics will be summarized.[redacted]

[redacted]

All summaries and analyses will be presented by treatment group.

Any deviations from the original statistical plan will be described in the final report.

9.3.2 Efficacy Analysis

9.3.2.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15. [redacted]

9.3.2.2 [redacted]

[redacted] model.

[redacted]

9.3.3 [redacted]

[redacted]

[redacted]

9.3.3.1.1 [redacted]

[redacted]

9.3.3.1.2 Incidence of TEAEs

A summary of TEAEs will be presented by SOC and PT by treatment group. If a subject reports the same PT multiple times, then [redacted] As with the PT, if a subject reports multiple AEs within the same SOC, [redacted]

9.3.3.1.3 Severity of TEAEs

A summary of TEAEs by SOC, PT, and severity will be presented by treatment group. Severity will be graded by the investigator as "Mild," "Moderate," or "Severe." [redacted]

9.3.3.1.4 Relationship of Treatment-Emergent Adverse Events to the IP

A summary of TEAEs by SOC, PT, and relationship to the IP will be presented by treatment group. The relationships indicate the investigator's assessment of whether or not the event was caused by the IP. The possible relationships are "Not Related," "Possibly Related," and "Related." [redacted]

9.3.3.1.5 Serious Adverse Events

Serious adverse events (SAEs) will be listed by subject; SAEs will be summarized by event and treatment group.

9.3.3.1.6 Adverse Events Leading to Study Drug Withdrawal

All AEs leading to study withdrawal or study drug withdrawal will be listed and may be summarized if appropriate.

9.3.3.2 [redacted]

[redacted]

9.3.3.2.2 [redacted]

[redacted]

[redacted]

[redacted]

9.3.3.2.3 [redacted]

[redacted]

9.3.3.2.4 [redacted]

[redacted]

[redacted]

[redacted]

9.3.4 Concomitant Medications

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IPs in the countries involved will be adhered to.

10.1 Protection of Human Subjects

10.1.1 Subject Informed Consent and Assent(as applicable)

Informed consent and assent (as applicable) must take place before any study specific procedures are initiated. Signed and dated written informed consent and assent(as applicable) must be obtained from each subject prior to enrollment into the study.

All informed consent forms and assent forms(as applicable) must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form and

assent form requires revision (eg, due to a protocol

amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent form and assent form(as applicable) is reviewed and approved by CRO prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent and assent (as applicable) is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by CRO and/or study sponsor and provided in writing by CRO and/or study sponsor prior to the consent process.

10.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with Institutional Review Board regulations. [redacted]

Only current IRB/ERC approved version of the ICF/Assent form will be used.

10.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

10.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of CRO, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

10.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests performed. The investigator's copy of the electronic case report forms (eCRFs) serves as the investigator's record of a subject's study-related data.

10.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all IPs and copies of eCRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

10.5 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Prior to the start of the study a signature and delegation list will be completed showing the signatures and hand written initials of all who are authorized to entry data or make corrections in the documents. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (eg, by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction when and why along with justification, by adding to the correction his/her initials as well as the date of the correction.

10.6 Handling of Biological Specimens

[redacted]

10.7 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. The study sponsor will have the final decision regarding the manuscript and publication.

11.0 REFERENCES

[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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12.2 Examination Procedures, Tests, Equipment, and Techniques

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Urine Pregnancy Tests (If Applicable)

Standard dipstick-based urine pregnancy tests will be administered to subjects that are of child bearing potential to assess pregnancy status as outlined in the [redacted]. Child bearing potential is defined as any female who has had her first menses, not had a hysterectomy or bilateral tubal ligation, and has not been post-menopausal for at least 12 consecutive months. Pregnancy is not to be considered an AE, but it is an important medical event that must be followed up as described in [redacted]

Blood Pressure (mmHg)

Systolic and diastolic blood pressure should be measured in the same arm each time using a sphygmomanometer with the subjects who have been in a resting state (seated upright) at least 5 minutes. Blood pressure will be recorded in mm Hg.

[redacted]

[redacted] must be assessed using an [redacted] chart and as indicated in the study flowchart in [redacted] The procedure used will be consistent with the recommendations provided for using the [redacted]. [redacted] should be evaluated at the [redacted] in the study (ie, [redacted]). [redacted] testing should be done with [redacted] correction.

A [redacted] will be considered [redacted] significant, and may indicate an [redacted]

Equipment

[redacted] If smaller reproduction [redacted] eg, from Prevent Blindness) wall charts are used, the subject viewing distance should be [redacted] (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only the 'R' charts, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

[redacted]

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (eg, 'that was a "C" not an "O"') before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

[redacted]

[redacted]

For Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a subject forgets his glasses), the reason for the change in correction should be documented.

