Intraocular Pressure–Lowering Effects and Safety of Topical Administration of a Selective ROCK Inhibitor, SNJ-1656, in Healthy Volunteers

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Objective: To investigate the effects and safety of topical administration of an ophthalmic solution of a selective Rho-associated coiled coil-forming protein kinase (ROCK) inhibitor, SNJ-1656, 0.003% to 0.1%, in healthy male adult volunteers.

Design: Randomized, double-masked, group-comparison, phase 1 clinical study. In the initial single-instillation trial, 45 healthy volunteers were randomly subdivided into 5 groups and treated with SNJ-1656 in concentrations of 0.003%, 0.01%, 0.03%, 0.05%, and 0.1% in stepwise fashion. In the repeated-instillation trial, 36 healthy volunteers were assigned to receive SNJ-1656 ophthalmic solution at the following concentrations and dosages: 0.05% once daily, 0.1% once daily, 0.05% twice daily, or 0.1% twice daily. In our studies, the administration of the solution and subsequent examinations (including intraocular pressure [IOP] measurements) were performed in a double-masked fashion.

Results: After single instillation of placebo or SNJ-1656, in concentrations of 0.003%, 0.01%, 0.03%, 0.05%, and 0.1%, the changes in IOP from the baseline were −0.91, −1.18, −1.48, − 2.20 (P=.04 vs placebo), −1.48, and −1.98 mm Hg, respectively, at 2 hours, and −0.63,−0.95, −1.79, −2.26 (P=.01 vs placebo), −1.95, and −3.00 mm Hg ($P<$ .001 vs placebo) respectively, at 4 hours. Significant IOP reductions after repeated instillation were also found. On slitlamp examination during the trial, there were no significant adverse findings except hyperemia of the bulbar and palpebral conjunctiva after instillation.

Conclusion: This clinical study demonstrated that SNJ-1656 is a safe topical agent effective in reducing IOP in human eyes.

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NUMEROUS DRUGS TO lower intraocular pressure (IOP) have been developed and used to treat glaucoma. Among them, prostaglandin analogues and adrenergic α_1-receptor antagonists have been shown to lower IOP by increasing uveoscleral (unconventional) outflow of aqueous humor,[1,2] whereas adrenergic β-receptor blockers, α_2-receptor agonists, and carbonic anhydrase inhibitors have been shown to reduce IOP by inhibiting aqueous humor production.[3-5] Pilocarpine and other miotic agents are believed to reduce IOP by increasing transcanalicular (conventional) aqueous outflow caused by contraction of the ciliary muscle (CM).[6] However, no IOP-lowering drugs directly modulating conventional outflow have been used clinically to treat glaucoma.

Rho guanosine triphosphatase, a member of the Rho subgroup of the Ras superfamily, participates in signaling pathways that lead to formation of actin stress fibers and focal adhesions.[7] Rho is also involved in diverse physiological functions associated with cytoskeletal rearrangement related to cell shape, cell motility, cytokinesis, and smooth muscle contraction.[8] Recently, several putative target molecules of Rho have been identified as Rho effectors, including Rho-associated coiled coil-forming protein kinase, termed p160ROCK, and its isoform, ROKa/Rho kinase/ROCK II.[9,10] ROCK has been shown to be expressed in ocular tissues, including the trabecular meshwork (TM) and CM.[11] In our previous study,[11] we demonstrated that instillation of Y-27632, a selective ROCK inhibitor, significantly reduced IOP, the mechanism of which was attributed to improved outflow.[11-13] Inhibition of ROCK activity has been shown to induce alterations in TM cellular responses such as migration, adhesion, and

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changes in cell shape.[11] Another selective ROCK inhibitor, Y-39983, 4-[(1*R*)-1-aminoethyl]-*N*-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl) benzamide monohydrochloride, is 30-fold more potent in inhibiting ROCK activity and has similar IOP-lowering effects at lower concentrations than Y-27632.[14]

The purpose of this clinical trial was to investigate the IOP-lowering effects and safety of SNJ-1656, an ophthalmic solution of Y-39983, in a single-instillation trial and a prolonged repeated-instillation trial. We report herein the first results, to our knowledge, of a clinical trial of an ophthalmic solution consisting of a selective ROCK inhibitor in human eyes.

