Objective: To determine whether a topical ophthalmic diclofenac sodium formulation containing a proprietary polymeric drug delivery system (ISV-205), when dosed concomitantly with 1% prednisolone acetate, is effective in blocking the intraocular pressure (IOP) response in humans.

Design: This was a multicenter, prospective, double-masked, parallel, vehicle-controlled study. We included 136 first-degree relatives of subjects with primary open-angle glaucoma. Subjects were randomized to receive 0.06% or 0.1% ISV-205 or vehicle while concomitantly receiving 1% prednisolone for 6 weeks.

Results: During the treatment period, the mean±SD maximum IOP increase (7.3±6.5 mm Hg for vehicle, 4.9±4.6 mm Hg for 0.06% ISV-205, and 5.9±4.9 mm Hg for 0.1% ISV-205) was significantly less with the 0.06% formulation than with placebo (P = .02). The overall mean change in IOP was 3.6, 2.0, and 2.4 mm Hg in the vehicle, 0.06% ISV-205, and 0.1% ISV-205 groups, respectively, which was significant between the 0.06% ISV-205 and vehicle groups (P = .05). Eight (17%) of the 46 subjects receiving vehicle terminated the study because of high IOPs, compared with 1 (2%) of the 45 subjects receiving 0.06% ISV-205 and 3 (7%) of the 45 subjects receiving 0.1% ISV-205 (P = .03). The number of subjects with a clinically important corticosteroid response (≥10-mm Hg increase) was greater in the vehicle group (12 [28%] of 43 subjects) compared with the 0.06% ISV-205 group (3 [7%] of 42 subjects) (P = .01). Adverse events were similar between treatments.

Conclusions: This study suggests that ISV-205 limits the corticosteroid-induced elevated IOP in first-degree relatives of subjects with glaucoma. Future studies are needed to confirm these results and explore the possible role of this drug in treating glaucoma.

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PHTHALMIC corticosteroids were first reported to cause intraocular pressure (IOP) elevation in the 1950s. Subsequent studies showed that corticosteroid-induced IOP elevation is relatively common,1,2 the magnitude of corticosteroid-induced IOP elevation varies markedly from one person to the next,3 and the extent of elevated IOP depends on the frequency and duration of the topical administration.4

Treatment exists to control corticosteroid-induced IOP elevation (eg, latanoprost and β-blockers). Ocular hypotensive agents, however, generally may be associated with ocular or systemic adverse effects that make them unacceptable to some subjects.5 In addition, a risk of glaucomatous damage may exist, from the corticosteroid response, before the discovery and treatment of the elevated IOP.

To address this problem, one company (InSite Vision Incorporated, Alameda, Calif) is investigating a prophylactic treatment approach using a topical ophthalmic diclofenac sodium formulation containing a proprietary polymeric drug delivery system (ISV-205) as a means to block corticosteroid-induced IOP elevation, rather than treat it once it has occurred. The proprietary polymeric drug delivery system (DuraSite) is used to enhance drug delivery and penetration.

In this study, we evaluated the ability of 0.06% or 0.1% ISV-205 (InSite Vision Incorporated), compared with vehicle, to block the IOP increase from concomitantly administered 1% prednisolone acetate in first-degree relatives of subjects with glaucoma.

METHODS

SUBJECTS

This double-masked, vehicle-controlled, clinical trial was performed at 5 investiga-
Subjects were randomly assigned to receive 1 of 2 concentrations (0.06% or 0.1%) of ISV-205 or vehicle instilled 3 times daily for 6 weeks while concomitantly receiving prednisolone 4 times daily.

The following were the inclusion criteria for this study: aged at least 18 years; had signed and dated an institutional review board–approved informed consent form; was likely to complete the study and comply with appropriate instructions; was a first-degree relative of a subject with primary open-angle glaucoma; was a healthy volunteer with IOPs of 21 mm Hg or lower in both eyes; and if of childbearing potential, then was practicing a medically acceptable form of birth control and demonstrated a negative result on a pregnancy test before enrolling into the study.

