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ORIGINAL RESEARCH

Efficacy and Safety of the Long-Acting Diquafosol Ophthalmic Solution DE-089C in Patients with Dry Eye: A Randomized, Double-Masked, Placebo-Controlled Phase 3 Study

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ABSTRACT

Introduction: DE-089C is a newly developed long-acting formulation of diquafosol ophthalmic solution with less frequent administration (three times daily) than the currently approved and clinically used diquafosol ophthalmic solution (six times daily), hereinafter referred to as DQS. DE-089C is desirable for achieving better patient adherence in clinical practice for dry eye therapy. The objective of this study was to confirm the efficacy and safety of DE-089C in patients with dry eye compared to placebo.

Methods: This randomized, multicenter, double-masked, placebo-controlled, parallel-group phase 3 study was conducted in Japan. Patients with aqueous-deficient dry eye satisfying Schirmer's test I results $\leq$ 5 mm/5 min were included. A total of 337 patients with dry eye were randomized in an equal ratio to treatment with DE-089C or placebo ophthalmic solution, three times daily for 4 weeks. The primary endpoint for efficacy was change in fluorescein corneal staining score from baseline to week 4. The incidence of adverse drug reactions was investigated for safety evaluation.

Results: The background characteristics of patients in the two groups were similar. Primary endpoint of change in fluorescein corneal staining score at week 4 in the DE-089C group was significantly improved compared with the placebo group (least squares mean difference -0.51, 95% CI -0.754 to -0.269, $P < 0.0001$). The secondary endpoint of the Lissamine green conjunctival staining score was also significantly improved in the DE-089C group compared to that in the placebo group, while other secondary endpoints were not achieved in this study. Commonly (incidence $\geq$ 1%) reported adverse drug reactions in the DE-089C group were eye irritation (3.6%) and eye discharge (1.8%) with mild severity, and the incidences of these two events were not higher than those in previous clinical studies on DQS.

Conclusion: The efficacy and safety of DE-089C administered three times daily at half the dosage of DQS in patients with dry eye were confirmed in this study.

Trial Registration: Japan Pharmaceutical Information Center ID, JapicCTI-205177.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02194-2.

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Keywords: Adherence; Diquafosol; Dry Eye; Dry Eye Sign; Dry Eye Symptom; Efficacy; New Formulation; Phase 3 Study; Safety

Key Summary Points

Why carry out this study?

Diquafosol is an agonist of the $P2Y_2$ receptor involved in tear and mucin secretion directly on the ocular surface, and diquafosol ophthalmic solution administered six times daily has been approved and widely used in Japan for the treatment of dry eye

To achieve better adherence, diquafosol ophthalmic solution with less frequent administration is desirable in clinical practice for the treatment of dry eye, a chronic disease requiring long-term treatment

DE-089C is a new long-acting formulation of diquafosol ophthalmic solution, which was developed by Santen Pharmaceutical Co., Ltd., for dry eye treatment administered three times daily, and a randomized, multicenter, double-masked, placebo-controlled, parallel-group phase 3 study of DE-089C was conducted in Japan

What was learned from the study?

In this study, DE-089C instillation three times daily significantly improved the primary endpoint of change in fluorescein corneal staining scores from baseline to week 4 in patients with dry eye compared with that in the placebo group

Secondary endpoint of the Lissamine green conjunctival staining score was also significantly improved in the DE-089C group compared to that in the placebo group, while other secondary endpoints were not achieved in this study

Commonly (incidence ≥ 1%) reported adverse drug reactions in the DE-089C group were eye irritation and eye discharge with mild severity, and the incidences of these two events were not higher than those in previous clinical studies on currently approved formulation of diquafosol ophthalmic solution

INTRODUCTION

Dry eye is defined as a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage [1]. It is a common eye disease with prevalence ranging from 5% to 50% worldwide, especially in Asia, with a higher prevalence of over 30% [2]. A significant risk factor for dry eye is reported to be older age, and dry eye is common in the elderly [2, 3]. However, it also frequently occurs over a wide age range because contact lens use and visual display terminal work are known to be risk factors for dry eye [4]. The high prevalence of dry eye in patients with a wide age range makes it a socially important disease.

