Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery

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PURPOSE: To examine the efficacy and safety of a new gel formulation loteprednol etabonate 0.5% in the treatment of inflammation and pain after cataract surgery.

SETTING: Seventeen United States clinical sites.

DESIGN: Prospective double-masked parallel-group study.

METHODS: Patients with anterior chamber cell (ACC) grade 2 or higher after cataract surgery were randomized to loteprednol etabonate 0.5% gel or vehicle 4 times a day for 14 days. Primary outcome measures included the proportion of patients with complete resolution of ACC and grade 0 (no) pain on postoperative day 8. Safety measures included adverse events, intraocular pressure (IOP), visual acuity, biomicroscopy and funduscopy findings, and tolerability (ocular symptoms and drop comfort).

RESULTS: The intent-to-treat population included 406 patients (203 per treatment). On day 8, 30.5% of patients in the loteprednol etabonate group and 16.3% of patients in the vehicle group had complete resolution of ACC, whereas 72.9% and 41.9%, respectively, had grade 0 pain (both $P<.001$). Significant treatment differences for complete resolution of ACC and grade 0 pain favoring loteprednol etabonate were also found on day 15 and day 18. One patient in each treatment group had a significant increase in IOP ($\geq$10 mm Hg). Analyses of pain, photophobia, and tearing favored loteprednol etabonate at different time points beginning on day 3. More than 85% of patients in each treatment group reported no discomfort on drop instillation.

CONCLUSION: Loteprednol etabonate gel 0.5% was efficacious and safe in treating postoperative inflammation and pain.

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Cataract surgery is a commonly performed ophthalmic procedure globally and is associated with low risks and few side effects. The surgery is now minimally invasive, and the associated risks have decreased considerably due to recent advances in phacoemulsification instrumentation and surgical advances, such as smaller incisions and better ophthalmic viscosurgical devices.[1] Despite these advancements, postoperative inflammation remains a challenge and mild pain is a common complaint of patients. Trauma at the site of surgery induces an inflammatory response initiated by the release of membrane phospholipids and culminating in the formation of prostaglandins, leukotrienes and other eicosanoids, and the recruitment of neutrophils and macrophages to the site.[2] This inflammation generally manifests as mild iritis along with corneal edema and increased cells and protein (flare) in the anterior chamber along with accompanying hyperalgesia or pain.[3] In addition to the classic signs of rubor, tumor, dolor, and color, ocular inflammation may result in sequelae such as posterior capsule opacification and cystoid macular edema (CME), culminating in suboptimum vision.[1] It is therefore routine practice to use topical corticosteroids to minimize inflammation and prevent its potential complications.

Although topical ocular corticosteroids provide strong antiinflammatory efficacy, they are associated

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with several unwanted effects, the most frequent of these being an increase in the intraocular pressure (IOP). Biologic and morphologic changes to the trabecular meshwork and a resultant increased resistance in aqueous humor outflow are the suspected causes of this increase in IOP.[4] The increase in IOP may result in corticosteroid-induced ocular hypertension and, eventually, glaucoma. An increase in IOP of 10 mm Hg or higher is generally considered clinically significant.[5,6] Older corticosteroids, such as dexamethasone and prednisolone, were for years the mainstay of treatment for ocular inflammation and often caused significant increases in IOP. Newer corticosteroids have since gained regulatory approval specifically for postoperative ocular inflammation and have been subject to trials for antiinflammatory efficacy, and safety in terms of their effect on IOP.

Only 3 topical corticosteroids—loteprednol etabonate, difluprednate, and rimexolone—have received United Stated Food and Drug Administration approval for the treatment of postoperative ocular inflammation.[3,7,8] Loteprednol etabonate has had numerous clinical trials and has proved efficacious and safe for this indication.[3,9] Studies[10–13] have also shown its efficacy and safety in treating inflammation associated with anterior uveitis, allergic conjunctivitis, giant papillary conjunctivitis, and inflammation associated with delayed tear clearance. Comprehensive reviews[14,15] describe the use of loteprednol etabonate for these indications and highlight that across all indications, loteprednol etabonate offers an efficacious and safe option in the treatment of ocular inflammation. Structurally, loteprednol etabonate differs from other ocular corticosteroids in that the carbon 20 ketone group in the prednisolone core structure is replaced with an ester. After exerting its effect at the site of action, it is rapidly metabolized to its inactive form. This ester-based design results in fewer side effects, particularly lower levels of increased IOP, without compromising efficacy.[15,A]

All previous trials used loteprednol etabonate 0.2% and 0.5% in their respective suspension formulations. More recently, data have also been made available on an ointment form of loteprednol etabonate 0.5%.[16] The present study aimed to determine the efficacy and safety of loteprednol etabonate in a new gel formulation when compared with vehicle for the treatment of inflammation and pain after cataract surgery. The gel formulation includes polycarbophil for increased ocular surface retention and glycerin and propylene glycol, 2 known demulcents. Unlike the current suspension formulations, the gel is nonsettling and does not require shaking to resuspend the drug particles and it provides consistent dose uniformity. The new formulation has a more physiologic pH, and the concentration of benzalkonium chloride (BAK) concentration has been reduced from 0.01% to 0.003%.

PATIENTS AND METHODS

Study Design

This was a multicenter randomized double-masked parallel-group study (NCT 01010633[B]) evaluating the efficacy and safety of the new gel formulation of loteprednol etabonate versus its vehicle. Patients were planned for enrollment across 20 sites in the United States. Ethical approval for the study was received from Schulman Associates IRB, Inc., Cincinnati, Ohio. The study was performed in accordance with the World Medical Association Declaration of Helsinki in its revised edition (2004), the relevant ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996, and applicable local regulations. All patients were required to provide written informed consent.