METHODS

We conducted this clinical trial as a randomized, double-masked, group-comparison, phase 1 clinical study in accordance with the ethical principles of the Declaration of Helsinki. Included in this study were healthy Japanese male volunteers, aged 20 to 35 years. Subjects with any history of ocular disease (including glaucoma), ocular surgery, or severe ocular trauma considered inappropriate for participation were excluded from the study. In addition, we excluded subjects with a history of liver, kidney, heart, digestive organ, or respiratory organ disorders; hematological diseases; or drug hypersensitivity. The subjects were considered eligible to participate if they had no abnormalities on ocular examination (including IOP) in either eye on screening by ophthalmologists. Subjects with a corrected visual acuity of less than 20/20, a cup-disc ratio of 0.6 or more in both eyes, or a difference in the cup-disc ratio of 0.2 or more between the eyes were excluded. Body weight was required to be within 80% to 120% of standard body weight value, calculated with the formula:

$$(\text{Height in Centimeters} - 100) \times 0.9 \text{ kg}.$$

During the trial, subjects were prohibited from continuing all medical treatment and from wearing contact lenses. Smoking and ingestion of caffeine, alcohol, and grapefruit were also prohibited during the trial.

First, the single-instillation trial of SNJ-1656 and placebo ophthalmic solution (vehicle of SNJ-1656) was conducted in stepwise fashion from July 6 to September 17, 2005, at Osaka Clinical Pharmacological Institute, Osaka, Japan. The study was begun at step 1 (SNJ-1656, 0.003%, and placebo). After the safety of the ophthalmic solution was confirmed by physician interviews, physical examinations, ophthalmologic monitoring, and laboratory tests, step 2 (SNJ-1656, 0.01%, or placebo) was started, followed in turn by steps 3 (SNJ-1656, 0.03%, or placebo), 4 (SNJ-1656, 0.05%, or placebo), and 5 (SNJ-1656, 0.1%, or placebo). Nine subjects for each step (6 in the test drug group and 3 in the placebo group) were included. SNJ-1656 (or placebo) was topically administered in both eyes at 9 AM. Intraocular pressure was measured with noncontact tonometry before instillation and at 1 (10 AM), 2 (11 AM), 4 (1 PM), 8 (5 PM), 12 (9 PM), and 24 (9 AM the following day) hours after instillation.

To investigate the safety of prolonged repeated administration of SNJ-1656, a 7-day repeated-instillation trial was conducted from January 14 to April 1, 2006, at Osaka Clinical Trial Hospital. The study was conducted in stepwise fashion from steps 1 (SNJ-1656, 0.05%, or placebo once daily), 2-1 (SNJ-1656, 0.1%, or placebo once daily), 2-2 (SNJ-1656, 0.05%, or placebo twice daily), and 3 (SNJ-1656, 0.1%, or placebo twice daily). However, steps 2-1 and 2-2 were concurrently conducted because the daily exposure of drug in the 0.05% twice-daily group is the same as that in the 0.1% once-daily group. Nine subjects for each step (6 in the test drug group and 3 in the placebo group) were included. Once-daily instillation was performed in both eyes at 9 AM on all 7 days. Twice-daily instillation was performed in both eyes of the subjects at 9 AM and 9:30 PM during the first 6 days and 9 AM on the seventh day. The IOPs were measured with noncontact tonometry before instillation and at 1 (10 AM), 2 (11 AM), 4 (1 PM), 8 (5 PM), and 12 (9 PM) hours after instillation in the morning on the third, fourth, fifth, and seventh days of the trial and remeasured on the eighth day at 24 hours (9 AM the following day) after the last instillation.