Subjects were excluded from this study if they had an uncontrolled systemic disease (cardiovascular disease, hypertension, or diabetes mellitus); had an unstable or an alteration of controlled systemic disease (cardiovascular disease, hypertension, diabetes, or a first-degree relative of a subject with primary open-angle glaucoma); participated in previous ISV-205 clinical studies; were first-degree offspring or siblings of subjects with primary open-angle glaucoma, participated in the study. These subjects completed the study.

Each subject randomly received either 1 of 2 concentrations of ISV-205 (0.06% or 0.1%) or vehicle. All study medications were administered as topical eye drops to one randomly selected eye (treated eye). The ISV-205 and vehicle were packaged in identical single-dose unit containers. Neither the investigators and their staff nor the subjects were told which drug the subject received.

At the screening/baseline visit (visit 1), the study drug (0.06% ISV-205, 0.1% ISV-205, or vehicle) was administered by a clinical study coordinator 3 times at approximately 4-hour intervals. A comfort query was performed after each of the 3 doses.

Subjects were examined again after a minimum of a 1-week washout (visit 2), and began the 6-week dosing period (weekly visits 3-8). During active treatment (visits 3-8), the study drug was administered 3 times a day (6-8 AM, 11 AM-1 PM, and 9-11 PM), and prednisolone acetate (Pred Forte; Allergan, Inc, Irvine, Calif) was administered 4 times a day (5-10 minutes before the administration of the study drug and at 1 additional afternoon dosage [4 or 6 PM]). At visit 8, the study medication and prednisolone were discontinued. Each subject was examined again (visit 9) after a 1-week medicine-free period.

At each visit, subjects underwent the following: Goldmann applanation tonometry between 7 and 10 AM, slitlamp biomicroscopy, and the determination of Early Treatment Diabetic Retinopathy Study visual acuity. At visits 1 and 9, automated double-threshold perimetry (Humphrey Field Analyzer; Humphrey Instruments, San Leandro, Calif) and dilated ophthalmoscopy also were performed.

### STATISTICAL ANALYSIS

The maximum change in IOP during the 6 weeks of using prednisolone and study drug was the primary efficacy variable. The significance level for all statistical tests was set at .05 and was 2-tailed. Differences among the treatments were evaluated with an analysis of variance as an intent-to-treat analysis.

Secondary efficacy end points that were evaluated by repeated analysis of variance measures included the overall mean change in IOP during the 6 weeks of treatment and the mean change in IOP at each visit. Also, subjects were categorized as corticosteroid responders based on the definition of a clinically significant change (≥10 mm Hg from baseline at visit 1). The responder rates and differences in the termination rate from the study were evaluated by a χ² test.

Safety was evaluated by the occurrence of adverse experiences and by changes from baseline in visual acuity, biomicroscopy, ophthalmoscopy, and visual fields. Differences in the reason for study exit also were evaluated by a χ² test. Comfort ratings and the incidence, severity, and duration of symptoms were evaluated by a χ² test. Subject characteristics were evaluated by either an analysis of variance or a χ² test.

### RESULTS

One hundred thirty-six subjects were randomly assigned to 1 of the 3 treatment groups. Table 1 shows the disposition of these subjects summarized by treatment group. One hundred nine (80.1%) of the enrolled subjects completed the study.

Table 2 summarizes the demographic characteristics by treatment group for the 136 subjects who enrolled into the study. There were no statistically signifi-
cant differences among the 3 treatment groups for age, sex, race, or iris color.