The first-line therapy for dry eye is treatment with ophthalmic solutions. Use of artificial tears, sodium hyaluronate ophthalmic solutions, rebamipide ophthalmic solution, and diquafosol ophthalmic solution have been approved in Japan for the treatment of dry eye. Diquafosol ophthalmic solution was launched in 2010 in Japan, and subsequently in other Asian countries, such as China and Korea. Diquafosol is an agonist of the $P2Y_2$ receptor, which is involved in tear and mucin secretion directly on the ocular surface [5, 6]. Diquafosol ophthalmic solution is reported to significantly improve dry eye signs, such as corneal and conjunctival epithelial damage, in several randomized controlled trials and improve tear film breakup time (BUT), Schirmer's test scores, and subjective symptoms in some studies [5, 6]. The efficacy of diquafosol ophthalmic solution for

several types of dry eye, including soft contact lens-related dry eye [7] and surgery-induced dry eye [8], has also been reported.

Because of the involvement of multiple factors in dry eye [3, 4], it is difficult to eliminate all risk factors. Therefore, continuous instillation of an ophthalmic solution for dry eye leads to improvement of its symptoms, and to maximize the effects of ophthalmic solution, it is important to instill the ophthalmic solution in compliance with the dosage regimen specified in the drug package insert. A web-based cross-sectional questionnaire survey with 2645 patients with dry eye in Japan revealed that the proportion of participants who instilled at the frequency specified in the package insert was 10.2% [9]. The majority (about 80%) of patients using diquafosol ophthalmic solution instilled the eye drop four times or fewer daily, which was nearly half of the specified frequency, six times daily. One of the reasons why patients instill the eye drop at a frequency lower than the specified was the high frequency of the dosage. A lower frequency of instillation than specified may lead to less effectiveness of the eye drop for dry eye. In the web-based cross-sectional questionnaire survey, improvement in the subjective symptoms score was significantly greater in patients who regularly instilled eye drops at the specified frequency than in patients who did not [9]. To achieve better adherence, a new formulation of diquafosol ophthalmic solution with less frequent administration and efficacy similar to that of the currently approved formulation is desired in clinical practice for the treatment of dry eye.

DE-089C is a new long-acting formulation of diquafosol ophthalmic solution developed by Santen Pharmaceutical Co., Ltd. and is designed to sustain the efficacy of diquafosol by the addition of polyvinylpyrrolidone to the solution. The efficacy of DE-089C administered three times daily for improving corneal epithelial damage score was confirmed to be similar with currently approved diquafosol ophthalmic solution administered six times daily in a rat model of dry eye. On the basis of this non-clinical study, a dosage of three times daily was recommended as the clinical dosage for DE-089C. The objective of this study was to confirm the efficacy and safety of three times a day dosage with 3% DE-089C ophthalmic solution in patients with dry eye, comparing with placebo ophthalmic solution.

METHODS

Study Design

This study was a randomized, multicenter, double-masked, placebo-controlled, parallel-group phase 3 study conducted between February 20 and July 30, 2020 in Japan, to evaluate the efficacy and safety of DE-089C in patients with dry eye. The study had a 2-week washout period, followed by a 4-week treatment period (Fig. 1). During the washout period, the patients received three times daily instillation of placebo ophthalmic solution (placebo), which was the vehicle of DE-089C ophthalmic solution containing polyvinylpyrrolidone. Investigators accessed the Randomization and Trial Supply Management (RTSM) system after confirming that the patient met all the inclusion and none of the exclusion criteria. Eligible patients were randomly assigned to the DE-089C ophthalmic solution (DE-089C)-treated group or placebo ophthalmic solution-treated group in equal ratios through the RTSM system, according to the randomization list pre-created by the third party. The patients received each study drug three times daily during the treatment period. Patients were asked to record the number of eye drop instillations per day on the patient diary every day during the study period. Total number of actual instillations during the study period was calculated from the patient diary records and divided by the total number of planned instillations to calculate the treatment compliance rate (%).

This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board of each site, and written informed consent was obtained from all participants before the initiation of the study. This study was registered with the Japan Pharmaceutical Information Center (JapicCTI-205177).