The study enrolled patients aged 18 years or older planning to have routine uncomplicated cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation not combined with other surgery. Only patients who, in the investigator's opinion, had a potential postoperative corrected distance visual acuity (CDVA) of at least 20/200 were included in the study. Female patients of childbearing potential were required to have a negative urine pregnancy test at screening. Additional inclusion criteria applicable on postoperative day 1 ensured that only patients who had cataract surgery and had grade 2 or higher (6 to 15 cells) anterior chamber cells (ACC) were included in the study.

The study excluded patients who were expected to require concurrent ocular therapy in either eye with nonsteroidal antiinflammatory drugs (NSAIDs), systemic NSAIDS (with the exception of ≤81 mg/d of acetylsalicylic acid), mast cell stabilizers, antihistamines, or decongestants 2 days before surgery or throughout the course of the study. Additional exclusion criteria included the systemic or ocular use of corticosteroids or glucocorticoids within 3 months before screening or during the course of the study, expected use of concurrent ocular therapy with immunosuppressants

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(eg, cyclosporine) throughout the study duration or within 30 days before surgery, a history or presence of chronic generalized systemic disease, severe ocular conditions, an elevated IOP (≥21 mm Hg) at screening, monocular patients, CDVA of 20/200 or worse in the non-study eye, or known hypersensitivity to the study drug or any of its components.

Study Treatments and Assessments

The investigational product in this study was loteprednol etabonate gel, manufactured by Bausch & Lomb, Inc.; it contains loteprednol etabonate 0.5% and the preservative BAK 0.003%. The vehicle was identical to the investigational product but did not contain loteprednol etabonate. For masking purposes, equal volumes of loteprednol etabonate gel or vehicle were filled in identical white 7.5 cc low-density polyethylene bottles with white polypropylene caps and packed into identical patient kit boxes.

Eligible patients completed 7 study visits to the clinic. Visit 1 (the screening visit), occurred within 14 days before surgery; informed consent was obtained and relevant medical and ophthalmic history recorded at this visit. The day of the cataract surgery was considered visit 2. Visit 3 occurred 18 to 34 hours after surgery. At visit 3 (postoperative day 1), patients with ACC grade 2 or higher (6 to 15 cells) were randomized to receive the study drug or vehicle in a 1:1 ratio stratified by site according to a unique computer-generated randomization scheme. Patients instilled 1 or 2 drops of the study medication 4 times a day (at approximately 4-hour intervals) for 14 days. The first dose of the study medication was administered at the clinic, and medication for the duration of the study was given to the patients. Visit 4 occurred on postoperative day 3, and visit 5 on postoperative day 8. The last study dose was the fourth dose instilled on the day before visit 6 (postoperative day 15). Visit 7, the study exit visit, occurred on postoperative day 18. To assess compliance of administration, patients recorded the date and time of each study drug administration in a diary provided by the sponsor. Patients brought their study drug and diary to the clinic at visits 4 through 6, at which time the study drug was weighed for accountability and patient diaries were reviewed to assess compliance of administration.

Patients could be placed on antiinflammatory rescue medication at the investigator's discretion any time during the study. Patients requiring rescue medication discontinued the study medication; however, they were followed until the end of the study. The use of topical antibiotics was permitted provided they were not formulated as a fixed-dose combination with a steroid. The choice and dosing of topical antibiotics was at the discretion of the investigator; patients were instructed to instill the antibiotic at least 15 minutes before instillation of study medication.

Investigators assessed ocular signs and symptoms, CDVA, and IOP at screening (visit 1) and all postoperative visits (days 3, 8, 15, and 18). Ocular signs (cells, flare, ciliary flush, chemosis, eyelid erythema, palpebral conjunctival injection, corneal staining, corneal edema, hyphema, posterior synechiae, anterior vitreous haze) were evaluated through slitlamp biomicroscopy. Ocular symptoms (pain, photophobia, itching, tearing, dryness, discharge) were assessed by the investigator through direct patient inquiry. The IOP was measured using applanation tonometry and was assessed within ±2 hours of the time of IOP assessment at the screening visit. Funduscopy was performed at screening and on day 15 (visit 6) only. The onset of adverse events and changes in concomitant medications were assessed at each study visit. To avoid confounding immediate procedure-related adverse events with treatment-emergent adverse events, baseline assessments were set for postoperative day 1. Treatment-emergent adverse events were new events that were not present at baseline or adverse events that subsequently worsened from baseline and were assessed as to severity and relationship to study treatment.

Anterior chamber cells and anterior chamber flare were graded on a scale of 0 to 4 (cells: 0 = no cells, 1 = 1 to 5 cells, 2 = 6 to 15 cells, 3 = 16 to 30 cells, 4 = 30 cells or more; flare: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) using a 1.0 mm × 1.0 mm high-power-field slit beam. Ciliary flush, hyphema, and posterior synechiae were graded as absent or present, while chemosis, eyelid erythema, palpebral conjunctival injection, bulbar conjunctival injection, corneal staining, corneal edema, and anterior vitreous haze were graded on a scale of 0 to 3 (0 = absent/none; 3 = severe). Ocular pain was defined as an unpleasant sensation in the eye, including foreign-body sensation, throbbing, stabbing, or aching and was based on a 0 to 5 scale (0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = moderately severe; 5 = severe). Photophobia, itching, tearing, dryness, and discharge were graded on a 0 to 3 scale (0 = absent; 3 = severe). Study drug comfort was assessed at postoperative days 3, 8, and 15 as drop sensation and was graded on a 0 to 3 scale (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Study medication effects on ocular symptoms were assessed at baseline and at each postoperative visit. Tolerability was measured as gel comfort reported at postoperative days 3, 8, and 15.

