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ARTICLE

A phase I study to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic profiles of ocular GLH8NDE in healthy male adults

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Abstract

GLH8NDE, a derivative of eupatilin, is currently under development to treat dry eye disease. We conducted a randomized, double-masked, placebo-controlled, single- and multiple-day study to evaluate safety, tolerability, pharmacodynamics, and pharmacokinetics of ocular GLH8NDE in healthy male adults. Subjects randomly received topical ocular dosing of GLH8NDE or its matching placebo for a day, then for 7 consecutive days with a 62-h washout at one of the following daily doses: 9, 18, 36 (Koreans), and 36 mg (Whites). The study drug was administered in divided doses over 10 h with 2- or 5-h intervals. Thirty-nine (97.5%) out of 40 subjects completed the study. A total of 17 subjects experienced 31 treatment-emergent adverse events, all of which were mild in severity and recovered without sequelae. Neither pathological changes in eye compartments nor clinically significant systemic effects were observed. GLH8NDE was rapidly absorbed reaching the peak concentration within 0.25–0.75 h postdose. The systemic exposure as measured by area under the concentration-time curve from time of administration up to the time of the last quantifiable concentration (AUC_{last}) after single-day administration of the same dose was 109% higher in Koreans than in Whites. In

conclusion, GLH8NDE was safe and well-tolerated in healthy Korean and White male adults at 9–36 mg/day after single- and multiple-day administrations.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?GLH8NDE (7-carboxymethyloxy-3′,4′,5′-trimethoxy flavone) is a derivative of eupatilin, which is currently under clinical development to treat dry eye disease (DED). GLH8NDE has been effective in various experimentally induced DED animal models. Ocular GLH8NDE has never been studied in humans.

WHAT QUESTION DID THIS STUDY ADDRESS?

This phase I study evaluated the safety, tolerability, pharmacodynamic, and pharmacokinetic profiles of ocular GLH8NDE in humans. In addition, the ethnic difference in the systemic exposure to GLH8NDE was assessed between Korean and White healthy male adults.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Ocular doses of GLH8NDE from 9 to 36 mg per day after single- and multiple-day administrations were safe and well-tolerated in Korean and White healthy male adults. GLH8NDE was rapidly absorbed in a dose-proportional manner. The systemic exposure to GLH8NDE was higher in Koreans than in Whites. GLH8NDE at 9 and 36 mg per day increased tear break-up time (TBUT) from baseline whereas TBUT was decreased in the placebo group.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study shows that GLH8NDE is safe and well-tolerated in healthy Korean and White male adults over the dose range of 9–36 mg per day. GLH8NDE has a potential to be developed as a useful treatment option for DED. Further research should take account the ethnic differences in the systemic exposure to GLH8NDE.

INTRODUCTION

Dry eye disease (DED) is one of the most common ocular surface diseases, from which millions of people are suffering worldwide.[1–4] A variety of extrinsic and intrinsic factors are associated with DED and its pathophysiology is still inadequately understood.[5–7] Due to the multifactorial nature of DED pathophysiology, DED should be treated based on interdisciplinary approaches. For example, a loss of tear film homeostasis can arise from a multitude of factors that encompass eyelid and blink abnormalities in addition to ocular surface or tear component deficiencies. These changes can induce focal or global tear film instability and tear hyperosmolarity in response to excessive evaporation from the ocular surface, which, in turn, contribute to the pathogenesis of DED and its perpetuation.[7] Cyclosporine, lifitegrast, or corticosteroids have been used to treat DED as eye drops.[8] Mitogen-activated protein kinase (MAPK) pathways are engaged in inflammatory responses by replaying, amplifying, and integrating the cellular signals. Controlling MAPK activities is important to treat DED because DED can be viewed as an inflammatory disease. Inflammatory actions via MAPK pathways might cause lacrimal damage, which decreases tear production. It eventually leads to DED. In this regard, DED may be treated by suppressing MAPK activities through anti-inflammatory action.[9–13]