To evaluate the safety of SNJ-1656, ophthalmologic findings and physiological conditions were examined during the trials. The palpebral and bulbar conjunctiva, cornea, anterior chamber, iris, and lens were examined with slitlamp microscopy at 9 AM, 10 AM, 1 PM, 5 PM, and 9 PM daily during the trial. Also, the ocular findings were scored according to the following criteria: 0 indicates no significant changes; 0.5, slight changes regarded as physiological; 1, mild changes requiring no treatment; 2, moderate changes requiring any treatment; and 4, severe changes requiring hospitalization. Pupil diameter was measured at constant illumination at 9 AM, 10 AM, 11 AM, 5 PM, and 9 PM. General physiological factors, including blood pressure, pulse, and body temperature, were also monitored at 9 AM, 10 AM, 1 PM, 5 PM, and 9 PM. Electrocardiograms were obtained at 9 AM and 11 AM. Ocular examinations included determination of best-corrected visual acuity, retinal fundus examination, full-field flash electroretinography (LE-1000; Tomey, Nagoya, Japan), examination of the corneal and conjunctival surfaces with fluorescein and rose bengal dye, the Schirmer lacrimal test, corneal endothelial cell count with a specular microscope (Noncon Robo Pachy SP-9000; Konan Medical Inc, Tokyo), determination of corneal thickness using pachymetry (Noncon Robo Pachy SP-9000), and hematological and urine examinations, all performed at 9 AM. In the repeated-instillation trial, slitlamp examination, Schirmer lacrimal and rose bengal tests, the measurement of pupil diameter and the monitoring of physiological factors were performed on the first, third, fifth, and seventh days of the trial. An electrocardiogram was obtained on the first, second, fourth, sixth, and seventh days. All examinations were reperformed on the last day of the trial and 1 week after the trial. Slitlamp photography was performed at baseline and whenever abnormal findings were obtained on slitlamp examination results. If volunteers experienced abnormal ocular symptoms, the volunteers indicated them on the patient data sheets. To minimize the adverse effects of SNJ-1656 in the subjects, the study was performed in ascending order from steps 1 to 5 in the single-instillation trial and steps 1, 2-1, 2-2, and 3 in the repeated-instillation trial.

In our studies, the ophthalmological solution was administered and subsequent examinations (including IOP measurements) were performed in a double-masked fashion. Unless otherwise indicated, data are expressed as mean±SD.

RESULTS

IOP-LOWERING EFFECT IN SINGLE-INSTILLATION TRIAL

In the single-instillation trial of SNJ-1656, the mean IOP at baseline was 14.05±2.53 mm Hg for the placebo group and, for the SNJ-1656 groups, 14.08±1.44 mm Hg for 0.003%, 13.73±1.49 mm Hg for 0.01%, 13.73±2.18 mm Hg for 0.03%, 13.19±1.35 mm Hg for 0.05%, and

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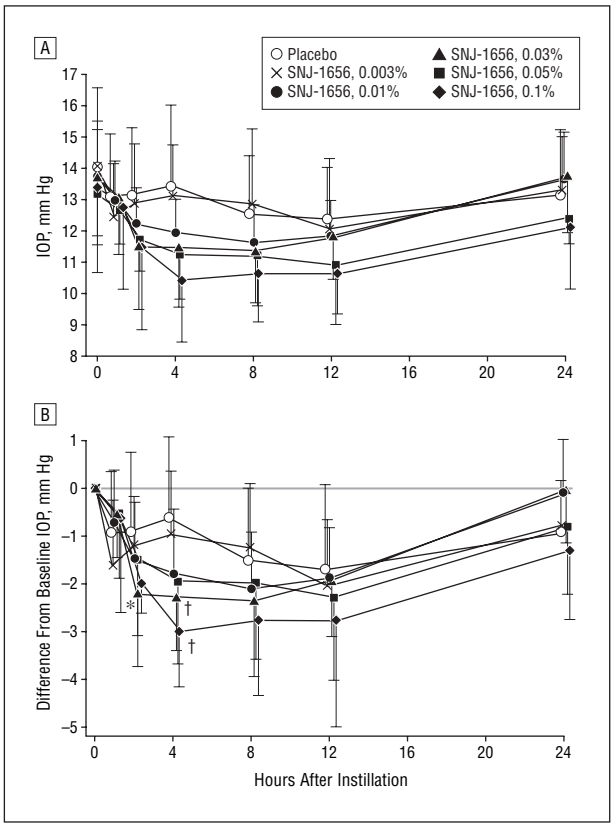

Figure 1. Levels of intraocular pressure (IOP) after single instillation of SNJ-1656. A, Levels of IOP decreased after instillation but were restored by 24 hours after instillation. B, Reduction of IOP after instillation of SNJ-1656 was dose dependent. Values are represented as mean±SD (SNJ-1656 group, 12 eyes in 6 subjects; placebo group, 30 eyes in 15 subjects). The significance of findings was evaluated by the Dunnett test (2-sided). *$P \leq .05$ compared with the placebo group. †$P \leq .01$ compared with the placebo group.