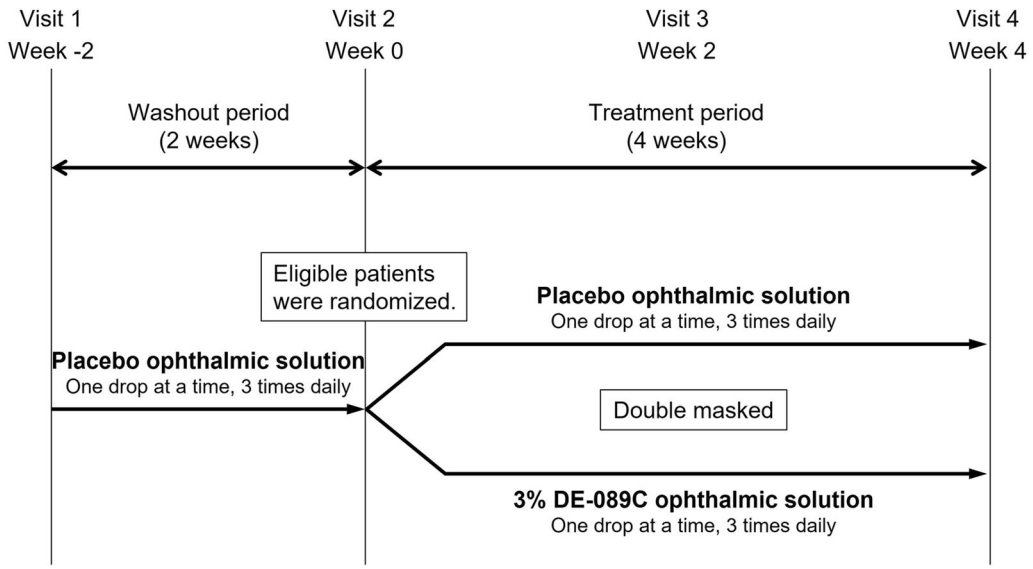

Fig. 1 Study design

Study Patients

Informed consent was obtained from male and female patients aged 20 years or older who were diagnosed with dry eye in both eyes. Inclusion criteria at visit 1 were to meet the following two criteria at least in one eye: (1) fluorescein corneal staining score [10] $\geq$ 1, and (2) score of dry sensation in eyes (dryness score) $\geq$ 1 in the Dry Eye-Related Quality-of-Life Score (DEQS) questionnaire [11]. Inclusion criteria at visit 2 before randomization were to meet the following all criteria at least in one eye which met the inclusion criteria at visit 1: (1) fluorescein corneal staining score $\geq$ 1; (2) dryness score $\geq$ 1 in the DEQS questionnaire; (3) Schirmer's test I results $\leq$ 5 mm/5 min; and (4) BUT $\leq$ 5 s.

Patients were excluded if they had eyelid closure failure including blepharospasm, a history of allogeneic hematopoietic stem cell transplantation, refractive corneal surgery, internal eye surgery within 90 days prior to visit 1, or continued treatment for obstruction of the lacrimal punctum until within 30 days prior to visit 1. Patients were also excluded if they had corneal conjunctival abnormalities other than dry eye affecting the ocular surface, ocular disease other than dry eye requiring treatment, allergic conjunctivitis that was likely to worsen during the treatment period, or a need for contact lens use during the treatment period.

Prohibited drugs or therapies during the treatment period were as follows: (1) combination use of any topical eye medications including eye drops, eye ointments, and injections; (2) use of corticosteroids except for topical dermal administration other than to the eyelids; (3) treatment for obstruction of the lacrimal punctum; (4) use of contact lenses or dry eye glasses; and (5) heat therapy for dry eye.

Efficacy Evaluation

The primary endpoint for efficacy was change in fluorescein corneal staining score from baseline to week 4. The key secondary endpoint was the change in dryness score on the DEQS questionnaire from baseline to week 4. Other secondary endpoints included change in Lissamine green conjunctival staining score from baseline to week 2 or 4, change in BUT from baseline to week 2 or 4, and change in Schirmer's test I result from baseline to week 4. Fluorescein corneal staining score, dryness score in the DEQS questionnaire, and BUT were assessed at all

visits. The Lissamine green conjunctival staining score was assessed at visit 2, 3, and 4. The Schirmer's test I score was assessed at visit 2 and 4.

Subjective symptoms of dry eye were assessed using the dry sensation score (column B) in the DEQS questionnaire before the BUT measurement.

For calculating BUT, after staining of tear film with 2 μL of 1% fluorescein solution, the interval between the last complete blink and the appearance of the first corneal black spot in the stained tear film was measured three times with a stopwatch for each eye, and the mean value of the measurements was calculated.

Fluorescein corneal staining was performed to evaluate corneal epithelial disorders after BUT measurement. For fluorescein corneal staining, the cornea was divided into three equal zones: upper, middle, and lower. Each zone had a staining score ranging between 0 and 3 points, with minimum and maximum total staining scores ranging between 0 and 9 points. The degree of staining was scored as follows: 0 = no staining, 1 = staining of less than half of the corneal area, 2 = staining of more than half of the corneal area, and 3 = staining of the whole corneal area.

Lissamine green staining was performed with 2 μL of 1% Lissamine green solution to evaluate conjunctival epithelial disorder. In Lissamine green staining, the conjunctiva was divided into the nasal and temporal areas. Each area had a staining score ranging between 0 and 3 points with the minimum and maximum total staining scores ranging between 0 and 6 points. The degree of staining was scored using the same criteria as those for fluorescein staining.