GLH8NDE (7-carboxymethyloxy-3′,4′,5′-trimethoxy flavone, GL PharmTech Corporation, Gyeonggi-do, Republic of Korea), a derivative of eupatilin increases mucus secretion by prostaglandin production.[14,15] GLH8NDE has shown to be effective in various experimentally induced DED animal models. For example, GLH8NDE increased mucosal secretion from cornea and conjunctival epithelial cells by elevating intracellular Ca^{2+} concentrations.[16] Furthermore, GLH8NDE blocks inflammatory responses by inhibiting nuclear factor-kappa B (NFkB) and MAPKs activation in various experimentally induced animal DED models.[17–21] GLH8NDE is an eye drop solution, a mixture of an active ingredient with several excipients, including sodium chloride as an isonic agent, benzalkonium chloride as preservative, sodium hydroxide and hydrochloric acid as buffering agents, polyoxyl 35 castor oil as a solubilizer, and water for injection

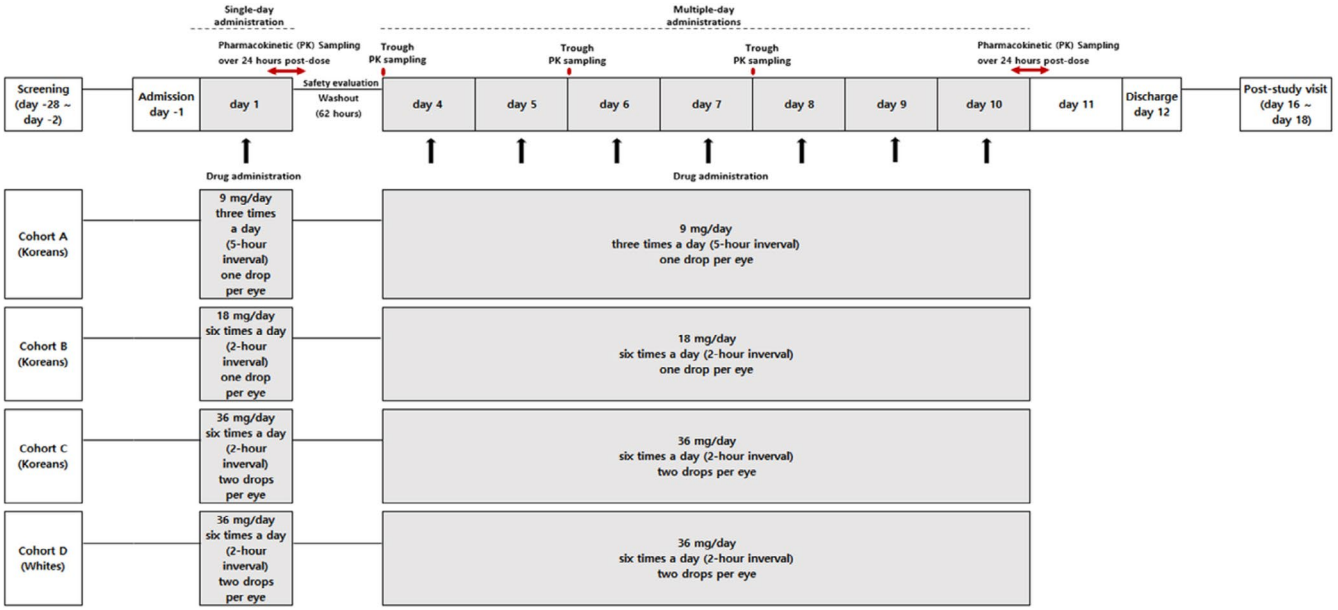

FIGURE 1 Flowchart of study

as solvents. The pH range is 6.0–8.0, and the osmotic pressure ratio is 0.9–1.1. The preclinical studies showed that GLH8NDE is not metabolized by the phase I or conjugation enzymes. Furthermore, GLH8NDE did not inhibit the enzymatic activity of the CYP 1A2, 2C9, 2C19, 2D6, or 3A4. All of the toxicological studies in animals reported no systemically significant adverse effects over the ranges of concentrations expected to be safe and effective in humans. Ocular topical GLH8NDE were tolerated up to 11% in rabbits. The concentration expected to be effective in humans from nonclinical potency was estimated to be around 3% (data on file).