Outcome Measures

The primary efficacy endpoints were the difference in the proportion of study eyes with complete resolution (grade 0) of ACC on day 8 and the difference in the proportion of study eyes with grade 0 (no) pain on day 8 in the loteprednol etabonate gel and vehicle groups. The secondary efficacy endpoints were the proportion of study eyes with (1) complete resolution of ACC, (2) complete resolution of anterior chamber flare, (3) complete resolution of ACC and flare combined, and (4) grade 0 pain, assessed at each visit. Change from baseline in the severity of ACC and flare both separately and combined at each visit were also assessed as secondary efficacy endpoints. Subjective endpoints included ocular symptoms and study gel comfort. Safety of the study drug was assessed by the incidence of adverse events, change in IOP from baseline, visual acuity, biomicroscopy, and funduscopy findings.

Statistical Analysis

Approximately 400 participants were targeted for randomization, with 200 patients per treatment group yielding 97% and 99% power for detecting a difference in the rates of complete resolution of ACC on day 8 and grade 0 pain on day 8, respectively, using the asymptotic Pearson chi-square test and resolution rate assumptions based on previous studies of loteprednol etabonate in different formulations.[16]

The primary efficacy endpoint analyses of resolution of ACC and grade 0 pain were performed by testing, in hierarchical order, the difference in the proportion of study eyes with complete resolution of ACC and the difference in the rates of grade 0 pain between treatments on day 8 using

the asymptotic Pearson chi-square statistic and a 2-sided $\alpha = 0.05$ level. Patients with missing data or placed on rescue medication before the visit being summarized were considered treatment failures in the analysis. Similar analyses were performed for complete resolution of ACC and flare combined and for flare separately on day 8 and for resolution of ACC, flare, and ACC and flare combined, and grade 0 (no) pain at all other postoperative visits. The change from baseline in ACC, flare, and composite ACC and flare, were analyzed using continuous and discrete variables by treatment and by visit, carrying the last observation forward for missing data or for patients placed on rescue medication.

The tolerability endpoint of gel comfort and ocular symptoms were summarized using discrete summary statistics by visit and by treatment group. The difference in proportion of study eyes with symptoms absent was analyzed excluding patients placed on rescue medication before the visit being summarized.

Safety endpoints were summarized by visit and treatment group; these were presented separately for data obtained before and after receiving rescue medication. The CDVA, biomicroscopy measures, and funduscopy measures were summarized using discrete summary statistics. The IOP was summarized using continuous summaries (including change from baseline and change from screening) and discrete summaries (including the proportion of patients with an increase in IOP $\geq$10 mm Hg from baseline and the proportion of patients with treatment-emergent IOP $\geq$30 mm Hg). Treatment-emergent adverse events were summarized using discrete summaries at the patient and event level by system organ class and preferred term for each treatment group. Significance for between-group differences in ocular and nonocular treatment-emergent adverse events was calculated using the Fisher exact test. Ocular treatment-emergent adverse events were summarized for treated eyes and fellow eyes separately. Similarly, treatment-emergent adverse events were summarized by severity and relationship separately.

The intent-to-treat population comprised all patients randomly assigned to receive 1 of the 2 treatments. The safety population comprised all patients in the intent-to-treat population who had received at least 1 dose of study drug. The per-protocol population included all patients who remained in the study through day 8 (visit 5) and did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study. Efficacy endpoint analyses were performed for the intent-to-treat population.

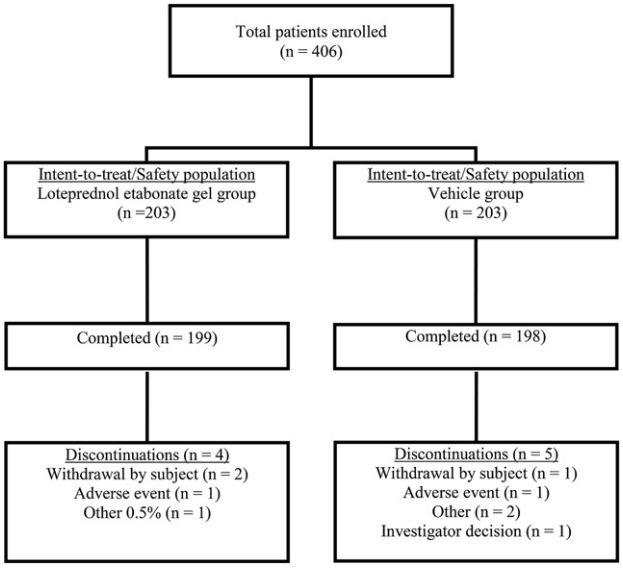

Figure 1. Participant flow.

RESULTS

Four hundred seventy-nine patients from 17 U.S. centers were screened. Of these, 406 patients had grade 2 or higher ACC on day 1, were randomized to the loteprednol etabonate gel or vehicle groups (203 each), and were included in the intent-to-treat and safety populations. Of the patients, 397 (199 in loteprednol etabonate gel group and 198 patients in vehicle group) completed the study. Figure 1 shows a detailed description of the participant flow. Eighteen (4.4%) patients had protocol deviations, leaving 388 patients (194 in each treatment group) in the per-protocol population.

Table 1 shows the patients' demographics. Most patients were white, and 231 (56.9%) were women. Similar ocular and nonocular medical histories were recorded in the treatment groups in the intent-to-treat population and were indicative of a study population nearing 70 years of age. For all study populations analyzed, demographic and baseline characteristics were generally similar in the treatment groups and across study centers.

Table 1. Patient demographics in the intent-to-treat population.