Schirmer's test I was performed without anesthesia to measure the tear volume for 5 min. The length in millimeters of tear fluid absorbed on the Schirmer's test strip from the edge of the strip was measured.

Evaluation of Feelings Experienced During Use of Eye Drops

Feeling of using the DE-089C ophthalmic solution was investigated using a questionnaire survey at visit 4. In the questionnaire, patients were asked the question "Is the feeling experienced during investigational drug instillation better, same, or worse comparing with previous eye drops, which was used immediately before the initiation of the study?" If patients had used ophthalmic solutions immediately before the initiation of the study, the question was asked for each ophthalmic solution.

Safety Evaluation

Safety was assessed in patients who had instilled the investigational eye drops at least once and for whom some information on safety was available. The frequency of adverse events and adverse drug reactions, defined as adverse events causally related to the study drug, was assessed during the 4-week treatment period.

Data Management

We captured the data in Electronic Data Capture system and cleaned up the data by system edit check and manual data review.

Statistical Analyses

The sample size was calculated with reference to a late phase II study of placebo-controlled 3% diquafosol eye drops six times daily [12]. A total of 143 patients per treatment group would provide 80% power to detect such a difference in the key secondary efficacy endpoint between the DE-089C group and placebo group using a two-sample two-sided *t* test with alpha level of 0.05. Taking both endpoints into consideration, we calculated that a total of 300 patients (150 patients per arm) were to be randomized, assuming that 5% patients would prematurely discontinue the study without providing any post-baseline information of the fluorescein corneal staining score.

The mean and SD for continuous variables and number and percentage of patients for categorical variables were calculated. For efficacy evaluation, mixed-effects models for repeated measures (MMRM) were conducted using the change from baseline to week 2 or 4

(evaluation point) in each efficacy endpoint as the dependent variable, treatment group, evaluation point, interaction of treatment group and evaluation point, interaction of baseline value in each efficacy endpoint and evaluation point as fixed effects, and patient as a random factor for the full analysis set (FAS) population. Least squares (LS) mean and 95% confidence interval (CI) of LS mean of each efficacy endpoint at week 4 in each group was estimated with MMRM. In addition, LS mean and 95% CI of group difference (DE-089C group − placebo group) in LS mean of each efficacy endpoint at week 4 were also estimated. Superiority was determined if the difference between the DE-089C and placebo groups in the primary endpoint of change in fluorescein corneal staining score at week 4 was statistically significant. For the secondary endpoint of change in Schirmer's test I result, the analysis of covariance (ANCOVA) model was used with Schirmer's test I values at baseline as the covariate. The significance level was set at $P < 0.05$. SAS® version 9.4 software (SAS Institute) was used for data analysis.

RESULTS

Patient Disposition

Informed consent was obtained from 413 patients, of whom 337 patients were randomly assigned to receive DE-089C or placebo at an equal ratio. Seven patients discontinued the study, and 330 patients completed the study (166 patients in the DE-089C group and 164 patients in the placebo group, respectively). The FAS included 168 patients in each group for efficacy evaluation. The safety analysis set (SAF) included 169 patients in the DE-089C group and 168 patients in the placebo group. The treatment compliance rate during the study period averaged 99.4% (SD, 1.936; minimum, 85.2%) in the DE-089C eye drops group and 99.7% (SD, 1.355; minimum, 92.0%) in the placebo eye drops group.

Patient Background

Background characteristics of patients in the two groups were similar (Table 1).

Efficacy Evaluation

Primary Endpoint (FAS)

Figure 2 shows the change from baseline in fluorescein corneal staining scores in each treatment group, and Table 2 shows change from baseline in fluorescein corneal staining scores in each treatment group and the group differences. Primary endpoint of change in fluorescein staining score at week 4 in the DE-089C group was significantly improved as compared to that with the placebo group (LS

Table 1 Baseline demographics and background characteristics of patients (SAF)

Characteristics	Placebo (N = 168)	DE-089C (N = 169)
Age, years (mean ± SD)	62.7 ± 15.4	61.9 ± 15.0
Gender, female, *n* (%)	146 (86.9)	153 (90.5)
Sjögren's syndrome *n* (%)	12 (7.1)	20 (11.8)
Fluorescein corneal staining score (mean ± SD)	2.7 ± 1.5	2.8 ± 1.6
Lissamine green conjunctival staining score (mean ± SD)	2.5 ± 1.4	2.5 ± 1.5
BUT, s (mean ± SD)	2.0 ± 1.1	2.2 ± 1.1
Schirmer's test I, mm (mean ± SD)	3.5 ± 2.9	3.9 ± 3.0
Dryness score in the DEQS questionnaire (mean ± SD)	1.9 ± 0.9	2.0 ± 0.9

