Phase 1 Clinical Trials of a Selective Rho Kinase Inhibitor, K-115

Hidenobu Tanihara, MD; Toshihiro Inoue, MD; Tetsuya Yamamoto, MD; Yasuaki Kuwayama, MD; Haruki Abe, MD; Makoto Araie, MD; for the K-115 Clinical Study Group

IMPORTANCE We conducted a series of phase 1 clinical trials to elucidate the efficacy and safety of the selective Rho kinase inhibitor K-115 as a candidate drug for the treatment of glaucoma. We report the intraocular pressure (IOP)-lowering effects and safety of K-115 based on our results.

OBJECTIVE To study the IOP-lowering effects and safety of topical administration of a selective Rho kinase inhibitor, K-115, in healthy male adult volunteers.

DESIGN AND SETTING Randomized, placebo-controlled, double-masked, group comparison phase 1 clinical trial.

PARTICIPANTS In the initial single-instillation trial, 50 healthy volunteers were subdivided into groups and treated with placebo or K-115 in concentrations of 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% in a stepwise manner. In the repeated-instillation trial, another 50 healthy volunteers were subdivided into groups and treated with placebo or K-115 in concentrations of 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% twice daily for 7 days in a stepwise manner.

MAIN OUTCOMES AND MEASURES In these clinical trials, the administration of eyedrops and associated examinations (including IOP measurements) were performed in a double-masked manner.

RESULTS After single instillation of placebo or K-115 in concentrations of 0.05%, 0.1%, 0.2%, 0.4%, and 0.8%, the changes in IOP from baseline were −1.6 mm Hg for placebo and −3.4, −2.2, −2.6, −4.0, and −4.3 mm Hg, respectively, for the different concentrations 2 hours after instillation. Similar to the single-instillation trial, IOP reductions in the repeated-instillation trial were found after each instillation, with maximal reduction 1 to 2 hours after instillation. In the safety trial, slight to mild conjunctival hyperemia was found in more than half of the participants treated with K-115; it was found after each instillation and spontaneously resolved within 1½ hours.

CONCLUSIONS AND RELEVANCE K-115 is a promising drug for lowering IOP in healthy adult eyes, with tolerable adverse events during at least short-term administration.
Glaucoma has been regarded as the leading cause of blindness in the world. Because several large-scale clinical studies have demonstrated a correlation between intraocular pressure (IOP) reduction and the onset and progression of glaucoma, IOP reduction has been considered a useful therapeutic intervention for the management of patients with glaucoma, even in patients with normal-tension glaucoma. For the treatment of glaucoma, several drugs to reduce IOP have been developed and used in clinical practice, such as prostaglandin analogues and adrenergic β-receptor antagonists. Prostaglandin analogues and some other agents lower IOP by improving uveoscleral outflow of aqueous humor. In contrast, β-blockers and carbonic anhydrase inhibitors cause IOP reduction by inhibition of aqueous humor production. In addition, miotic agents (including pilocarpine) have been shown to lower IOP by contraction of ciliary muscle and subsequent improvement in outflow. To date, no IOP-lowering drugs directly modulating conventional outflow route have been available clinically to treat glaucoma.

Recently, some investigators have reported a significant association between outflow facilities of aqueous humor and cytoskeletons in cell components of the conventional outflow route, suggesting therapeutic potential of some drugs related to cytoskeletal rearrangement. Therefore, cytoskeletal drugs have been regarded as candidates for novel IOP-lowering agents. In previous studies, it has been suggested that a selective Rho kinase inhibitor, Y-27632, could rearrange actin cytoskeletons and change cellular behavior in human trabecular meshwork cells, as well as cause significant IOP reduction in animal experiments. Additional investigations have demonstrated that Rho kinase inhibitors could induce changes in cell-cell junction-associated proteins and actin cytoskeleton in Schlemm canal endothelial cells and permeability in cell monolayers. Also, physiological investigations on protein kinase inhibitors (including Rho kinase inhibitors) revealed improvement in total outflow facility, suggesting modulation of conventional outflow and resultant IOP reduction. Indeed, some clinical trials have demonstrated a significant IOP reduction in human eyes treated with Rho kinase inhibitor eyedrops.