13.42±2.73 mm Hg for 0.1% concentrations, with no significant differences among the groups. The IOP levels in eyes administered SNJ-1656 first decreased and then returned to baseline levels by 24 hours after instillation (**Figure 1**A). The change in IOP from the baseline was –0.91, –1.18, –1.48, –2.20, –1.48, and –1.98 mm Hg at 2 hours and –0.63, –0.95, –1.79, –2.26, –1.95, and –3.00 mm Hg at 4 hours in the placebo, 0.003%, 0.01%, 0.03%, 0.05%, and 0.1% groups, respectively. Statistical analyses demonstrated significant differences in the magnitude of IOP reduction between the SNJ-1656– and placebo-treated eyes for 0.03% to 0.1% solutions ($P=.04$ at 2 hours and $P=.01$ at 4 hours for the 0.03% solution; $P<.001$ at 4 hours for the 0.1% solution [2-sided Dunnett test]) (Figure 1B). With SNJ-1656, 0.1%, mean IOP was 12.79±2.64, 11.44±2.58, 10.42±1.97, 10.63±1.56, 10.63±1.30, and 12.10±2.00 mm Hg at 1, 2, 4, 8, 12, and 24 hours after the instillation, respectively. Maximal IOP change with SNJ-1656, 0.1%, –3.00±1.16 mm Hg from the baseline IOP, was observed at 4 hours after instillation, and the IOP then slowly returned to near-baseline levels during the next 24 hours. The maximal IOP reduction after instillation of SNJ-1656, 0.1%, was larger than the reductions after instillation of lower concentrations (0.003% to 0.05%) of SNJ-1656. Similar, but weaker IOP-lowering effects were observed with lower concentrations of SNJ-1656.

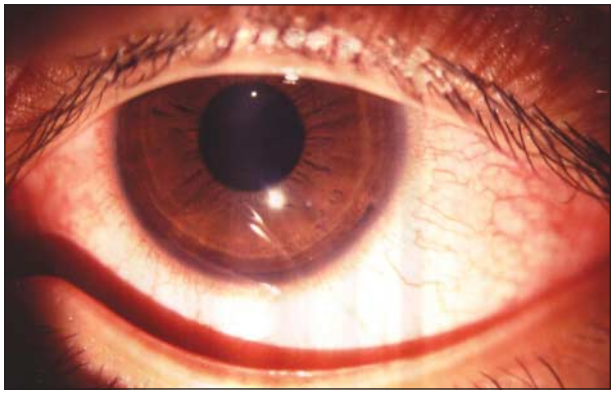

Figure 2. Bulbar conjunctival hyperemia after instillation of SNJ-1656, 0.1%.

SAFETY IN SINGLE-INSTILLATION TRIAL

On slitlamp examination during the trial, there were no significant findings except hyperemia of the bulbar and palpebral conjunctiva in eyes treated with SNJ-1656 (**Figure 2**). This finding as a treatment-related adverse event occurred in all 6 eyes with instillation of the 0.1% concentration and in 5 of the 6 eyes with instillation of the 0.05% concentration (**Table 1**). One subject with ocular hyperemia caused by SNJ-1656, 0.1%, experienced blurred vision, and another treated at this dose experienced photophobia. In contrast, with the 0.003% and 0.01% concentrations of SNJ-1656, fewer incidences of ocular hyperemia occurred, and no hyperemia occurred in the placebo group. The bulbar conjunctival hyperemia disappeared in all eyes, including those receiving the 0.1% concentration of SNJ-1656 (**Table 2**), by 12 hours after the instillation. Monitoring of pupil diameter showed no significant changes in pupil size during the trial. No significant changes were found between the preinstillation and postinstillation electroretinograms or the examination findings in the ocular fundus, the corneal endothelial cell count, or the corneal thickness. In addition, physiological examination results including blood pressure, pulse, body temperature, electrocardiograms (a wave, b wave, and amplitude), and hematological and urine testing showed no significant differences among volunteers administered SNJ-1656 or placebo.