SAF safety analysis set, *SD* standard deviation, *BUT* tear film breakup time, *DEQS* Dry Eye-Related Quality-of-Life Score

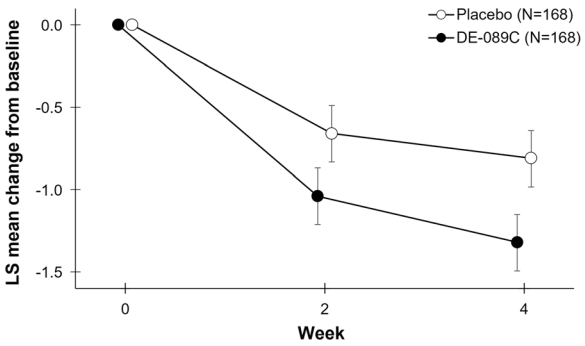

Fig. 2 Change in fluorescein corneal staining scores (MMRM FAS). Data are expressed as the LS mean change from baseline to week 2 or 4. Error bar shows 95% CI. Fluorescein corneal staining score was significantly improved in the DE-089C group compared to the placebo group at week 2 and 4 ($P = 0.0022$ and < 0.0001, respectively). *MMRM* mixed-effects models for repeated measures, *FAS* full analysis set, *LS* least squares, *CI* confidence interval

mean difference − 0.51, 95% CI − 0.754 to − 0.269, $P < 0.0001$). Therefore, the superiority of DE-089C group over placebo group in improving corneal epithelial damage was verified. In addition, a statistically significant improvement was observed at week 2 (Table 2).

Secondary Endpoints (FAS)

LS mean and 95% CI of the LS mean of scores in secondary endpoints in each group and the group difference in LS mean are shown in Table 3.

Dryness Score in the DEQS Questionnaire No significant difference was found in the improvement of the dryness score in the DEQS between the DE-089C and placebo groups at week 4. In addition, no significant differences were observed at week 2.

Lissamine Green Conjunctival Staining The improvement in Lissamine green staining score at all time points in the DE-089C group was significantly greater than that in the placebo group.

BUT No significant difference was noted in the improvement of BUT between the DE-089C and placebo groups at any time point.

Schirmer's Test I No significant difference was observed in the improvement of Schirmer's test I between the DE-089C and placebo groups at week 4.

Evaluation of Feeling Experienced During Use of DE-089C Ophthalmic Solution (Questionnaire Survey) (FAS)

In the DE-089C group, 89.4% of patients who used the currently approved formulation of diquafosol ophthalmic solution (DQS) immediately prior to initiation of the study reported

Table 2 Change from baseline in fluorescein corneal staining scores (MMRM FAS)

	Placebo (*N* = 168)	**DE-089C (*N* = 168)**
Week 2		
LS means (95% CI) in each group	− 0.66 (− 0.832 to − 0.489)	− 1.04 (− 1.212 to − 0.869)
Group difference (95% CI)	− 0.38 (− 0.623 to − 0.138)	
P value	0.0022	
Week 4		
LS means (95% CI) in each group	− 0.81 (− 0.984 to − 0.639)	− 1.32 (− 1.494 to − 1.152)
Group difference (95% CI)	− 0.51 (− 0.754 to − 0.269)	
P value	< 0.0001	

MMRM mixed-effects models for repeated measures, *FAS* full analysis set, *LS* least squares, *CI* confidence interval

Table 3 Analysis for secondary endpoints

Secondary endpoints	Placebo (N = 168[c])	DE-089C (N = 168[c])
Change from baseline in dryness score[a]		
Week 2		
LS means (95% CI) in each group	− 0.52 (− 0.665 to − 0.378)	− 0.55 (− 0.693 to − 0.406)
Group difference (95% CI)	− 0.03 (− 0.231 to 0.175)	
P value	0.7840	
Week 4		
LS means (95% CI) in each group	− 0.69 (− 0.828 to − 0.559)	− 0.82 (− 0.956 to − 0.689)
Group difference (95% CI)	− 0.13 (− 0.319 to 0.060)	
P value	0.1808	
Change from baseline in Lissamine green conjunctival staining score[a]		
Week 2		
LS means (95% CI) in each group	− 0.35 (− 0.524 to − 0.183)	− 0.66 (− 0.826 to − 0.485)
Group difference (95% CI)	− 0.30 (− 0.544 to − 0.061)	
P value	0.0141	
Week 4		
LS means (95% CI) in each group	− 0.44 (− 0.615 to − 0.264)	− 0.77 (− 0.944 to − 0.594)
Group difference (95% CI)	− 0.33 (− 0.577 to − 0.082)	
P value	0.0093	
Change from baseline in BUT[a]		
Week 2		
LS means (95% CI) in each group	0.46 (0.292 to 0.630)	0.65 (0.480 to 0.817)
Group difference (95% CI)	0.19 (− 0.052 to 0.426)	
P value	0.1242	
Week 4		
LS means (95% CI) in each group	0.56 (0.368 to 0.757)	0.77 (0.573 to 0.961)
Group difference (95% CI)	0.21 (− 0.070 to 0.479)	
P value	0.1439	
Change from baseline in Schirmer's test I[b]		
Week 4		
LS means (95% CI) in each group	1.52 (0.768 to 2.262)	2.26 (1.515 to 3.009)
Group difference (95% CI)	0.75 (− 0.311 to 1.805)	