K-115 is a novel Rho kinase inhibitor with IOP-lowering effects in rabbits and monkeys. Preclinical studies demonstrated that K-115 can facilitate outflow, suggesting improvement in conventional outflow by this Rho kinase inhibitor as well as other Rho kinase inhibitors (K. Mizuno, PhD, written communication, June 2008). Based on these findings, we conducted a series of phase 1 clinical trials to elucidate the efficacy and safety of this Rho kinase inhibitor as a candidate drug for the treatment of glaucoma. Herein, we report the IOP-lowering effects and safety of K-115 based on our results of phase 1 clinical trials.

Methods

We conducted these phase 1 clinical trials as randomized, placebo-controlled, double-masked, group comparison studies in accord with the ethical principles of the Declaration of Helsinki. Candidate participants for the clinical trial were provided with full information regarding the protocol, and written informed consent was obtained before study enrollment.

Included in these studies were healthy Japanese male volunteers aged 20 to 35 years. Individuals with ocular disease (including glaucoma) or those having past ocular surgery were excluded from the studies. Persons were considered eligible to participate if they had no abnormalities on general and ocular examinations, their results on a screening laboratory test were normal, and their IOP levels were 13 mm Hg or higher in at least 1 eye at the screening examinations. Individuals with a corrected visual acuity of less than 20/20 were excluded from the study. In addition, we excluded persons with a history of liver, kidney, heart, or endocrine system diseases or drug hypersensitivity. Body mass index was required to be within 80% to 120% of the standard body mass index (calculated as weight in kilograms divided by height in meters squared) of 22.0. During trials, participants must have discontinued all medical treatments and could not wear contact lenses.

The single-instillation trial of K-115 or placebo ophthalmic solution (vehicle of K-115) was conducted in a stepwise manner. The study was begun at step 1 (K-115 [0.05%] or placebo). After the safety of the ophthalmic solution was confirmed by a physician and by general and ophthalmologic examinations and laboratory tests, step 2 (K-115 [0.1%] or placebo) was started, followed in turn by step 3 (K-115 [0.2%] or placebo), step 4 (K-115 [0.4%] or placebo), and step 5 (K-115 [0.8%] or placebo). Ten participants for each step were randomly assigned to K-115 or placebo. The allocation ratio of K-115 to placebo was 4:1 (8 in the K-115 group and 2 in the placebo group). K-115 or placebo was topically administered in both eyes at 9 AM. The IOP was measured before instillation and at 0.5 (9:30 AM), 1 (10 AM), 2 (11 AM), 4 (1 PM), 6 (3 PM), 9 (6 PM), 12 (9 PM), 15 (12 PM), 23 (8 AM the next day), and 47 (8 AM 2 days later) hours after instillation. The IOP was measured using noncontact tonometry (CT-90A; Topcon Corporation).

To investigate the safety of prolonged repeated administration of K-115, a 7-day repeated-instillation trial was conducted. Different candidates fulfilling the same eligibility criteria as those for the single-instillation trial were screened. The repeated-instillation trial was conducted in stepwise fashion from step 1 (K-115 [0.05%] or placebo twice daily), step 2 (K-115 [0.1%] or placebo twice daily), step 3 (K-115 [0.2%] or placebo twice daily), step 4 (K-115 [0.4%] or placebo twice daily), and step 5 (K-115 [0.8%] or placebo twice daily). Ten participants for each step (8 in the K-115 group and 2 in the placebo group) were included. Twice-daily instillation was performed in both eyes of the participants at 9 AM and 9 PM during days 1 to 6 and at 9 AM on day 7. The IOP was measured before the first instillation and at 1 (10 AM), 2 (11 AM), 4 (1 PM), 6 (3 PM), and 11 (8 PM) hours after the morning instillation (9 AM) on days 1 to 7; at 2 hours (11 PM) after the evening instillation (9 PM) on days 1 to 6; and was remeasured at 14 (11 PM), 23 (8 AM on day 8), and 47 (8 AM on day 9) hours after the last instillation.
To evaluate the safety of K-115, ophthalmologic findings, physiological assessments, and laboratory test results (including hematology, blood chemistry, and urinalysis) were examined during the trials. The eyelid, cornea, anterior chamber and lens, and conjunctiva (palpebral and bulbar) were examined with slitlamp microscopy during the trial. The ocular findings at these sites were scored according to the following criteria: 0 indicates no significant changes; 0.5, slight changes; 1, mild changes; 2, moderate changes; and 3, severe changes. Pupil diameter was measured at constant illumination using a Haab pupillometer at 8 AM, 10 AM, and 8 PM. General physiological factors (including pulse, blood pressure, body temperature, and electrocardiography) were also monitored at 7 AM. Ocular examinations (including slitlamp microscopy and examination of the corneal and conjunctival surfaces with fluorescein) were conducted at 8 AM and 8 PM. Laboratory tests were performed at 9 AM during the trial. If participants experienced abnormal symptoms, the findings were recorded on the patient data sheets.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 10)</th>
<th>K-115 Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05% (n = 8)</td>
<td>0.1% (n = 8)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Conjunctival follicle</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin conjugated increased</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protein urine present</td>
<td>0</td>
<td>1</td>
</tr>
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</table>
In our studies, the ophthalmic solution was administered and subsequent examinations (including IOP measurements) performed in a placebo-controlled, double-masked fashion. The IOP and change in IOP from baseline are given in millimeters of mercury. Unless otherwise indicated, numerical data are expressed as means (SDs). The analysis of covariance model (including terms for baseline and group) was applied to the change from baseline data, and Dunnett tests were conducted to compare adjusted means of the K-115 and placebo groups. In all analyses, 2-sided tests for statistical significance at \( \alpha = .05 \) were used. All analyses were performed by Kowa Company Ltd, Nagoya, Japan, using statistical software (SAS 9.1.3; SAS Inc).