IOP-LOWERING EFFECT OF REPEATED-INSTILLATION TRIAL

In the repeated-instillation trial, once-daily administration (steps 1 and 2-1) decreased IOP levels after instillation at 9 AM on each day in the SNJ-1656– and placebo-treated eyes (**Figure 3**A), whereas such a pattern of changes in IOP was unclear with twice-daily administration (steps 2-2 and 3; Figure 3B). The change in IOP from baseline was significantly larger in eyes treated with SNJ-1656 once daily (steps 1 and 2-1; Figure 3C) or twice daily (steps 2-2 and 3; Figure 3D) than in eyes treated with placebo. The mean changes in IOP from the baseline on the seventh day were –1.86±1.93, –2.78±0.98, and –3.70±1.12 mm Hg ($P=.01$, vs placebo [2-sided Dunnett test]) at 2 hours, and –1.58±1.56, –1.87±0.93, and –4.12±1.39 mm Hg ($P<.001$) at 4 hours in the groups

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Table 1. Treatment-Related Adverse Events in Single-Instillation Trial of SNJ-1656[a]

Symptom/Signs	SNJ-1656 Concentration				
	0.003% (n=6)	0.01% (n=6)	0.03% (n=6)	0.05% (n=6)	0.1% (n=6)
Bulbar conjunctival hyperemia	1	0	2	5	6
Palpebral conjunctival hyperemia	1	0	0	0	0
Blurred vision	0	0	0	0	1
Photophobia	0	0	0	0	1

[a] Data are expressed as number of volunteers with reported treatment-related adverse events. No treatment-related adverse events occurred in the placebo group (n=15).

Table 2. Change in Score of Bulbar Conjunctival Hyperemia After Instillation of SNJ-1656, 0.1%, in the Single-Instillation Trial[a]

Time After Instillation, h	Score		
	0	0.5	1
0	12	0	0
1	0	0	12
4	0	4	8
8	2	7	3
12	4	8	0
24	8	4	0

[a] Data are expressed as number of eyes of the 12 eyes in 6 volunteers. No eyes achieved scores of 2 or 3. Scores are described in the "Methods" section.

receiving placebo and SNJ-1656 at concentrations of 0.05% (step 1) and 0.1% (step 2-1), once daily, respectively. Changes in IOP on the seventh day were –0.92±1.32, –3.45±1.18 ($P<.001$), and –2.51±1.74 mm Hg ($P=.02$) at 2 hours, and –1.19±1.10, –2.87±1.34 ($P=.01$), and –2.94±1.75 mm Hg ($P=.01$) at 4 hours in the groups receiving placebo and SNJ-1656 at concentrations of 0.05% (step 2-2) and 0.1% (step 3), twice daily, respectively. The IOP-lowering effects of SNJ-1656 on the seventh day were similar to those on the first day in once- or twice-daily administration. The maximal changes in IOP in the SNJ-1656 groups were observed from 2 to 4 hours after instillation.

SAFETY IN REPEATED-INSTILLATION TRIAL

Hyperemia of the bulbar and palpebral conjunctiva as a treatment-related adverse event was observed in all steps in the repeated-instillation trial (**Table 3**). Some subjects treated with SNJ-1656, 0.1% (2 volunteers in step 2-1 and 1 volunteer in step 3), experienced blurred vision. One volunteer in step 3 complained of photophobia, ocular fatigue, and dryness of the eyes. In all of the subjects with these adverse events, ocular hyperemia and other ocular symptoms disappeared spontaneously after the cessation of SNJ-1656 instillation. The bulbar conjunctival hyperemia disappeared in all eyes, including those receiving once-daily and twice-daily SNJ-1656, 0.1% (**Table 4**), by 8 hours after the instillation. There were no significant differences in pupil diameter between SNJ-1656 and placebo administrations. In addition, there were no other abnormal findings on slitlamp examination, no other ocular symptoms, and no significant abnormal physiological findings, including those for blood pressure, pulse, body temperature, and the electrocardiograms during the trial. There were no clinically significant changes from baseline in visual acuity, ocular fundus characteristics, corneal endothelial cell count, corneal thickness, electroretinographic findings, or laboratory values (hematologic analysis, blood chemistry, or urinalysis results) after the trial in the SNJ-1656 groups.