INTRAOCULAR PRESSURE

The ISV-205 study medicine limited the increase in IOP induced by prednisolone, as evidenced by the follow-
ing. First, a significantly smaller mean maximum
increase in IOP occurred during the 6 weeks of dosing
among the 3 treatment groups, with the 0.06% ISV-205
group having the least elevation in pressure (mean±SD:
4.9±4.6, 5.9±4.9, and 7.3±6.5 mm Hg in the 0.06%
ISV-205, 0.1% ISV-205, and vehicle groups, respec-
tively; \( P = .05 \)). In addition, a significantly lower pres-
sure existed in the 0.06% ISV-205 group, specifically
compared with vehicle (\( P = .02 \)) (Figure 1). Second, a
smaller mean increase in IOP was noted between the
vehicle and the 0.06% ISV-205 groups after 3 (visit 5,
\( P = .03 \)) and 5 (visit 7, \( P = .01 \)) weeks of treatment
(Figure 2). Third, the overall mean±SD change in
pressure was significantly lower (\( P = .05 \)) in the 0.06%
ISV-205 group than in the vehicle group during the 6
weeks with 0.06% ISV-205 (2.0±4.2 mm Hg) and 0.1%
ISV-205 (2.4±4.8 mm Hg) treatment compared with
vehicle (3.6±6.6 mm Hg). Fourth, 8 (17%) of the 46
subjects in the vehicle group were terminated from the
study because of high IOPs compared with 1 (2%) of
the 45 subjects in the 0.06% ISV-205 group and 3 (7%)
of the 45 subjects in the 0.1% ISV-205 group (\( P = .03 \)).
Finally, significantly (\( P = .01 \)) more subjects were corti-
costeroid responders (\( \geq 10 \) mm Hg increase) in the
vehicle group (12 [28%] of 43 subjects) than in the
0.06% ISV-205 group (3 [7%] of 42 subjects). Furthermore,
a significant difference was observed between vehicle and 0.06% ISV-205 when subjects were grouped by
different levels of pressure elevation (\( P = .03 \))
(Table 3).

SAFETY

No significant differences were observed in the inci-
dence of any individual adverse event or clinical mea-
sure among groups. A trend to increased stinging/ 
burning was noted, however, by unsolicited reports
(Table 4) and subject ratings of comfort (\( P = .09 \)). The
stinging/burning was most frequently rated as mild in se-
verity and lasted less than 1 minute.

The number of subjects terminating the study be-
cause of adverse effects was similar among the 3 treat-
ment groups: 1 subject (2%) taking vehicle, 1 (2%) tak-
ing 0.06% ISV-205, and 0 taking 0.1% ISV-205. Two serious
adverse events were reported during the study. One sub-
ject using vehicle had a myocardial infarction, and one
using 0.1% ISV-205 had serious injuries resulting from a

Table 2. Demographic Characteristics for Each Treatment Group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Groups (n = 136)</th>
<th>Vehicle Group (n = 46)</th>
<th>0.06% ISV-205 Group (n = 45)</th>
<th>0.1% ISV-205 Group (n = 45)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.2 ± 12.2</td>
<td>42.7 ± 13.1</td>
<td>44.7 ± 12.1</td>
<td>48.3 ± 10.6</td>
<td>.08</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99 (73)</td>
<td>30 (65)</td>
<td>35 (78)</td>
<td>34 (76)</td>
<td>.36</td>
</tr>
<tr>
<td>Male</td>
<td>37 (27)</td>
<td>16 (35)</td>
<td>10 (22)</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92 (68)</td>
<td>33 (72)</td>
<td>29 (64)</td>
<td>30 (67)</td>
<td>.75</td>
</tr>
<tr>
<td>Black</td>
<td>25 (18)</td>
<td>6 (13)</td>
<td>9 (20)</td>
<td>10 (22)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>18 (13)</td>
<td>7 (15)</td>
<td>6 (13)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Iris color</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>70 (51)</td>
<td>23 (50)</td>
<td>25 (56)</td>
<td>22 (49)</td>
<td>.79</td>
</tr>
<tr>
<td>Blue</td>
<td>26 (19)</td>
<td>7 (15)</td>
<td>8 (18)</td>
<td>11 (24)</td>
<td></td>
</tr>
<tr>
<td>Hazeln</td>
<td>40 (29)</td>
<td>16 (35)</td>
<td>12 (27)</td>
<td>12 (27)</td>
<td></td>
</tr>
<tr>
<td>Relation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>113 (83)</td>
<td>41 (89)</td>
<td>39 (87)</td>
<td>33 (73)</td>
<td>.27</td>
</tr>
<tr>
<td>Parent and sibling</td>
<td>11 (8)</td>
<td>2 (4)</td>
<td>4 (9)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>12 (9)</td>
<td>3 (7)</td>
<td>2 (4)</td>
<td>7 (16)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of subjects in each group unless otherwise indicated. Percentages may not total 100 because of rounding. The abbreviation is explained in the first footnote to Table 1.
†An analysis of variance was used for age; and a likelihood ratio \( \chi^2 \) test was used for sex, race (white vs other), iris color (brown vs other), and relation.
The mechanism by which corticosteroids increase IOP is a topic of investigation. In studies using a human trabecular meshwork cell culture system, researchers\(^8-10\) reported that 1 to 3 weeks of treatment with the corticosteroid dexamethasone caused a progressive induction of the trabecular meshwork–inducible glucocorticoid response (TIGR) protein/myocilin (MYOC) protein in human trabecular meshwork cells. The time course of the protein induction and the dose-response curve paralleled those of IOP elevation caused by corticosteroids in humans.\(^3,4,9,10\) These studies led to the cloning of the MYOC gene from the commercial preparation, to block the corticosteroid-induced IOP elevation of inflammation following cataract extraction and for discomfort following corneal refractive surgery.