Table 3 continued

Secondary endpoints	Placebo (N = 168[c])	DE-089C (N = 168[c])
P value	0.1657	

LS least squares, *CI* confidence interval, *BUT* tear film breakup time, *MMRM* mixed-effects models for repeated measures, *ANCOVA* analysis of covariance
[a]MMRM analysis
[b]ANCOVA
[c]For the analysis of change from baseline in Schirmer's test I, N = 166 for each group

that "Feeling with use of eye drops was better in DE-089C than DQS, or same between two ophthalmic solutions" (Table 4). Among patients who used hyaluronic acid, rebamipide, or artificial tears immediately prior to initiation of the study, the percentage of patients who answered that DE-089C was better than or the same as prior eye drops was 80.0%, 91.7%, and 69.2%, respectively (Table 4). Meanwhile, in the placebo group, similar results were obtained with the DE-089C group.

Safety (SAF)

No deaths or serious adverse events were reported. Incidence of adverse events was 9.5% (16/168 patients) in the placebo group and 13.6% (23/169 patients) in the DE-089C group. In DE-089C group, all reported adverse events were mild, and adverse events with incidence ≥ 1% included eye irritation (3.6%), eye discharge (1.8%), and conjunctival hemorrhage (1.2%). Adverse drug reactions with incidence ≥ 1% in the DE-089C group were eye irritation (3.6%) and eye discharge (1.8%) (Table 5). Regarding visual acuity, anterior segment examination, and intraocular pressure, no clinically significant changes from baseline were observed in both groups.

DISCUSSION

In the present study, DE-089C, a new long-acting formulation with a reduced clinical dosing of three times a day of diquafosol ophthalmic solution was shown to significantly improve the primary endpoint of change in fluorescein corneal staining scores from baseline to week 4 compared to that of placebo in patients with dry eye. The secondary endpoint of Lissamine green conjunctival staining score was also significantly improved in the DE-089C group compared to that with the placebo group, while other secondary endpoints were not achieved in this study. The efficacy of diquafosol administered three times daily was demonstrated in a clinical study for the first time.

Patients with aqueous-deficient dry eye satisfying Schirmer's test I results ≤ 5 mm/5 min were included in this study. Overall, the background characteristics of the patients in the DE-089C and placebo groups were similar. Mean age of study patients was 61.9 and 62.7 years in the DE-089C and placebo groups, respectively, and more female patients were enrolled than male patients with the female proportion of 90.5% and 86.9% in the DE-089C and placebo groups, respectively. The mean age and proportion of woman in this study were similar to those in the DQS, currently approved formulation of diquafosol ophthalmic solution (six times daily) group in the previous phase 2b and phase 3 studies on DQS [12, 13]. Many study patients were elderly and female in this study as observed in the previous phase 2b and phase 3 study on DQS. These are consistent with a report that dry eye is common among elderly people and women [2, 3].

DE-089C instillation three times daily significantly improved the primary endpoint of change in fluorescein corneal staining scores from baseline to week 4 compared to that in placebo in patients with dry eye. The secondary endpoint of Lissamine green conjunctival staining score was also significantly improved

Table 4 Feelings experienced during use of DE-089C ophthalmic solution compared with those experienced during use of prior eye drops (questionnaire survey)