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[redacted]

The investigator or study staff will also be asked to record the time these 2 measurements were obtained.

[redacted]

[redacted]

In addition to the [redacted], subjects will be asked to assess their pain via a diary at home [redacted] to each dose, and for [redacted] after the [redacted] dose, until the [redacted]

For this the following pain assessment criteria where [redacted].

[redacted]

In addition to the above, dosing information shall be completed by the patient/caregiver in the pain ans dosing diary along with any information related to the adverse events noted. Detailed diary completion instructions will be provided to all subjects. If necessary, a caregiver may transcribe the subject's pain assessment on to the diary for subjects who are unable to write. In this case, study staff must review the diary with the subject and ensure the subject agrees with the recorded Information

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12.3 Protocol Amendment Summary

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

12.4 Investigator's Signature

Protocol Title:

A Randomized, Double-Masked, Parallel Group, Multicenter, Study To Evaluate Efficacy And Safety of SPARC's SDN -037 Twice Daily Compared With Vehicle For The Treatment Of Inflammation And Pain Associated With Ocular Surgery.

Protocol Number: CLR_16_31

Version No. Date 01

Amendment No. Date 02, 02 Aug 2019

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by CRO and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

[redacted]

[redacted]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use

Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------

DUREZOL® is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery (1.1)
- The treatment of endogenous anterior uveitis (1.2)

----------DOSAGE AND ADMINISTRATION----------

- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response. (2.1)
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

DUREZOL contains 0.05% difluprednate, as a sterile preserved ophthalmic emulsion for topical ophthalmic use only. (3)

----------CONTRAINDICATIONS----------

DUREZOL, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. (4)

----------WARNINGS AND PRECAUTIONS----------

- **Intraocular pressure (IOP) increase:** Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored. (5.1)
- **Cataracts:** Use of corticosteroids may result in posterior subcapsular cataract formation. (5.2)
- **Delayed healing:** The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. (5.3)
- **Bacterial infections:** Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated. (5.4)
- **Viral infections:** Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.5)
- **Fungal infections:** Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. (5.6)

----------ADVERSE REACTIONS----------

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis

DUREZOL is also indicated for the treatment of endogenous anterior uveitis.

2 DOSAGE AND ADMINISTRATION

2.1 Ocular Surgery

Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

2.2 Endogenous Anterior Uveitis

Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

3 DOSAGE FORMS AND STRENGTHS

DUREZOL contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

4 CONTRAINDICATIONS

The use of DUREZOL, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, IOP should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

5.5 Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

DUREZOL should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL. The preservative in DUREZOL may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL.

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP *[see Warnings and Precautions (5.1)]*
- Posterior subcapsular cataract formation *[see Warnings and Precautions (5.2)]*
- Secondary ocular infection *[see Warnings and Precautions (5.4)]*
- Perforation of the globe *[see Warnings and Precautions (5.3)]*

6.1 Ocular Surgery

Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

6.2 Endogenous Anterior Uveitis

A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL. The most common adverse reactions of those exposed to DUREZOL occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL, since DUREZOL is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL is administered to a nursing woman.

8.4 Pediatric Use

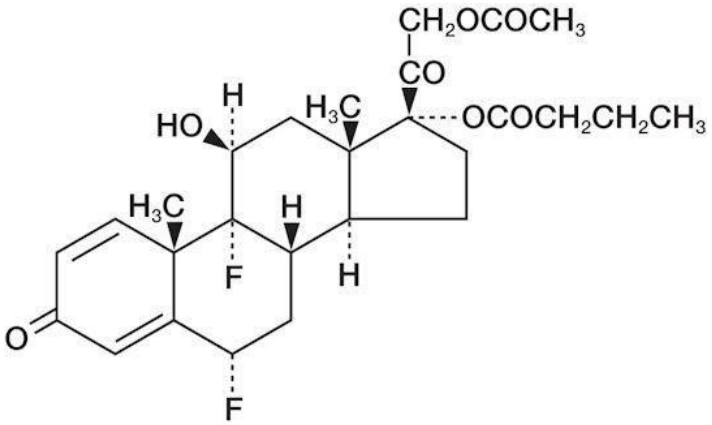
DUREZOL was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (39 DUREZOL; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

DUREZOL (difluprednate ophthalmic emulsion) 0.05% is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The chemical name is 6α,9difluoro-11β,17,21-trihydroxypregna-1,4- diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4). Difluprednate is represented by the following structural formula:



Difluprednate has a molecular weight of 508.56, and the empirical formula is $C_{27}H_{34}F_2O_7$.