Figure 2. Levels of Intraocular Pressure (IOP) During Repeated Instillation of K-115

A, Levels of IOP. Day 1 indicates IOP levels after the first instillation, and day 7 indicates IOP levels after the last instillation. Pre indicates baseline levels. The second instillation on day 1 was administered at 12 hours after the first instillation. Values are means (SDs). B, Reduction in IOP. Values are means (SDs). C, Reduction in IOP after the last instillation. Values are estimates (95% CIs).
Results

IOP-Lowering Effects and Safety in the Single-Instillation Trial of K-115
In the single-instillation trial, 3 eyes with baseline IOP levels at 10 or lower were excluded from subsequent analyses. In the remaining 47 eyes, the mean IOP at baseline was 15.1 (2.3) for the placebo group (n = 9), and the mean IOPs for the K-115 group were 14.3 (2.5) for 0.05% (n = 8), 13.1 (1.8) for 0.1% (n = 7), 14.5 (2.5) for 0.2% (n = 8), 13.9 (1.5) for 0.4% (n = 7), and 13.1 (1.4) for 0.8% (n = 8). No significant differences were observed among the concentrations. The IOP levels in the eyes treated with K-115 are shown in Table 1. The changes in IOP from baseline were −1.6, −3.4, −2.2, −2.6, −4.0, and −4.3 for placebo and 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively, at 2 hours after instillation. Maximal and significant IOP reduction from baseline was found at 2 hours after instillation in the K-115 group at higher concentrations (0.4% and 0.8%). The differences in IOP reduction between the K-115 and placebo groups were −1.8, −0.6, −0.9, −2.4, and −2.7 in the 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively. Statistical analysis showed significant differences in IOP reduction from baseline between the K-115 and placebo groups for the 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively. Statistical analyses showed significant differences in IOP levels between baseline and 2 hours after instillation (P < .05) but no significant differences between the K-115 and placebo groups.

Conjunctival hyperemia was observed in 0 of 10 participants in the placebo group and in 1, 1, 7, 7, and 8 of 8 participants after instillation of K-115 in the 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively (Table 2). Conjunctival hyperemia was found after each instillation. Most findings of conjunctival hyperemia appeared at 30 minutes after instillation and were transient symptoms that disappeared within 1½ hours. The incidence rate and severity and duration of conjunctival hyperemia were unchanged in the repeated-instillation trial compared with the single-instillation trial (Table 3). No other significant adverse events were found by ophthalmologic tests, including slitlamp microscopy. In addition, physiological examination results and laboratory test findings showed no significant differences between participants administered K-115 or placebo.

Efficacy and Safety in the Repeated-Instillation Trial of K-115
In the repeated-instillation trial, twice-daily administration of K-115 decreased IOP levels after instillation, with maximal reduction at 1 to 2 hours after instillation (Figure 2). The mean IOP at baseline ranged from 14.1 to 16.1 for the K-115 and placebo groups, with no significant differences between the groups. The changes in IOP from baseline at 2 hours after the first and last instillations were −2.9 and −2.6, −2.7 and −3.1, −2.5 and −3.2, −2.5 and −3.3, −3.8 and −2.7, and −4.0 and −4.1 for placebo and the 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively. Statistical analyses showed significant differences in IOP levels between baseline and 2 hours after instillation (P < .05) but no significant differences between the K-115 and placebo groups.