Parameter	LE Gel (n = 203)	Vehicle (n = 203)	Overall (N = 406)
Age (y)			
Mean ± SD	69.3 (8.73)	69.0 (9.80)	69.1 (9.27)
Median	69.0	71.0	71.0
Range	50, 91	36, 88	36, 91
Race, n (%)			
White	176 (86.7)	182 (89.7)	358 (88.2)
Black/African American	20 (9.9)	16 (7.9)	36 (8.9)
American Indian/ Alaskan Native	0	1 (0.5)	1 (0.2)
Asian	2 (1.0)	3 (1.5)	5 (1.2)
Native Hawaiian/Pacific Islander	1 (0.5)	0	1 (0.2)
Other	4 (2.0)	1 (0.5)	5 (1.2)
Sex, n (%)			
Male	94 (46.3)	81 (39.9)	175 (43.1)
Female	109 (53.7)	122 (60.1)	231 (56.9)
Ethnicity, n (%)			
Not Hispanic and not Latino	188 (92.6)	189 (93.1)	377 (92.9)
Hispanic or Latino	15 (7.4)	14 (6.9)	29 (7.1)

LE = loteprednol etabonate

At baseline (postoperative day 1, visit 3), the mean ACC severity was 2.3 ± 0.47 in the loteprednol etabonate gel group and 2.3 ± 0.46 in the vehicle group, with 303 patients (74.6%) having grade 2 (6 to 15 cells) ACC, 99 patients (24.4%) having grade 3 (16 to 30 cells) ACC, and 4 patients (1.0%) having grade 4 (>30 cells) ACC at baseline. The mean flare severity was 0.9 ± 0.70 in the loteprednol etabonate gel group and 0.9 ± 0.64 in the vehicle group, while the mean combined ACC and flare was 3.1 ± 0.89 and 3.2 ± 0.83, respectively. At baseline, 112 patients (55.2%) in the loteprednol etabonate gel group and 106 patients (52.2%) in the vehicle group reported grade 1 or higher (minimal) pain. Concomitant topical antibiotics varied and included, in order of overall frequency, moxifloxacin, gatifloxacin, besifloxacin, and bacitracin–polymyxin B.

Two hundred thirty-two patients (57.1%), 86 (42.4%) in the loteprednol etabonate gel group and 146 (71.9%) in the vehicle group, required rescue medication during the study. Almost all rescue therapies were initiated after postoperative day 3. The cumulative number of patients requiring rescue medication in the loteprednol etabonate gel group and the vehicle group, respectively, was 17 (8.4%) and 70 (34.5%) by postoperative day 8 (visit 5) and 35 (17.2%) and 105 (51.7%) by postoperative day 15 (visit 6). All other rescue medication was initiated after the 2-week study treatment ended.

Nearly all patients returning diaries, 198 (99%) in the loteprednol etabonate gel group and 181 (100%) in the vehicle group, provided complete diary data and reported administering 4 doses (±20%) per day through postoperative day 8.

Efficacy

Primary Efficacy Endpoints

Figure 2 shows the primary endpoints and treatment differences in the intent-to-treat and per-protocol population. In the intent-to-treat population, complete resolution of ACC on day 8 was observed in 30.5% (62) of patients and 16.3% (33) of patients randomized to the loteprednol etabonate gel group and vehicle group, respectively, when missing values and data from patients placed on rescue medication were imputed as failures ($P<.001$). Grade 0 pain was reported by 72.9% (148) of patients and 41.9% (85) of patients randomized to the loteprednol etabonate gel group and vehicle group, respectively, when missing values and data from patients placed on rescue medication were imputed as failures ($P<.001$). Results for the per-protocol population were similar to those obtained for the intent-to-treat population.

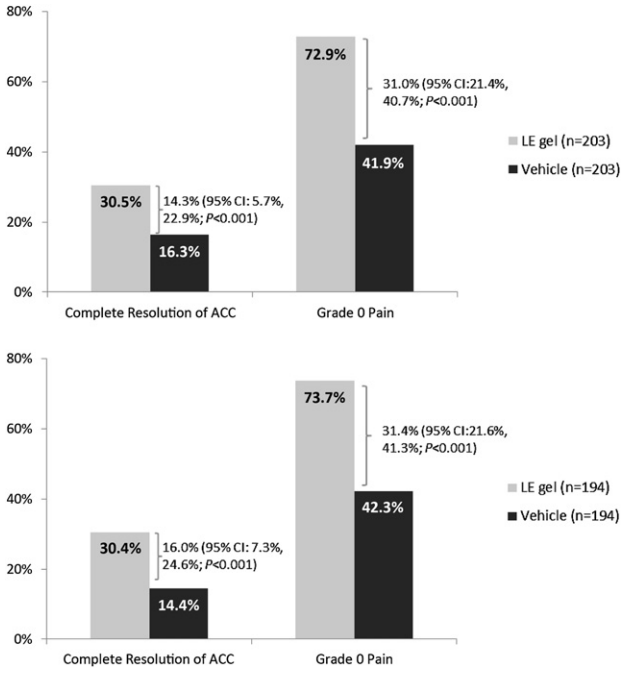

Figure 2. Proportion of patients with complete resolution of ACC and grade 0 pain at day 8 (visit 5) in the intent-to-treat population (*top*) and per-protocol population (*bottom*) (ACC = anterior chamber cell; LE = loteprednol etabonate).