COMMENT

The IOP-lowering effects of SNJ-1656 in healthy adult volunteers were demonstrated in this study, which included a single-instillation stage and a prolonged repeated-instillation stage. The study solution SNJ-1656 is an ophthalmic solution of Y-39983, a novel selective ROCK inhibitor, which has been reported to exhibit potent IOP-reducing activity in rabbits and monkeys.[14] Our findings obtained in this single-instillation trial demonstrated that SNJ-1656 at concentrations ranging from 0.003% to 0.1% reduced IOP in a dose-dependent fashion without systemic or severe local ocular adverse effects. Mean IOPs in eyes treated with SNJ-1656, 0.03%, were significantly lower from 2 to 4 hours after instillation than IOPs in eyes treated with placebo. The repeated-instillation trial also showed that IOP reductions from baseline were significantly larger in eyes with SNJ-1656 applications once daily and twice daily than in eyes treated with placebo. Maximal IOP reduction was observed from 2 to 4 hours after the instillation of SNJ-1656. No significant systemic adverse events were observed. In addition, because IOP returned to baseline levels by 24 hours after instillation, and statistical difference from placebo in twice-daily administration was more than that in once-daily administration, twice-daily administration of this ophthalmic solution can be recommended as clinically useful.

In both the single- and repeated-instillation trials, the subjects experienced ocular treatment-related adverse events, although no systemic adverse events were observed. In our clinical trial, the most frequent adverse event was ocular hyperemia. Most of the subjects experienced no hyperemia or trace to mild hyperemia. In all cases,

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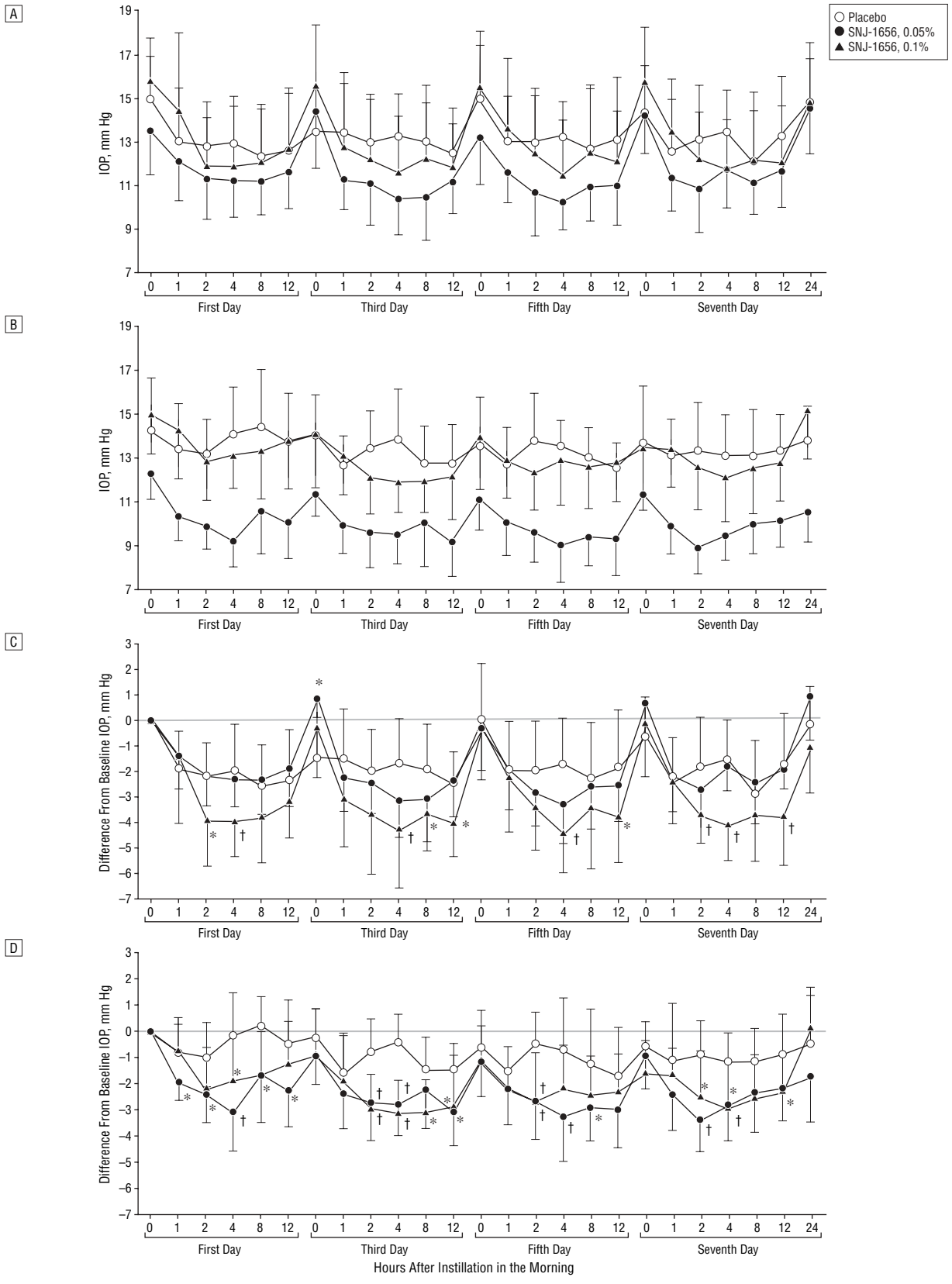