Those preclinical results suggest that GLH8NDE could be developed as an effective treatment for DED. However, the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of ocular GLH8NDE in humans have not been previously investigated. Here, we report the findings of a phase I single- and multiple-day dose escalation study of GLH8NDE eye drops at 9–36 mg in healthy volunteers. In addition, we compared the systemic exposure to GLH8NDE between Koreans and Whites.

METHODS

Study subjects and design

A randomized, double-masked, placebo-controlled, escalating-dose phase I clinical trial was conducted. Men aged 20–50 years were eligible if they had no abnormalities in physical and ocular examinations. Subjects were excluded if their intraocular pressure (IOP) was greater than or equal to 22 mmHg, tear break-up time (TBUT) was less than or equal to 10 s, or unanesthetized Schirmer's test result was less than 10 mm.[22] Subjects with ocular disease, a history of ocular disease or surgery, or those using contact lenses were also excluded. Smoking was not allowed during the entire study.

Eligible subjects were admitted to the Clinical Trial Center at Seoul National University Hospital, Seoul, Republic of Korea, a day before study drug administration. Four cohorts of 10 subjects randomly received topical ocular dosing of GLH8NDE or its matching placebo (the same vehicle as GLH8NDE) as eye drops in a ratio of 8:2 at one of the following daily doses: 9 mg (cohort A), 18 mg (cohort B), 36 mg (Koreans, cohort C), and 36 mg (Whites, cohort D). Because the maximum strength of GLH8NDE eye drop solution was only 5% (1.5 mg/30 μl), it was given in divided doses that is, 3, 6, 6 (2 drops for each eye), and 6 (2 drops for each eye) times a day, with a 5-, 2-, 2-, and 2-h interval. A trained physician administered the study drug to subjects sitting with their heads bending backward. Subjects were required not to move for 3 min after drug administration. After a 62-h washout, multiple-day administrations began and continued for 7 consecutive days (Figure 1).

This study was approved by the institutional review board of Seoul National University Hospital (clinicaltrials.gov registration no.: NCT04104997) and was performed in full compliance with the Korean Good Clinical Practice and the principles of the Declaration of Helsinki. All the subjects provided written informed consent before participating in the study.

Tolerability evaluations

Systemic tolerability was assessed by physical examination, vital signs, 12-lead electrocardiogram (ECG), reporting of treatment-emergent adverse events (TEAEs) from the subjects, and clinical laboratory tests. TEAEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA version 23.0). Furthermore, ocular symptoms were evaluated for foreign body sensation, ocular dryness, burning or pain, photophobia, poor vision, and involuntary tearing (0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time).[23] Conjunctival hyperemia was also graded (0 = none/absence, 1 = mild, 2 = moderate and 3 = severe).[24] Other ocular examinations included best corrected visual acuity measured by Hancheonsuk's eye chart, anterior segment photograph, curvature of anterior segment, a dilated ophthalmoscopy, IOP, and slit lamp microscope.

Pharmacodynamic evaluation

TBUTs were measured on both eyes before (i.e., at screening) and after treatments (i.e., on days 2 and 11). A drop of 2% sodium fluorescein was instilled to the eye. Then, the subject blinked, and thereby a film was formed over the cornea. The subject was then asked not to blink during which time black or lines start to appear indicating dry spots. An ophthalmologist measured the interval between the last blink and the first dry spot was taken as TBUT using a stopwatch.