Secondary Efficacy Endpoints

Secondary endpoints were analyzed for the intent-to-treat population only. Table 2 shows the proportion of patients with complete resolution of ACC, resolution of flare, resolution of ACC and flare combined, and grade 0 (no) pain on postoperative day 3 to day 18, while Figure 3 shows the mean change from baseline in ACC and flare, both individually and combined on these days. With the exception of resolution of ACC and ACC and flare combined on day 3, all secondary endpoints were significantly better in the loteprednol etabonate gel group than in the vehicle group ($P \leq .006$). The mean change from baseline in ACC, anterior chamber flare, and ACC and flare severity combined were also significantly better in the loteprednol etabonate gel group than in the vehicle group at all visits ($P<.001$).

Subjective Outcomes

At baseline, ocular pain, photophobia, and tearing, mostly mild, was reported by 53.7%, 59.6%, and 41.4% of patients, respectively. Excluding patients placed on rescue medication, analysis of these symptoms at postoperative follow-up visits showed that fewer patients treated with loteprednol etabonate gel reported pain ($P<.001$ at days 3, 8, and 15), photophobia ($P=.024$ at day 3 and $P<.001$ at day 8), and tearing ($P=.014$ at day 3). The majority of patients had no discharge, dryness, or itching at baseline,

Table 2. Proportion of patients with complete resolution of ACC, flare, ACC and flare combined, and grade 0 (no) pain 3 to 18 days postoperatively (intent-to-treat population) (loteprednol etabonate group = 203; vehicle group = 203).

	Day 3 (Visit 4)					Day 8 (Visit 5)		
Parameter	LE Gel, n (%)	Vehicle, n (%)	Diff (%)	95% CI	*P* Value	LE Gel, n (%)	Vehicle, n (%)	Diff (%)
Complete resolution of ACC	17 (8.4)	11 (5.4)	3.0	−2.5, 8.4	.240	62* (30.5)	33* (16.3)	14.3*
Complete resolution of flare	93 (45.8)	66 (32.5)	13.3	3.4, 23.2	.006	138 (68.0)	76 (37.4)	30.5
Complete resolution of ACC and flare	16 (7.9)	10 (4.9)	3.0	−2.3, 8.2	.224	60 (29.6)	33 (16.3)	13.3
Grade 0 (no) pain	153 (75.4)	96 (47.3)	28.1	18.5, 37.6	<.001	148* (72.9)	85* (41.9)	31.0*

ACC = anterior chamber cell; Diff = difference; LE = loteprednol etabonate
*Primary endpoints

and these symptoms were improved or did not change from baseline in both treatment groups at follow-up visits.

At each visit, more than 85% patients in each group reported drop sensation as "none." There was 1 report of severe sensation (day 15, vehicle group), and moderate sensation was reported by less than 3% of patients in either group at all visits.

Safety

The mean exposure was 12.3 ± 3.46 days in the loteprednol etabonate gel and vehicle group and 9.2 ± 4.87 days in the vehicle group. Thirty-eight patients (18.7%) in the loteprednol etabonate gel group and 44 patients (21.7%) in the vehicle group experienced at least 1 ocular treatment-emergent adverse event before the use of any rescue medication ($P=.537$). The most common ocular treatment-emergent adverse events were ocular inflammation, eye pain, photophobia, foreign-body sensation, and conjunctival hemorrhage and were consistent with those observed after cataract surgery. Table 3 shows the ocular treatment-emergent adverse events that were considered drug related. The number of patients with at least 1 ocular treatment-emergent adverse event considered drug related was 9 (4.4%) in the loteprednol etabonate gel group and 14 (6.9%) in the vehicle group. Most were mild to moderate in severity. The only drug-related ocular treatment-emergent adverse events reported at a rate greater than 1% (n = 2) in either treatment group were anterior chamber inflammation and eye pain. Blurred vision, a consideration with gel formulations, was reported by 1 patient (vehicle group).

Nonocular treatment-emergent adverse events were reported by 9 patients (4.4%) in each treatment group. The only nonocular treatment-emergent adverse events reported at a rate of at least 1% (n = 2) in any treatment group were nausea (loteprednol etabonate gel, n = 3; vehicle, n = 1), bronchitis (loteprednol etabonate gel, n = 2; vehicle, n = 2), and headache (loteprednol etabonate gel, n = 1; vehicle, n = 2). None of the nonocular treatment-emergent adverse events was judged as treatment related.

Six serious adverse events were reported by 4 patients. Two serious adverse events, both nonocular, occurred before randomization. Treatment-emergent serious adverse events included 2 serious ocular adverse events (1 case each of CME in both treatment groups) and 2 serious nonocular adverse events (bronchitis and exacerbated systolic congestive heart failure in the same patient in the vehicle group). All treatment-emergent serious adverse events reported were unrelated to study drug.

The mean baseline (postoperative day 1) IOP was similar between treatment groups (loteprednol etabonate gel, 15.2 ± 3.76 mm Hg; vehicle, 15.1 ± 3.73 mm Hg). Figure 4 shows the mean change in IOP in each group from baseline to each postoperative visit through day 18. There was no significant difference between treatment groups in the mean change from baseline at these visits, and mean IOP was consistently lower than baseline in both treatment groups at these visits. One patient in each treatment group had a clinically significant increase from baseline in IOP (≥10 mm Hg) in the study eye before the end of study treatment. Latanoprost was used to treat the IOP increase in the loteprednol etabonate group.

The baseline CDVA ranged from 20/20 to 20/60 in 190 study eyes (93.6%) in the loteprednol etabonate gel group and in 190 study eyes (93.6%) in the vehicle group. As expected after cataract surgery, most patients had an improvement in visual acuity at day 18, with a CDVA for patients with non-missing data ranging from 20/15 to 20/30 in 113 (87.6%) of 129 study eyes in the loteprednol etabonate gel group and 53 (88.3%) of 60 study eyes in the vehicle group. Few study eyes in either treatment group had a loss of more than 2 lines of CDVA at days 3 to 18 (loteprednol etabonate gel, n = 7; vehicle, n = 9 at worst-visit analysis), and there were no between-treatment differences in the percentage of patients with a loss of more than 2 lines at any visit.