Each mL of DUREZOL contains: **ACTIVE:** difluprednate 0.5 mg (0.05%); **INACTIVE:** boric acid, castor oil, glycerin, polysorbate 80, water for injection, sodium acetate, edetate disodium, sodium hydroxide (to adjust the pH to 5.2 to 5.8). The emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg. **PRESERVATIVE:** sorbic acid 0.1%.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and may delay or slow healing. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotreines by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Difluprednate is structurally similar to other corticosteroids.

12.4.1 12.3 Pharmacokinetics

Difluprednate undergoes deacetylation in vivo to 6α, 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%) four times per day 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 DUREZOL is limited.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Difluprednate was not genotoxic in vitro in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An in vivo micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long-term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

13.2 Animal Toxicology and/or Pharmacology

In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1-1.25 mcg/kg/day.

14 CLINICAL STUDIES

14.1 Ocular Surgery

Clinical efficacy was evaluated in 2 randomized, double-masked, placebo-controlled trials in which subjects with an anterior chamber cell grade greater than or equal to "2" (a cell count of 11 or higher) after cataract surgery were assigned to DUREZOL or placebo (vehicle) following surgery. One drop of DUREZOL or vehicle was self-instilled either 2 times per day or 4 times per day for 14 days, beginning the day after surgery. The presence of complete clearing (a cell count of 0) was assessed 3, 8 and 15 days post surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant benefit was seen in the 4 times per day DUREZOL-treated group in ocular inflammation, at Days 8 and 15, and reduction of pain, at Days 3, 8 and 15, when compared with placebo. The consolidated clinical trial results are provided below.

Figure 1 Percent of Subjects With Anterior Chamber Cells Clearing (Cell Count = 0)

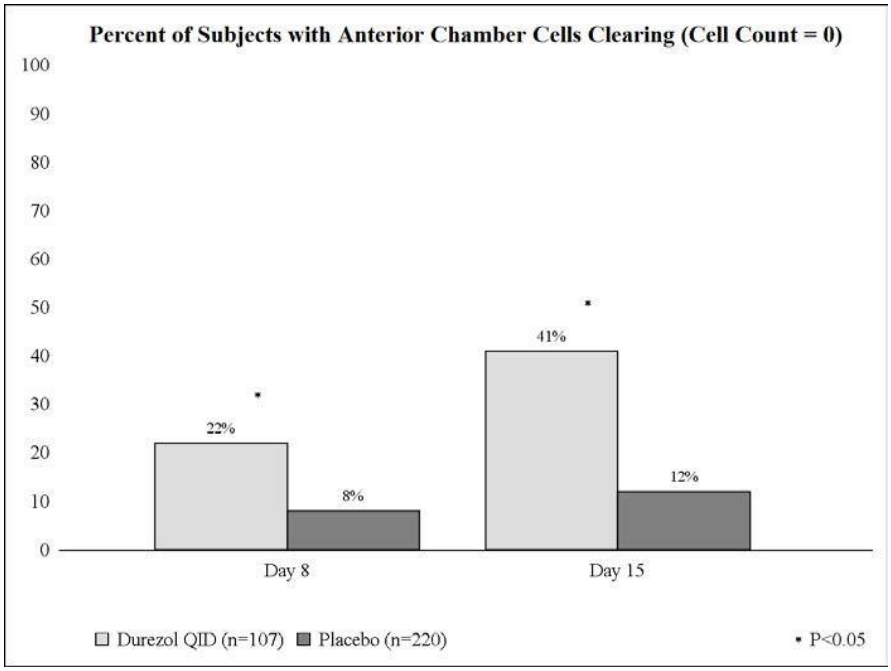
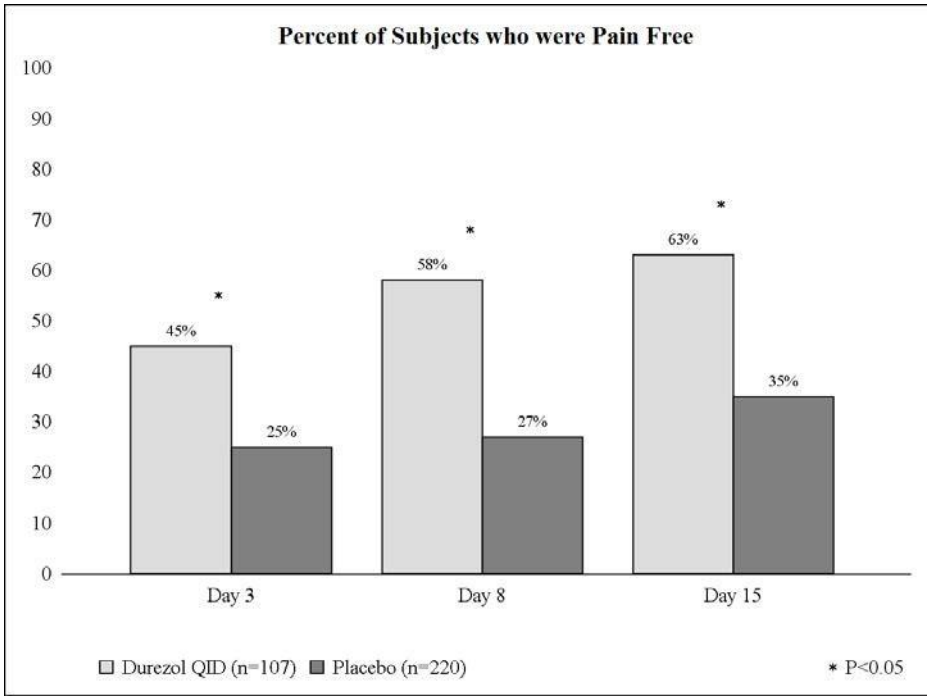