In the estimation of safety for the K-115 and placebo groups, all 50 eyes were analyzed. Conjunctival hyperemia was found by slitlamp microscopy in 0 of 10 participants in the placebo group and in 5, 4, 5, 2, and 7 of 8 participants in the K-115 group for the 0.05%, 0.1%, 0.2%, 0.4%, and 0.8% concentrations, respectively (Table 1). Findings of conjunctival hyperemia appeared at 30 minutes to 1 hour after instillation and remained for 30 minutes to 5½ hours after onset. In 3 participants at the 0.05% concentration and in 2 participants at the 0.4% concentration, a conjunctival follicle was found in the palpebral conjunctiva. All conjunctival hyperemia and conjunctival follicles were slight to mild and spontaneously resolved. No other significant adverse events were found by ophthalmologic tests, including slitlamp microscopy. In addition, physiological examination results and laboratory test findings showed no significant differences between participants administered K-115 or placebo.

Table 2. Adverse Events in the Repeated-Instillation Trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 10)</th>
<th>0.05% (n = 8)</th>
<th>0.1% (n = 8)</th>
<th>0.2% (n = 8)</th>
<th>0.4% (n = 8)</th>
<th>0.8% (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
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<td>1</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Eye discharge</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Laryngopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Blood amylase increased</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hematocrit decreased</td>
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<td>1</td>
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<tr>
<td>Hemoglobin decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Red blood cell count decreased</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>White blood cell count increased</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

Rho kinase inhibitors have been shown to induce basic cellular changes such as cytoskeleton rearrangement and cell adhesion, cell contraction, cell motility, and cell-cell contact in the trabecular meshwork and Schlemm canal, resulting in the modulation of conventional outflow of aqueous humor.12-14,21,22 These findings seem to be in agreement with the outflow facilitation effects in conventional outflow shown by physiologically

Table 3. Conjunctival Hyperemia Scores After the First and Last Instillations in the Repeated-Instillation Triala

<table>
<thead>
<tr>
<th>Time After Instillation, h</th>
<th>Placebo (n = 10)</th>
<th>K-115 (0.05%) (n = 8)</th>
<th>K-115 (0.1%) (n = 8)</th>
<th>K-115 (0.2%) (n = 8)</th>
<th>K-115 (0.4%) (n = 8)</th>
<th>K-115 (0.8%) (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Palpebral Conjunctiva</td>
<td>Bulbar Conjunctiva</td>
<td>Palpebral Conjunctiva</td>
<td>Bulbar Conjunctiva</td>
<td>Palpebral Conjunctiva</td>
<td>Bulbar Conjunctiva</td>
</tr>
<tr>
<td></td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
<td>0 0.5 1 2 3 0 0.5 1 2 3</td>
</tr>
<tr>
<td>Pre</td>
<td>10 0 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
</tr>
<tr>
<td>0.5</td>
<td>10 0 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
</tr>
<tr>
<td>2</td>
<td>10 0 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
</tr>
<tr>
<td>4</td>
<td>10 0 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
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</tr>
<tr>
<td>8</td>
<td>10 0 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
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<tr>
<td>9</td>
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<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
<td>10 0 0 0 0</td>
</tr>
</tbody>
</table>

Abbreviation: Pre, baseline level.

a Conjunctival hyperemia was scored according to the following criteria: 0 indicates no significant changes; 0.5, slight changes; 1, mild changes; 2, moderate changes; and 3, severe changes. The data showed worse scores for instillation in both eyes.
In addition, because IOP-lowering mechanisms related to direct modulation of conventional outflow by Rho kinase inhibitors differ from those of other antiglaucoma medications with inhibitory effects on aqueous humor production and increasing effects on uveoscleral outflow, the combination of a Rho kinase inhibitor with other IOP-lowering drugs may have additive effects on IOP reduction.