Prior eye drop	Placebo		DE-089C	
	(*N* = 168)		(*N* = 168)	
DQS	*N* = 66		*N* = 66	
Better eye drop	Placebo or same	Prior eye drop	DE-089C or same	Prior eye drop
N	58	8	59	7
% (95% CI)	87.9% (77.51–94.62%)	12.1% (5.38–22.49%)	89.4% (79.36–95.63%)	10.6% (4.37–20.64%)
Hyaluronic acid	*N* = 94		*N* = 90	
Better eye drop	Placebo or same	Prior eye drop	DE-089C or same	Prior eye drop
N	72	22	72	18
% (95% CI)	76.6% (66.74–84.71%)	23.4% (15.29–33.26%)	80.0% (70.25–87.69%)	20.0% (12.31–29.75%)
Rebamipide	*N* = 33		*N* = 36	
Better eye drop	Placebo or same	Prior eye drop	DE-089C or same	Prior eye drop
N	31	2	33	3
% (95% CI)	93.9% (79.77–99.26%)	6.1% (0.74–20.23%)	91.7% (77.53–98.25%)	8.3% (1.75–22.47%)
Artificial tears	*N* = 15		*N* = 13	
Better eye drop	Placebo or same	Prior eye drop	DE-089C or same	Prior eye drop
N	12	3	9	4
% (95% CI)	80.0% (51.91–95.67%)	20.0% (4.33–48.09%)	69.2% (38.57–90.91%)	30.8% (9.09–61.43%)
Others	*N* = 11		*N* = 13	
Better eye drop	Placebo or same	Prior eye drop	DE-089C or same	Prior eye drop
N	11	0	12	1
% (95% CI)	100.0% (71.51–100.00%)	0.0% (0.00–28.49%)	92.3% (63.97–99.81%)	7.7% (0.19–36.03%)

DE-089C new long-acting formulation of 3% diquafosol ophthalmic solution (three times daily), *DQS* currently approved formulation of 3% diquafosol ophthalmic solution (six times daily), *CI* confidence interval

in the DE-089C group compared with that in the placebo group. These data demonstrated the efficacy of DE-089C over placebo in improving corneal and conjunctival epithelial damage. A preliminary post hoc integrated analysis for change in fluorescein corneal staining score in the present study and the previous DQS phase 2b study (six times daily) [12] indicated that the improvement in fluorescein corneal staining score was similar between these formulations (Table S1 in the supplementary material). The concentration of diquafosol is 3% in both formulations, and the effect on corneal fluorescein staining scores is considered equivalent. Therefore, DE-089C, with a lower frequency of instillation than DQS, is suggested to have comparable efficacy for corneal epithelial damage in dry eye with DQS. The longer efficacy duration of DE-089C than DQS is thought to be achieved by the addition of polyvinylpyrrolidone into the ophthalmic solution of DE-089C, and this has been

Table 5 Incidence of adverse drug reactions (≥ 1%)

Events	Placebo (*N* = 168)	DE-089C (*N* = 169)
Any	1 (0.6%)	12 (7.1%)
Eye irritation	0	6 (3.6%)
Eye discharge	0	3 (1.8%)

supported by the results of non-clinical studies of DE-089C. Polyvinylpyrrolidone has been reported to retain water in its polymer structure and has an affinity for mucin [14, 15]. Therefore, after the instillation of DE-089C, water and mucin secreted from the patient's eye by the pharmacological action of diquafosol seems to bind to polyvinylpyrrolidone in the ophthalmic solution, which may lead to retention of water and mucin in the patient's eye for a longer period with a lower frequency of instillation than DQS.

The dryness score was not significantly improved in the DE-089C group compared with the placebo group in the present study, although DE-089C significantly improved corneal epithelial damage. One possible reason for the lack of significant differences could be the insufficient sample size. Since the dryness score is a secondary endpoint, the sample size was not designed to detect significant differences in it. However, the change in the dryness score in the DE-089C group was greater than that in the placebo group. Therefore, the instillation of DE-089C ophthalmic solution may improve dry sensation in patients with dry eye, although this cannot be confirmed in the current study. In the post hoc analysis, the dryness score among patients who were not previously treated with DQS was significantly improved in the DE-089C group compared to the placebo group at week 4 (Table S2 in the supplementary material).

The secondary endpoint of change in BUT was not achieved in this study. One possible reason for the lack of significant differences could be that the sample size was also insufficient. The sample size was not designed to detect significant differences in BUT. A preliminary post hoc integrated analysis for change from baseline in BUT in the present study and the DQS phase 2b study (six times daily) [12] indicated that there was no statistically significant difference in improvement of BUT between these formulations at week 2 and 4 (Table S1 in the supplementary material). The concentration of diquafosol is 3% in both formulations, and the effect on BUT is also considered equivalent. Mean change from baseline in BUT in the DE-089C group was approximately 0.75 s at week 4 in this study, while it was reported to be approximately 1.95 s at week 52 in patients treated with DQS in a previous long-term treatment study of DQS [16]. Therefore, a longer treatment period (e.g., 52 weeks) is thought to be necessary to verify the improvement in BUT in patients treated with DE-089C.