Table 2. (Cont.)

Day 8 (Visit 5)		Day 15 (Visit 6)					Day 18 (Visit 7)				
95% CI	*P* Value	LE Gel, n (%)	Vehicle, n (%)	Diff (%)	95% CI	*P* Value	LE Gel, n (%)	Vehicle, n (%)	Diff (%)	95% CI	*P* Value
5.7, 22.9*	<.001*	102 (50.2)	44 (21.7)	28.6	19.2, 38.0	<.001	96 (47.3)	45 (22.2)	25.1	15.7, 34.5	<.001
20.8, 40.3	<.001	151 (74.4)	76 (37.4)	36.9	27.5, 46.4	<.001	119 (58.6)	58 (28.6)	30.0	20.4, 39.7	<.001
4.7, 21.9	.001	101 (49.8)	44 (21.7)	28.1	18.7, 37.5	<.001	96 (47.3)	45 (22.2)	25.1	15.7, 34.5	<.001
21.4, 40.7*	<.001*	154 (75.9)	77 (37.9)	37.9	28.5, 47.3	<.001	121 (59.6)	54 (26.6)	33.0	23.4, 42.6	<.001

Dilated funduscopy findings were comparable across treatment groups at screening and day 15. No fundus pathology was reported in the majority of study eyes. Two study eyes (both in the loteprednol etabonate gel group) had an increase in retinal abnormalities compared with screening; the abnormalities were judged clinically insignificant.

As expected, biomicroscopy findings showed few patients with worsening ocular signs in the loteprednol etabonate gel group. Fewer patients in the loteprednol etabonate gel group had increased worsening of eyelid erythema at days 3, 8, and 15 ($P \leq .040$); increased ACC, flare, ciliary flush, chemosis, bulbar conjunctival injection, corneal staining, and corneal edema at days 3 and 8 ($P \leq .028$); and increased palpebral conjunctival injection at day 3 ($P < .001$).

DISCUSSION

This multicenter randomized double-masked parallel-group study found that loteprednol etabonate gel was significantly more efficacious than vehicle in resolving inflammation and pain after cataract surgery. The proportion of patients with complete ACC resolution and grade 0 (no) pain was greater in the loteprednol etabonate gel treatment group than in the vehicle treatment group at day 8 and day 15 (all $P < .001$), with a difference in treatment effect of 14.3% and 31.0% at day 8 and 28.6% and 37.9% at day 15, for ACC resolution and grade 0 (no) pain, respectively. Fewer patients in the loteprednol etabonate gel group than in the vehicle group required rescue medication, and secondary endpoints were supportive of findings for primary endpoints. Treatment with loteprednol etabonate gel led to a greater proportion of patients with complete resolution of anterior chamber flare and pain at all follow-up visits and of cells and flare combined at days 8, 15, and 18 ($P \leq .006$). Consistent with previous reports,[16] resolution of flare occurred more rapidly than resolution of ACC, with a greater proportion of eyes treated with loteprednol etabonate gel having no flare as early as postoperative day 3.

Treatment with loteprednol etabonate gel was well tolerated and safe. Patient reports of ocular pain, photophobia, and tearing were significantly better in patients treated with loteprednol etabonate gel at most postoperative visits, while symptoms of ocular discharge, dryness, and itching, reported by few patients at baseline, were similar between treatment groups. Most patients across treatment groups reported no discomfort on drop instillation, and drug-related ocular adverse events were few and comparable between treatment groups. Blurred vision, an adverse event of interest with gel formulations, was reported by only 1 patient (0.5%) in the vehicle group. This finding is likely attributable to the transition of the gel formulation to a fluid after instillation in the eye.[C] The gelling agent in loteprednol etabonate gel, polycarbophil, is sensitive to the electrolytes in tears and becomes considerably less viscous on contact with tears. It follows that the formulation would not be expected to block absorption of concomitant medications provided these medications are instilled at a reasonable interval (10 to 15 min) after instillation of loteprednol etabonate gel. The mean IOP in all study eyes was consistently lower than baseline at all post-treatment visits in both treatment groups, and only 1 patient (0.5%) in each group had a clinically significant increase ($\geq$10 mm Hg) in IOP over baseline. The finding of few clinically significant IOP elevations with loteprednol etabonate is due to the rapid metabolism of unbound loteprednol etabonate to inactive metabolites by naturally occurring esterases.[17]

Results in this study are consistent with those reported with other formulations of loteprednol etabonate 0.5% in the treatment of inflammation and pain following cataract surgery.[3,9,16,D] The efficacy and safety of loteprednol etabonate ophthalmic suspension 0.5% was studied in 2 randomized vehicle-controlled trials.[3,9] In both studies, patients with an anterior chamber inflammation (sum of ACC and anterior chamber flare) severity grade 3