Bioanalytical assay

The plasma concentrations of GLH8NDE were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Eupatilin was used as the internal standard. The plasma samples were deproteinized using 90 μl of acetonitrile and 10 μl of 2 ng/ml eupatilin. A phenyl hexyl column (Luna Phenylhexyl, 2 × 100 mm, 3 μm) was used with a gradient mobile phase consisting of 0.1% formic acid in distilled water:acetonitrile (63:37 to 5:95, vol/vol) at a flow rate of 0.4 ml/min. An LC-MS/MS system was used in the positive ionization mode with electrospray and multiple reaction monitoring modes. Transition ions at *m/z* 382.2 to 371.1 and 345.1 to 330.1 were followed for GLH8NDE and eupatilin, respectively. The lower limit of quantification for GLH8NDE was 5 pg/ml. The intra- and inter-day accuracies were 93.8–101.8% and 96.7–100.5%, respectively. The calibration curves were linear in the range of 5–5000 pg/ml.

Pharmacokinetic evaluations

Serial blood samples were collected at 0 (predose), 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after the last dosing of single- and multiple-day administrations. Additionally, predose trough samples were collected on days 4, 6, and 8 to evaluate if steady-state was achieved. The observed values were used to decide the maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}). The area under the plasma concentration-time curve (AUC) from time zero to time of last measurable concentration (AUC_{last}) was calculated using the log-linear trapezoidal rule. AUC from time zero to infinity (AUC_{inf}) was the sum of AUC_{last} and C_{last}/λ_z, where C_{last} is the last measurable concentration, and λ_z is the terminal elimination rate constant determined by linear regression of the terminal portion (using >3 points) of the log-transformed plasma concentration-time curves. The terminal elimination half-life ($t_{1/2}$) was ln2 divided by λ_z. AUC measured up to 24 h (AUC_{0-24h}) and the ratio of exposure after the first to the last dose (accumulation ratio [R]) were determined only for multiple-day administrations. The Phoenix WinNonlin (version 8.0; Certara, Princeton, NJ, USA) was used to estimate PK parameters using a noncompartmental method.

Statistical analysis

No formal statistical sample size estimation was performed due to the exploratory nature of this study. Demographic and baseline characteristics, PK and PD parameters were summarized using descriptive statistics. The Kruskal-Wallis test was performed to compare demographic characteristics and PK parameters between cohorts. A binomial proportion test was conducted to compare the frequency of TEAEs between treatment groups (GLH8NDE vs. placebo). Differences in TBUT between before and after treatments were assessed using the Wilcoxon signed-rank test. A power model was fit using log-transformed C_{max} and AUC_{last} to decide if the C_{max} and AUC_{last} of GLH8NDE was dose-proportional. A p value of less than 0.05 was considered statistically significant. All the statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Subjects

A total of 40 male subjects were randomized, of whom 39 completed the study as planned. A subject in cohort C (Koreans, 36 mg/day) withdrew the consent after administration of the study drug. All of the subjects were healthy young men, and none of the demographic characteristics

showed a statistically significant difference among the cohorts (Table 1).

Tolerability evaluations

GLH8NDE was well-tolerated (Table 2). No serious adverse events (AEs) occurred during the study. Neither clinically significant changes nor abnormal findings were observed in physical examination, vital signs, 12-lead ECG, or clinical laboratory tests. A total of 17 subjects (13 and 4 in the GLH8NDE and placebo groups, respectively) experienced 31 TEAEs, all of which were mild in severity and recovered without sequelae.

Overall, the proportion of subjects experiencing TEAEs did not show a statistically significant difference between the GLH8NDE and placebo groups ($p = 0.7025$). Furthermore, the proportion of subjects experiencing TEAEs in the GLH8NDE groups did not increase in a dose-dependent manner; subjects in cohort A (i.e., the lowest GLH8NDE dose group reported the greatest number of TEAEs). No significant difference in the frequency and characteristics of TEAEs was noted between Koreans and Whites who received the same dose of GLH8NDE at 36 mg/day.