Safety evaluation showed that commonly (incidence ≥ 1%) reported adverse drug reactions in the DE-089C group were eye irritation (3.6%) and eye discharge (1.8%) with mild severity. These adverse drug reactions have already been reported in a phase 2b study of DQS with incidence of 12.5% (12/96 patients) for eye irritation [12] and in a phase 3 study of DQS with incidence of 6.3% (9/144 patients) for eye irritation and 2.8% (4/144 patients) for eye discharge [13]. Two post-marketing surveillance studies of DQS conducted in real-world clinical practice also reported the incidence of these adverse drug reactions, with 0.9% (30/3196 patients) and 2.4% (14/580 patients) for eye irritation, and 0.9% (30/3196 patients) and 2.9% (17/580 patients) for eye discharge [17, 18]. The incidence of adverse drug reactions of eye irritation and eye discharge reported in the present study was not higher than those in phase 2b and phase 3 studies of DQS, and are already identified risks for the diquafosol ophthalmic solution. Therefore, the adverse drug reactions of DE-089C were considered acceptable. Regarding visual acuity, anterior segment examination, and intraocular pressure, no clinically significant changes from baseline were observed in the DE-089C and placebo groups. Regarding the safety evaluations in this study, the tolerability of DE-089C was confirmed.

DE-089C contains a polymer, polyvinylpyrrolidone, in the ophthalmic solution. The properties of the solution were

reported to vary depending on the added lubricating agents, including polyvinylpyrrolidone [19], and the added polyvinylpyrrolidone possibly affected the feeling experienced during use of DE-089C. Moreover, dry eye is a chronic disease requiring long-term treatment, and feeling experienced during use of eye drops may be significantly associated with adherence to treatment with eye drops for dry eye therapy. Therefore, the feeling experienced during use of DE-089C compared with prior eye drops was investigated using a questionnaire survey in the present study. Most (89.4%) patients reported that "Feeling with use of DE-089C was comparable to or better than that of DQS". Therefore, DE-089C is expected to have the same or better usability as DQS. Furthermore, many (69.2–91.7%) patients reported that feeling experienced during use of DE-089C was comparable to or better than that of ophthalmic solutions such as hyaluronic acid, rebamipide, or artificial tears, suggesting that DE-089C has the same or better usability as currently approved eye drops in Japan. More detailed data than those in Table 4 are shown in Table S3 in the supplementary material for reference.

A new long-acting formulation of diquafosol ophthalmic solution, DE-089C, was shown to improve keratoconjunctival epithelial damage with acceptable safety profiles. It was also suggested to have the same or better feeling experienced during use of eye drops compared to DQS and other eye drops for dry eye. The frequency of eye drop administration of DE-089C (three times daily) is less than that of currently approved eye drops for dry eye treatment in Japan [20]. A web-based cross-sectional questionnaire survey with 2645 patients with dry eye in Japan revealed that 26.6% of patients use DQS three times daily, the highest percentage of all patients [9], suggesting that DE-089C with a dosage of three times daily is well accepted by patients with dry eye. Therefore, DE-089C may be an optimal therapeutic option for patients with dry eye who have trouble with continuous eye drop use because of the frequent prescribed daily dose and is expected to increase patient adherence to dry eye therapy and encourage long-term treatment with eye drops, which contributes to better outcomes for dry eye.

A limitation of this study is that the duration of DE-089C treatment was short, with a 4-week treatment, although dry eye is a chronic disease requiring a long-term treatment. A long-term study is needed to evaluate the safety and efficacy of DE-089C in the future. Head-to-head studies are required to directly compare the efficacy and safety of DE-089C with other eye drops for dry eye. Finally, the efficacy of DE-089C was verified in patients with aqueous-deficient dry eye in this study, and therefore the efficacy of DE-089C in patients with other types of dry eye is uncertain.

CONCLUSIONS

This study confirmed the efficacy and safety of a new long-acting formulation of diquafosol ophthalmic solution with a reduced clinical dosing compared to available formulation, DE-089C, in patients with dry eye. DE-089C is effective at a lower frequency of administration than the currently approved formulation of diquafosol ophthalmic solution. Therefore, DE-089C may contribute to improvement in treatment adherence of patients with dry eye, which will lead to the better eye outcomes.

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Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration. Informed consent was obtained from all patients for being included in the study. This study was approved by the institutional review board at each site, and was registered at the Japan Pharmaceutical Information Center (JapicCTI-205177).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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