In this study, we evaluated if 0.1% and 0.06% ISV-205 could block the corticosteroid-induced IOP elevation in first-degree relatives of subjects with primary open-angle glaucoma. Such individuals have had a 70% chance of showing an exaggerated IOP elevation when given corticosteroids for 6 weeks.\(^12,13\) The 1% prednisolone formulation was chosen to induce the IOP increase in this study because it is one of the strongest ocular corticosteroids commercially available.\(^14\)

This study showed that ISV-205 limited the IOP elevation associated with prednisolone treatment, as demonstrated by the following. First, there was a significantly lower maximum increase in pressure in the 0.06% ISV-205 group compared with the vehicle group. Second, there were consistently smaller increases at individual visits compared with the vehicle group. These 2 differences were significant for the 0.06% ISV-205 group at visits 5 and 7. Third, the overall mean change in pressure was significantly lower in the 0.06% ISV-205 group, and a trend existed in the 0.1% ISV-205 group, compared with vehicle. Fourth, fewer subjects left the study because of a high IOP in the ISV-205 groups compared with the vehicle group. Last, there were fewer subjects in the 0.06% ISV-205 group who were corticosteroid responders (≥10-mm Hg increase in pressure) than in the vehicle group.

The reason why the IOP elevation was blunted is not known exactly, but it presumably was due to diclofenac in the ISV-205 formulation blocking the induction of the TIGR/MYOC protein generated from the trabecular meshwork cells. By preventing this induction and subsequent deposition in the meshwork, diclofenac may work to maintain outflow facility. However, any prevention of reduced outflow from diclofenac has not been shown directly in human studies or in vitro. In addition, the exact mechanism of diclofenac in these subjects remains unknown.

In this study, the 0.06% concentration was apparently more effective than the 0.1% concentration in pre-

### Table 4. Adverse Events\(^*\)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vehicle Group (n = 46)</th>
<th>0.06% ISV-205 Group (n = 45)</th>
<th>0.1% ISV-205 Group (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular discomfort</td>
<td>8 (17)</td>
<td>16 (36)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>6 (13)</td>
<td>6 (13)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (4)</td>
<td>7 (16)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (9)</td>
<td>4 (9)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>3 (7)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Vision abnormality</td>
<td>2 (4)</td>
<td>0</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Unintentional injury</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

\(^*\)Data are given as number (percentage) of subjects in each group with at least one report of an adverse event by descending frequency. Only events occurring in 2 or more subjects are reported. The abbreviation is explained in the first footnote to Table 1.