Figure 2 Percent of Subjects Who Were Pain Free



14.2 Endogenous Anterior Uveitis

Clinical efficacy was evaluated in two randomized, double masked active controlled trials in which patients who presented with endogenous anterior uveitis were treated with either DUREZOL 4 times daily or prednisolone acetate ophthalmic suspension, 1%, 8 times daily for 14 days. Both studies demonstrated that DUREZOL was equally effective as prednisolone acetate ophthalmic suspension, 1% in treating subjects with endogenous anterior uveitis. The results are found in Table 1 below.

12.4.2 Table 1: Mean Change from Baseline in Anterior Chamber Cell Grade*

Study 1 time point	**DUREZOL N=57**	**Prednisolone Acetate N=53**	**Difference† (95% CI)**
Baseline	2.6	2.5	0.0 (-0.22, 0.28)
Day 3	-1.0	-1.0	-0.1 (-0.35, 0.25)
Day 7	-1.6	-1.5	-0.0 (-0.31, 0.25)
Day 14	-2.0	-1.8	-0.2 (-0.46, 0.10)
Day 21	-2.2	-1.9	-0.3 (-0.53, 0.01)
Day 28	-2.2	-2.1	-0.1 (-0.37, 0.18)
Day 35	-2.1	-2.0	-0.1 (-0.39, 0.20)
Day 42	-2.1	-2.1	0.0 (-0.27, 0.34)
Study 2 time point	**DUREZOL N=50**	**Prednisolone Acetate N=40**	**Difference† (95% CI)**
Baseline	2.4	2.4	0.0 (-0.21, 0.29)
Day 3	-0.9	-0.9	-0.0 (-0.34, 0.25)
Day 7	-1.7	-1.6	-0.1 (-0.35, 0.21)

Day 14	-1.9	-1.8	-0.1 (-0.34, 0.20)
Day 21	-2.0	-2.0	0.0 (-0.25, 0.28)
Day 28	-2.0	-2.0	0.0 (-0.21, 0.26)
Day 35	-2.1	-2.0	-0.1 (-0.32, 0.16)
Day 42	-2.0	-1.9	-0.1 (-0.36, 0.24)

*with 5 grades: 0 = 0 cells; 1 = 1 to 10 cells; 2 = 11 to 20 cells; 3 = 21 to 50 cells; and 4 = greater than 50 cells

†adjusted for baseline AC cell grade and study center and based on ITT dataset with LOCF for missing data

CI = confidence interval

16 HOW SUPPLIED/STORAGE AND HANDLING

DUREZOL (difluprednate ophthalmic emulsion) 0.05% is a sterile, aqueous topical ophthalmic emulsion supplied in an opaque plastic bottle with a controlled drop tip and a pink cap in the following sizes:

5 mL in a 8 mL bottle……..NDC 0065-9240-07

12.4.3 Storage and Handling

Store at 15°C to 25°C (59°F to 77°F). Do not freeze. Protect from light. When not in use, keep the bottles in the protective carton.