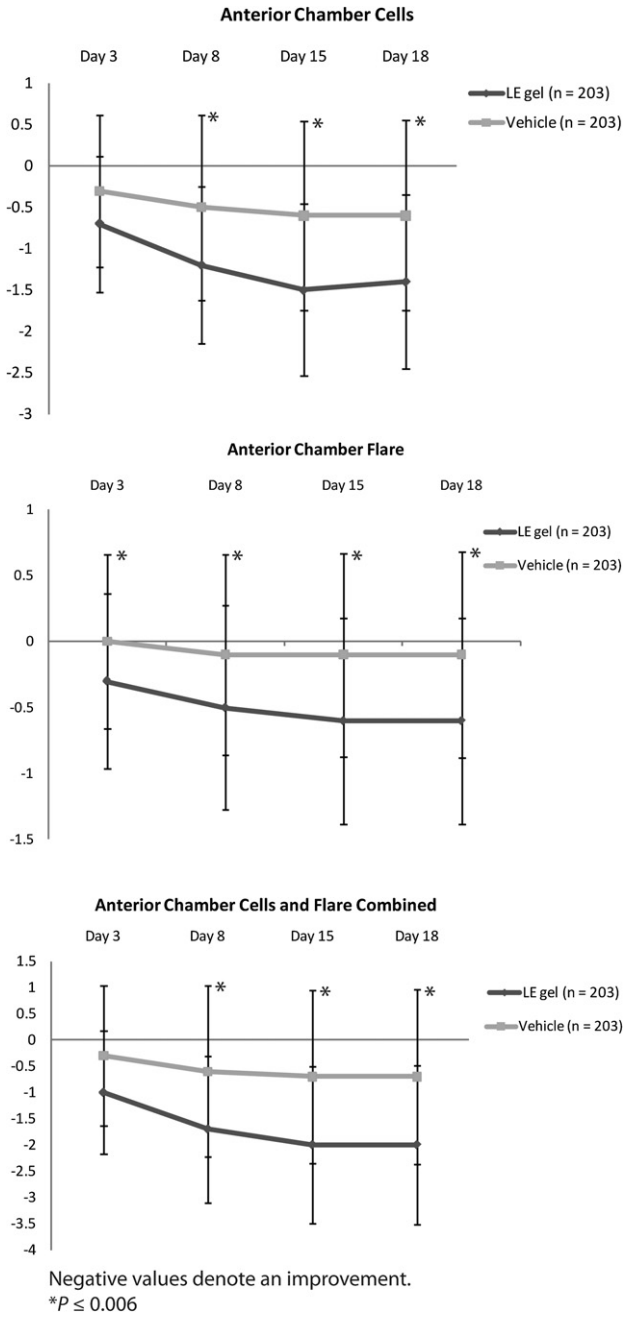

Figure 3. Mean (SD) change from baseline in anterior chamber cell (ACC) and flare severity, individually and combined, for the loteprednol etabonate gel and vehicle groups (intent-to-treat population) (LE = loteprednol etabonate).

or higher (scale of 0 to 9) on the day after surgery received loteprednol etabonate suspension or vehicle administered 4 times daily for 14 days. Sixty percent and 31% of patients in the first study and 68% and 35% patients in the second study treated with loteprednol etabonate suspension and vehicle, respectively, had resolution of ACC, defined as 5 cells or less at the final visit ($P<.001$). Results for pain resolution and postoperative discomfort, reported

Table 3. Drug-related ocular treatment-emergent adverse events before rescue medication.*

Parameter	Number (%)	
	LE Gel (n = 203)	Vehicle (n = 203)
Patients with at least 1 related ocular adverse event	9 (4.4%)	14 (6.9%)
Total drug-related adverse events	16	25
Anterior chamber inflammation	3 (1.5%)	3 (1.5%)
Eye pain	2 (1.0%)	3 (1.5%)
Photophobia	2 (1.0%)	2 (1.0%)
Foreign-body sensation in eyes	0	2 (1.0%)
Eye pruritus	2 (1.0%)	2 (1.0%)
Anterior chamber cells	0	2 (1.0%)
Vision blurred	0	1 (0.5%)
Eye irritation	1 (0.5%)	1 (0.5%)
Lacrimation increased	2 (1.0%)	0
Anterior chamber flare	0	1 (0.5%)
Eyelids pruritus	0	1 (0.5%)
Macular edema	1 (0.5%)	0
Eye swelling	0	1 (0.5%)
Photopsia	0	1 (0.5%)
Pupillary disorder	0	1 (0.5%)
IOP Increased	1 (0.5%)	0

LE = loteprednol etabonate; IOP = intraocular pressure
*A patient was counted at most once for a given preferred term (except for total number of adverse events)

separately,[D] indicated that 84% of at-risk patients treated with loteprednol etabonate suspension compared with 56% of at-risk patients treated with vehicle across the 2 studies had grade 0 (no) pain at the final visit ($P<.05$), while 79% of patients treated with loteprednol etabonate suspension and 42% patients treated with vehicle had resolution of postoperative discomfort.[D] A clinically significant increase (≥10 mm Hg) in IOP was seen in 3 patients (1.4%) in the loteprednol etabonate group and 1 patient (0.3%) in the vehicle group across the 2 studies.[3,9] Comstock et al.[16] studied the safety and efficacy of an ointment formulation of loteprednol etabonate 0.5% pooled across 2 studies. Again, patients with an anterior chamber inflammation grade 3 or higher (scale of 0 to 9) on the day after surgery were randomized to loteprednol etabonate ointment or vehicle administered 4 times daily for 14 days. The proportion of patients with resolution of ACC, defined in this study as no cells seen on day 8 in the loteprednol etabonate ointment and vehicle groups, was approximately 30% and 13%, respectively, increasing to approximately 48% and 20% on day 15; while 75.5% and 43.1% patients in the loteprednol etabonate ointment and vehicle groups, respectively, had grade 0 (no) pain on day 8. Clinically significant

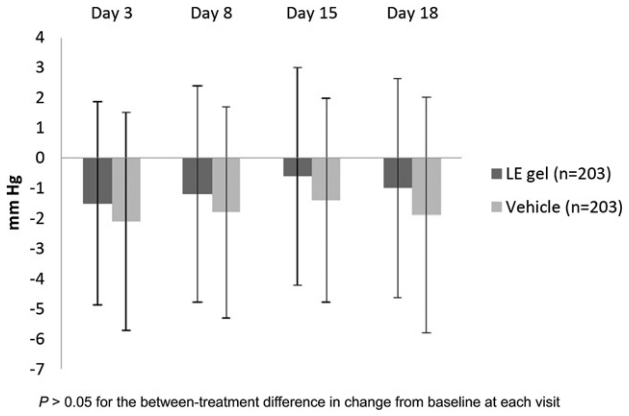

Figure 4. Change from baseline in mean (±SD) IOP in the loteprednol etabonate and vehicle groups (safety population) (LE = loteprednol etabonate).

increases in IOP (≥10 mm Hg) were observed in 3 patients (0.7%) in the loteprednol etabonate ointment group and 1 patient (0.3%) treated with vehicle.