Most TEAEs were ophthalmic in origin. Conjunctival hyperemia was the most common TEAE across the entire cohorts, followed by eye irritation and abnormal sensation in the eyes. Headache was also frequently reported, although it was observed only in the lowest dose group of GLH8NDE (i.e., 9 mg/day).

Pharmacodynamic evaluation

GLH8NDE, particularly at 9 and 36 mg/day, increased TBUT from baseline in both eyes, although it did not reach statistical significance (Figure 2). In contrast, TBUT was consistently decreased in the placebo group (Figure 2).

Pharmacokinetic evaluations

GLH8NDE was rapidly absorbed after ocular administration with the peak concentration occurring in 0.25–0.75 h after single-day administration of GLH8NDE (Table 3). Several subjects showed greater than 1 peak of GLH8NDE concentrations (Figure 3). The PK parameters of GLH8NDE single-day administration increased in a dose-proportional manner. The slopes of a regression line (95% confidence interval [CI]) over the doses for C_{max} and AUC_{last} were 1.0381 (0.6180–1.4583) and 1.0459 (0.5691–1.5227), respectively. Dose-normalized C_{max} and AUC_{last} were not statistically different between doses over the range of 9–36 mg/day after single- and multiple-day administrations (Table 3). The systemic exposure to GLH8NDE as measured by AUC_{last} after single-day administration of the same dose was 109% higher in Koreans than in Whites ($p = 0.041$; Figure 3, Table 3). After multiple administrations, no accumulation was observed in all doses of GLH8NDE (Table 3). The steady-state of GLH8NDE was reached on day 7, which was 3 days after the multiple-day administrations started on day 4 (Figure S2).

DISCUSSION

Single and multiple ocular administrations of GLH8NDE at 9–36 mg/day were safe and well-tolerated in Koreans and Whites. Evidence is that all of the TEAEs were mild in severity, and the proportion of subjects experiencing TEAEs was comparable between the GLH8NDE

TABLE 1 Baseline characteristics of subjects

	Treatment						*p* value*
	GLH8NDE						
Characteristics	9 mg/day (*N* = 8)	18 mg/day (*N* = 8)	36 mg/day (*N* = 8)	36 mg/day (*N* = 8)	Placebo (*N* = 8)	Total (*N* = 40)	
Ethnicity							
Koreans, *n* (%)	8 (80.0)	8 (80.0)	8 (80.0)	–	6 (60.0)	30 (75.0)	
Whites, *n* (%)	–	–	–	8 (80.0)	2 (20.0)	10 (25.0)	
Age (years)	34.00 ± 6.19	32.00 ± 10.03	31.25 ± 9.07	29.38 ± 3.93	30.50 ± 6.65	31.43 ± 7.27	0.7835
Height (cm)	174.29 ± 4.59	171.98 ± 3.96	172.31 ± 4.53	176.43 ± 5.41	177.28 ± 6.83	174.46 ± 5.34	0.1833
Weight (kg)	73.11 ± 6.51	67.23 ± 9.71	67.24 ± 6.45	73.44 ± 10.71	76.05 ± 9.17	71.41 ± 8.98	0.3043
BMI (kg/m^2)	24.09 ± 2.27	22.69 ± 2.89	22.66 ± 2.28	23.51 ± 2.42	24.15 ± 1.78	23.42 ± 2.32	0.5499

Data are presented as the mean ± SD.

Abbreviation: BMI, body mass index.

*Kruskal-Wallis test.