**Comment**

The mechanism by which corticosteroids increase IOP is a topic of investigation. In studies using a human trabecular meshwork cell culture system, researchers\(^8-10\) reported that 1 to 3 weeks of treatment with the corticosteroid dexamethasone caused a progressive induction of the trabecular meshwork–inducible glucocorticoid response (TIGR) protein/myocilin (MYOC) protein in human trabecular meshwork cells. The time course of the protein induction and the dose-response curve paralleled those of IOP elevation caused by corticosteroids in humans.\(^3,4,9,10\) These studies led to the cloning of the major corticosteroid-induced species, which has become known as the TIGR/MYOC gene for adult and juvenile open-angle glaucoma.\(^11\)

Researchers\(^8-10\) later determined that the diclofenac dose dependently inhibited the induction of TIGR/MYOC protein in human trabecular meshwork cells treated with dexamethasone for 1 to 3 weeks. Subsequently, ISV-205 was developed. This preparation was designed to prolong the corneal contact of diclofenac to provide sufficient aqueous levels, which may not be available from the commercial preparation, to block TIGR/MYOC gene induction. Commercial diclofenac sodium (Voltaren; Novartis, Atlanta, Ga) is indicated for the treatment of inflammation following cataract extraction and for discomfort following corneal refractive surgery.

In this study, we evaluated if 0.1% and 0.06% ISV-205 could block the corticosteroid-induced IOP elevation in first-degree relatives of subjects with primary open-angle glaucoma. Such individuals have had a 70% chance of showing an exaggerated IOP elevation when given corticosteroids for 6 weeks.\(^12,13\) The 1% prednisolone formulation was chosen to induce the IOP increase in this study because it is one of the strongest ocular corticosteroids commercially available.\(^14\)

This study showed that ISV-205 limited the IOP elevation associated with prednisolone treatment, as demonstrated by the following. First, there was a significantly lower maximum increase in pressure in the 0.06% ISV-205 group compared with the vehicle group. Second, there were consistently smaller increases at individual visits compared with the vehicle group. These 2 differences were significant for the 0.06% ISV-205 group at visits 5 and 7. Third, the overall mean change in pressure was significantly lower in the 0.06% ISV-205 group, and a trend existed in the 0.1% ISV-205 group, compared with vehicle. Fourth, fewer subjects left the study because of a high IOP in the ISV-205 groups compared with the vehicle group. Last, there were fewer subjects in the 0.06% ISV-205 group who were corticosteroid responders (≥10-mm Hg increase in pressure) than in the vehicle group.

The reason why the IOP elevation was blunted is not known exactly, but it presumably was due to diclofenac in the ISV-205 formulation blocking the induction of the TIGR/MYOC protein generated from the trabecular meshwork cells. By preventing this induction and subsequent deposition in the meshwork, diclofenac may work to maintain outflow facility. However, any prevention of reduced outflow from diclofenac has not been shown directly in human studies or in vitro. In addition, the exact mechanism of diclofenac in these subjects remains unknown.

In this study, the 0.06% concentration was apparently more effective than the 0.1% concentration in pre-
venting the IOP elevation. The reason for this finding was not determined exactly, and should be explained by future studies. Perhaps there was an inconsistent response to the corticosteroid or a variable compliance among subjects that could explain this unexpected finding.

The ISV-205 was safe and tolerable in this study. However, there was a trend with both formulations for mild burning/stinging of a short duration following instillation of the medicine compared with the vehicle.

The results of this study are important for several reasons. First, they may point to a new treatment for subjects who are receiving corticosteroids for uveitis, inflammation, or postsurgical complications to help prevent a concomitant IOP elevation. Such a concomitant treatment would have the advantage of preventing an elevated pressure and possible glaucomatous damage. Second, and perhaps most important, because the TIGR protein is more frequent in subjects with glaucoma, ISV-205 might lead to treatments that help prevent or treat this disease as well.1

This study suggests that ISV-205 limits a corticosteroid-induced IOP increase in first-degree relatives of subjects with glaucoma.

This study did not evaluate the effect of ISV-205 long term in treating the subjects who have used topical corticosteroids long term. In addition, this study did not evaluate the effect of ISV-205 in subjects with primary open-angle glaucoma or in preventing pressure elevations in subjects predisposed to high IOPs. Future research hopefully will clarify the use, if any, of ISV-205 in clinical medicine.

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REFERENCES