Results with loteprednol etabonate gel are also similar to those reported for difluprednate and rimexolone. Korenfeld et al.[7] studied the efficacy and safety of difluprednate ophthalmic emulsion 0.05% compared with vehicle in the treatment of postoperative inflammation in 2 studies. Patients with ACC grade 2 or higher (>10 cells) on the day after surgery instilled difluprednate or placebo 2 times daily in the first study and 4 times daily in the second study for 14 days followed by a 14-day tapering schedule in each study. A total of 30%, 35%, and 9% of patients in the twice-daily difluprednate group, 4-times daily difluprednate group, and the pooled placebo group, respectively, had grade 0 ACC (defined as ≤1 cell) on day 8, increasing to 55%, 63%, 15%, respectively, on day 15 ($P<.0001$ versus placebo for all). Results in a separate analysis in which grade 0 ACC was defined as no cells showed resolution rates of 22% in the difluprednate group and 7% in the vehicle group at day 8, increasing to 41% versus 11% at day 15.[E] Both difluprednate treatment regimens were also effective in resolving pain compared with a placebo. However, the proportion of patients with IOP elevations appeared higher than that observed in loteprednol etabonate studies, with 3 patients (3%) in each difluprednate group having a 10 mm Hg or higher increase in IOP from baseline compared with 2 patients (1%) in the placebo group. Assil et al.[8] and Bron et al.[18] studied the clinical safety and efficacy of rimexolone 1% ophthalmic suspension in the treatment of postoperative inflammation after cataract surgery. In both studies, patients with an anterior chamber inflammation grade 3 or higher (scale 0 to 9) on the day after surgery were randomized to rimexolone or placebo instilled 4 times daily for 14 days. By day 8, 17.7% and 1.7% of patients in the first study and 33.3% and 14.3% of patients in the second study receiving rimexolone and placebo, respectively, had resolution of anterior chamber inflammation (defined as <5 cells and no flare), increasing to 50.0% and 21.1% in the first study and 59.7% and 19.6% in the second study by day 15. Rates for ACC individually were not reported in these studies. Clinically significant IOP elevations (≥10 mm Hg), reported in the Assil et al.[8] study only, were observed in 2 patients (1.5%) in the rimexolone group and 2 patients (3.2%) in the placebo group. Although these studies suggest the efficacy of loteprednol etabonate gel is similar to that of difluprednate and rimexolone, with potentially better IOP outcomes compared with difluprednate, due to the use of different patient entry criteria and/or definitions for grade 0 ACC across these studies, further head-to-head comparative studies are needed.

Along with the effective control of inflammation and pain after ocular surgery provided by loteprednol etabonate 0.5%, the gel formulation provides the benefits associated with a more physiologic pH, a reduced level of BAK, and a non-settling formulation that does not require shaking. It also contains polycarbophil as well as glycerin and propylene glycol, 2 known demulcents. Benzalkonium chloride is a preservative that kills microorganisms by disrupting cell membranes and causing cell lysis. In vitro studies, however, suggest BAK may result in corneal epithelial cell dysfunction and ocular surface disorders, particularly with long-term use.[19,20] To minimize a potential negative impact of BAK, the concentration of this preservative in the gel formulation was reduced from 0.01% to 0.003% in the loteprednol etabonate suspension formulation. The more physiologic pH of loteprednol etabonate gel, specifically a pH of 6.0 to 6.5 and closer to that of tears, may lead to better comfort in patients. Indeed, more than 85% of patients in both treatment groups reported no discomfort on drop instillation, and the majority of patients in both treatment groups had no dryness, itching, or discharge. Finally, the non-settling nature of the gel formulation eliminates shaking to resuspend the drug particles. Because patients may not always follow instructions and vigorously shake suspension formulations before use, the non-settling nature of the gel formulation provides consistent dose uniformity and ease of instillation for patients.

In conclusion, results from this study indicate that loteprednol etabonate 0.5% gel is an efficacious, safe, and well-tolerated topical ocular corticosteroid for the treatment of postoperative ocular inflammation and pain that is associated with a low risk of clinically significant increases in IOP.

WHAT WAS KNOWN

- Loteprednol etabonate, an ocular topical corticosteroid, has been approved in the US and many European countries in its 0.5% suspension form for the treatment of inflammation and pain after cataract surgery.
- Studies have found that it is efficacious and safe in the treatment of postoperative inflammation and pain, with a low potential to cause clinically significant increases ($\geq$10 mm Hg) in IOP.

WHAT THIS PAPER ADDS

- This study evaluated a new gel formulation of loteprednol etabonate for the treatment of pain and inflammation after cataract surgery. This new formulation is non-settling for consistent dose uniformity, has a more physiologic pH, and a reduced level of the preservative benzalkonium chloride.
- Results suggest that loteprednol etabonate 0.5% gel is efficacious and safe in treating postoperative inflammation and pain; furthermore, formulation changes may provide added benefit to patients.

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