Figure 3. Levels of intraocular pressure (IOP) during repeated instillation of SNJ-1656. Levels of IOP in eyes with once-daily instillation of SNJ-1656 and placebo decreased after every 9 AM instillation (A), whereas diurnal changes in IOP were unclear with twice-daily administration (B). Reduction of IOP was significantly larger in eyes with SNJ-1656 administered once daily (C) or twice daily (D) than in eyes treated with placebo. Values are represented as mean±SD (12 eyes in 6 subjects). The significance of findings was evaluated by the Dunnett test (2-sided). *$P \leq .05$ compared with the placebo group. †$P \leq .01$ compared with the placebo group.

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Table 3. Treatment-Related Adverse Events in Repeated-Instillation Trial of SNJ-1656[a]

	Once-Daily Administration (n=6)		Twice-Daily Administration (n=6)	
Symptom/Signs	SNJ-1656, 0.05%	SNJ-1656, 0.1%	SNJ-1656, 0.05%	SNJ-1656, 0.1%
Bulbar conjunctival hyperemia	2	6	5	5
Palpebral conjunctival hyperemia	1	3	3	1
Blurred vision	0	2	0	1
Photophobia	0	0	0	1
Ocular fatigue	0	0	0	1
Dryness of the eyes	0	0	0	1

[a] Data are expressed as number of volunteers with reported treatment-related adverse events. No treatment-related adverse events occurred in the placebo group.

Table 4. Change in Score of Bulbar Conjunctival Hyperemia After Instillation of SNJ-1656, 0.1%, on the Seventh Day in the Repeated-Instillation Trial[a]

Time After Instillation, h	Score		
	0	0.5	1
	Once-Daily Instillation		
0	12	0	0
1	0	4	8
4	3	8	1
8	9	3	0
12	12	0	0
24	12	0	0
	Twice-Daily Instillation		
0	12	0	0
1	2	4	6
4	6	6	0
8	10	2	0
12	12	0	0
24	12	0	0

[a] Data are expressed as number of eyes in the 12 eyes in 6 volunteers. No eyes achieved scores of 2 or 3. Scores are described in the "Methods" section.