TABLE 2 Summary of treatment emergent adverse events

System organ class *Preferred Term*	Treatment: GLH8NDE 9 mg/day (Koreans, *N* = 8)	GLH8NDE 18 mg/day (Koreans, *N* = 8)	GLH8NDE 36 mg/day (Koreans, *N* = 8)	GLH8NDE 36 mg/day (Whites, *N* = 8)	Placebo (Koreans, Whites, *N* = 8)	Total (*N* = 40)
Eye disorders						
Eye irritation	2 (25.0)				1 (12.5)	3 (7.5)
Conjunctival hyperemia	6 (75.0)	4 (50.0)		1 (12.5)	3 (37.5)	12 (30)
Abnormal sensation in eye	1 (12.5)	1 (12.5)			1 (12.5)	3 (7.5)
Ocular discomfort					1 (12.5)	1 (2.5)
Nervous system disorders						
Amnesia	1 (12.5)					1 (2.5)
Headache	4 (50.0)					4 (10.0)
Renal and urinary disorders						
Renal colic		1 (12.5)				1 (2.5)
Respiratory, thoracic and mediastinal disorders						
Rhinorrhea		1 (12.5)				1 (2.5)
Skin and subcutaneous tissue disorders						
Rash maculo-papular	2 (25.0)					2 (5.0)
Total number of subjects	7 (87.5)	5 (62.5)		1 (12.5)	4 (50.0)	17 (42.5)

Data are presented as the number of subjects (%).

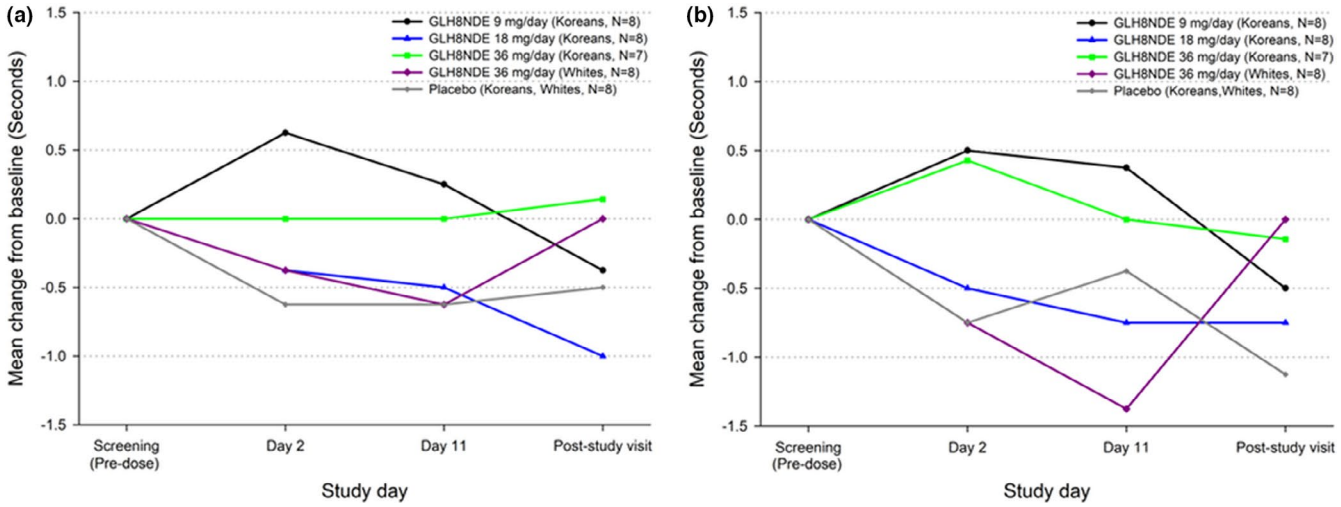

FIGURE 2 Mean tear break-up time by visit in right (a) and left (b) eyes. Day 2, 24 h after single-day administration; day 11, 24 h after the last multiple-day administrations

and placebo groups (Table 2). Furthermore, GLH8NDE at 9 and 36 mg/day showed an increasing tendency in TBUT from baseline (Figure 2) although the changes were within the normal range and failed to reach statistical significance. Ocular GLH8NDE was rapidly absorbed (Figure 3). It is worthy to note that the systemic exposure