13.0 PATIENT COUNSELING INFORMATION

13.1 Risk of Contamination

This product is sterile when packaged. Advise patients not to allow the dropper tip to touch any surface, as this may contaminate the emulsion.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

13.1.1.1 Risk of Secondary Infection

If pain develops, or if redness, itching, or inflammation becomes aggravated, advise patients to consult a physician.

13.1.1.2 Contact Lens Wear

DUREZOL should not be instilled while wearing contact lenses. Advise patients to remove contact lenses prior to instillation of DUREZOL. The preservative in DUREZOL may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL.

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List of Changes

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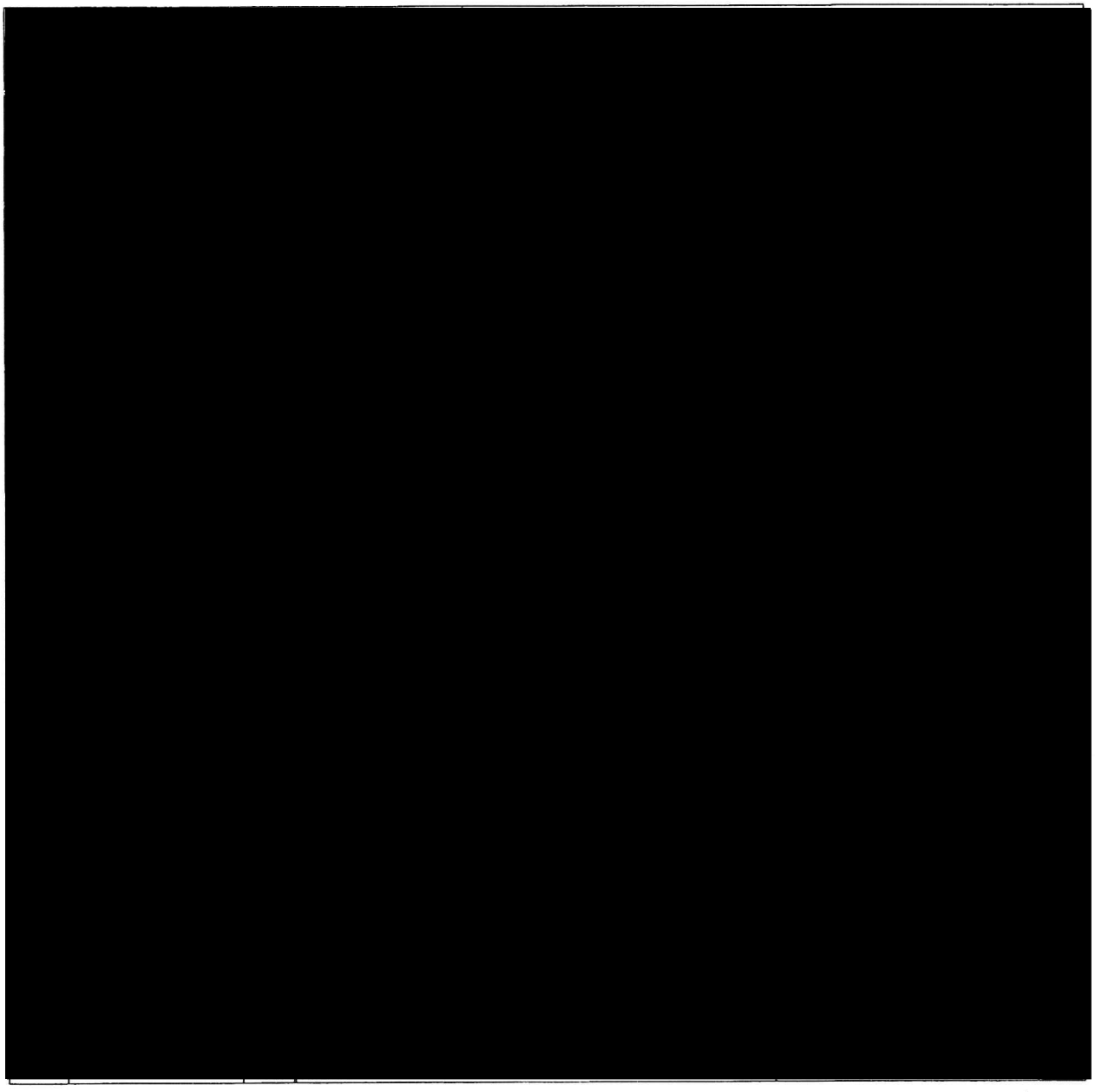
Contents:



List of Changes

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