ocular hyperemia was transient and disappeared spontaneously after the cessation of SNJ-1656 instillation. Because the disappearance of hyperemia was confirmed in all eyes on slitlamp examination, SNJ-1656 did not seem to pose any safety problems for patients treated with lower concentrations. The occurrence of ocular hyperemia is consistent with findings in our previous animal experiments, in which similar conjunctival hyperemia (and minor hemorrhage) was found in rabbits and monkeys after frequent instillation of higher doses of SNJ-1656.[14] Hyperemia may be the result of relaxation of the blood vessels because ROCK inhibition induces smooth muscle relaxation.[11] Also, sporadic subconjunctival hemorrhage may be caused by impairment of barrier function or morphologic changes in vascular endothelial cells.[14] There were no clinically relevant effects of SNJ-1656 on visual acuity, ocular fundus characteristics, corneal endothelial cell count, corneal thickness, or electroretinographic findings. In addition, no clinically significant effects on blood pressure, pulse, body temperature, or electrocardiographic findings were noted with administration of SNJ-1656. The results of this study thus indicate that the IOP-lowering efficacy of SNJ-1656 was significant in healthy volunteers and that the adverse effects of its administration did not matter. Because we observed no systemic adverse events in this study, we believe that the use of SNJ-1656 is safe, even for patients with systemic disease.

Aqueous outflow in the conventional pathway is regulated by the contraction and relaxation of the CM, and also by the TM, which possesses smooth muscle–like properties.[15] It is thought that CM contraction distends the TM and increases aqueous outflow, whereas TM contraction decreases aqueous outflow.[6] Aqueous outflow is thus inversely influenced by the contractility of TM and CM. The contraction and relaxation of smooth muscle are regulated by myosin light chain phosphorylation/dephosphorylation. ROCK is involved in one of the major pathways of myosin light chain phosphorylation and is thought to regulate actomyosin-based contractility in many types of cells by phosphorylation of ROCK substrates.[16-18] Involvement of ROCK in the control of IOP via regulation of the aqueous conventional outflow pathway has principally been demonstrated by 2 types of evidence: effects on the cellular behavior of TM, and the contribution of ROCK to the contractility of CM and TM. Recent studies have indicated that cytoskeletal drugs, including ROCK inhibitors, decrease aqueous outflow resistance by modulating cytoplasmic fibers.[19] In previous studies,[11,20] we found that the selective ROCK inhibitor Y-27632 causes alterations in cell shape; decreases actin stress fibers and focal adhesions in cultured human TM cells; elicits profound effects on TM cell activities, including adhesion, gel contraction, and cell motility; and decreases IOP in rabbit eyes. It has also been shown that Y-27632 increases aqueous outflow in enucleated, perfused porcine eyes[21] and that topical application of Y-39983 significantly decreases IOP in monkey eyes.[14,22] The inhibitors Y-27632 and Y-39983 induce relaxation of carbachol-contracted rabbit CM strips and TM[11,13] and contract monkey TM, exhibiting involvement of phosphorylation of myosin phosphatase by ROCK.[23] Collectively, these findings suggest that TM is a target for the development of new cytoskeletal drugs, including ROCK inhibitors, for new treatment of glaucoma. Based on the findings of the present study, SNJ-1656 can be considered a candidate drug for lowering IOP by increasing conventional outflow with few adverse effects.

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In conclusion, our findings demonstrated that SNJ-1656 is a safe topical agent that is effective in reducing IOP in healthy adult volunteers. However, because our trial was attempted primarily to evaluate the safety of SNJ-1656 in healthy subjects, further clinical trials will be required for elucidation of IOP-lowering effects in patients with ocular hypertension and/or primary open-angle glaucoma.

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Financial Disclosure: Drs Tanihara and Azuma are contracted with Senju Pharmaceutical Co, Ltd as medical experts.

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Mr. Sydney Stephenson communicated notes of 43 cases of conjunctivitis in which diphtheria bacilli were found. . . . As regards treatment, Mr. Stephenson advised liberal and early doses of antitoxin, with a 1 in 5000 solution of corrosive sublimate applied to the conjunctiva by means of a small spray.

Reference: Marshall CD. Diphtheria of the conjunctiva. *Arch Ophthalmol*. 1902;31:268-269.

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