In the safety trial, ocular hypemia in the bulbar and palpebral conjunctiva was frequently observed, especially at higher concentrations of K-115 (0.2%, 0.4%, and 0.8%). Most conjunctival hypemia findings appeared at 30 minutes after each instillation and spontaneously resolved within 1½ hours. In addition to its transient nature, the severity of ocular conjunctival hypemia was slight to mild in all cases. In the single-instillation trial, no dose-response relationship was observed between concentrations of K-115 and the incidence rate of conjunctival hypemia. On the other hand, conjunctival hypemia in the repeated-instillation trial was marked at higher concentrations of K-115 (0.2%, 0.4%, and 0.8%). This suggests that conjunctival hypemia occurred in a dose-dependent manner. Overall, conjunctival hypemia was a tolerable adverse event at all doses of K-115 in the present study; the severity and duration of conjunctival hypemia were not increased with repeated instillation.

Because the IOP-lowering effects of K-115 were found as long as 15 hours after instillation, there is a dissociation between the time course of transient conjunctival hypemia and long-lasting IOP-lowering effects of K-115. Because this dissociation was reported in clinical trials using other Rho kinase inhibitors,17,18 we hypothesize that the occurrence of conjunctival hypemia is a common characteristic of Rho kinase inhibitors. Laboratory studies25,26 have shown that Rho kinase inhibitors cause blood vessel relaxation and modulation in vascular endothelial cells, which is in agreement with our hypothesis. Also, we should judge the clinical relevance of blood vessel dilation (in addition to conjunctival hypemia) by Rho kinase inhibitors in the eye in a comprehensive manner because the results of some investigations have suggested potential neuroprotective effects of increased blood flow on glaucomatous optic neuropathy.27,28 The Rho kinase inhibitors K-115, Y-27632, and Y-39983 have been shown to increase circulation in retinal and ciliary vessels29,30 and to have potential neuroprotective or neuroregenerative properties in animal models.31,33,34 suggesting potential as a neuroprotective drug in addition to its use as an IOP-lowering agent for the treatment of glaucoma.

In conclusion, K-115 is a promising drug candidate for lowering IOP in healthy adult eyes, with tolerable adverse events during at least 7 days after instillation. Further clinical trials will be needed to determine its therapeutic value in the treatment of glaucoma.

ARTICLE INFORMATION
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Author Contributions: Study concept and design: Tanihara, Kuwayama, and Abe. Acquisition of data: Inoue and Yamamoto. Analysis and interpretation of data: All authors. Drafting of the manuscript: Tanihara. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Tanihara and Araie. Obtained funding: Tanihara and Inoue. Administrative, technical, and material support: Inoue. Study supervision: Yamamoto, Kuwayama, Abe, and Araie.

Conflict of Interest Disclosures: Dr Tanihara has served as a consultant for Kowa, Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, Pfizer Japan, and MSD. Dr Yamamoto has served as a board member of Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, and Pfizer Japan and has served as a consultant to Kowa Company Ltd, MSD, and Otsuka Pharmaceutical. Dr Kuwayama has served as a board member of Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, and Pfizer Japan and has served as a consultant to Kowa Company Ltd, MSD, Wallamoto Pharmaceutical, and Bausch & Lomb Japan. Dr Abe has served as a board member of Alcon Japan and Pfizer Japan and has served as a consultant to Kowa Company Ltd. Dr Araie has served as a board member of Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, and Pfizer Japan; has served as a consultant to Kowa Company Ltd, MSD, Topcon Corporation, and Allergan Japan; has received payment for lectures (including service on speakers bureaus) for Carl Zeiss Japan; and is the owner of a patent for Topcon Corporation.
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Role of the Sponsor: The sponsor participated in the design of the study and the conduct of the study, as well as the data collection, data management, and data analysis of the study.
K-115 Clinical Study Group Members: Junichi Azuma, MD, and Makoto Ando, MD, Neishinichi Medical Group Incorporated, Osaka Pharmacology Clinical Research Hospital, Osaka, Japan.
Additional Contributions: We thank the physicians who cooperated in this clinical trial.
Correction: This article was corrected on May 12, 2014, for an error in the key for Figure 1.
TrialsofaSelectiveRhoKinaseInhibitor,K-115
increasesoutflowfacility.

GeigerBH-7disruptstheactincytoskeletonand

function.

Acto-myosindrugeffectsandaqueousoutflow
11
10

3
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normaleye. *ArchOphthalmol.*


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contractionandmotilityinculturedhumancorneal
mesenchymalcells.* ExpEyeRes.*

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