TABLE 3 Summary of pharmacokinetic parameters of GLH8NDE

Parameter, single-day administration	GLH8NDE 9 mg/day (Koreans, *N* = 8)	GLH8NDE 18 mg/day (Koreans, *N* = 8)	GLH8NDE 36 mg/day (Koreans, *N* = 7)	GLH8NDE 36 mg/day (Whites, *N* = 8)	*p* value*
C_{max} (ng/L)	196.8 ± 37.0	468.1 ± 381.0	885.3 ± 370	663.8 ± 570	
C_{max}/dose (ng/L/mg)	21.9 ± 4.11	26.0 ± 21.2	24.6 ± 10.4	18.4 ± 15.9	0.9298
AUC_{last} (ng·h/L)	1215.6 ± 448.9	2660.2 ± 1893.5	6059.6 ± 4316.2	2902.4 ± 2186.8	
AUC_{last}/dose (ng·h/L/mg)	135.1 ± 49.9	147.8 ± 105.2	168.3 ± 119.9	80.6 ± 60.7	0.9028
AUC_{inf} (ng·h/L)	1393.7 ± 463.1	2845.1 ± 1914.3	6668.2 ± 4671.5	3516.3 ± 2318.1	
AUC_{inf}/dose(ng·h/L/mg)	154.9 ± 51.5	158.1 ± 106.4	185.2 ± 129.8	97.7 ± 64.4	0.8199
T_{max} (h)	0.25 [0.17–6.00]	0.50 [0.17–4.00]	0.75 [0.17–6.00]	0.33 [0.17–2.50]	
Parameter, multiple-day administration	**GLH8NDE 9 mg/day (Koreans, *N* = 8)**	**GLH8NDE 18 mg/day (Koreans, *N* = 8)**	**GLH8NDE 36 mg/day (Koreans, *N* = 7)**	**GLH8NDE 36 mg/day (Whites, *N* = 8)**	***p* value***
$C_{max,ss}$ (ng/L)	271.7 ± 117.9	579.4 ± 386.0	745.0 ± 261.0	544.4 ± 211.2	
$C_{max,ss}$/dose (ng/L/mg)	30.2 ± 13.1	32.2 ± 21.4	20.7 ± 7.25	15.1 ± 5.87	0.4228
$C_{min,ss}$ (ng/L)	33.0 ± 19.6	115.2 ± 112.1	68.2 ± 49.3	90.9 ± 76.1	
$AUC_{0\text{-}24h}$ (ng·h/L)	2040.4 ± 797.0	4720.6 ± 3508.0	5442.1 ± 2304.1	3876.0 ± 1879.4	
$T_{max,ss}$ (h)	0.77 [0.17–3.00]	0.47 [0.17–1.50]	0.85 [0.17–3.00]	1.75 [0.17–6.00]	
$t_{1/2,ss}$ (h)	9.79 ± 2.78	8.59 ± 3.44	8.30 ± 2.81	9.08 ± 4.50	
R	1.67 [0.93–2.69]	1.83 [0.78–2.62]	1.02 [0.51–2.01]	1.29 [0.93–6.15]	

AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; AUC_{inf}/dose, dose-normalized AUC_{inf}; $AUC_{0\text{-}24h}$, area under the concentration–time curve, determined over 24 h; AUC_{last}, area under the plasma concentration-time curve from zero until the last quantifiable time point; AUC_{last}/dose, dose-normalized AUC_{last}; C_{max}, maximum plasma concentration; C_{max}/dose, dose-normalized C_{max}; $C_{max,ss}$ maximum plasma concentration at steady-state; $C_{max,ss}$/dose, dose-normalized $C_{max,ss}$; T_{max}, time to reach C_{max}; $T_{max,ss}$, time to reach $C_{max,ss}$ at steady-state; $C_{min,ss}$ minimum plasma concentration at steady-state; R, accumulation ratio based on AUC measured up to 24 h; $t_{1/2,ss}$, elimination half-life at steady-state.

Data are presented as the mean ± SD except for T_{max} and *R*, for which the median and range are shown.

*Kruskal-Wallis test; analysis set, Koreans 9–36 mg/day.

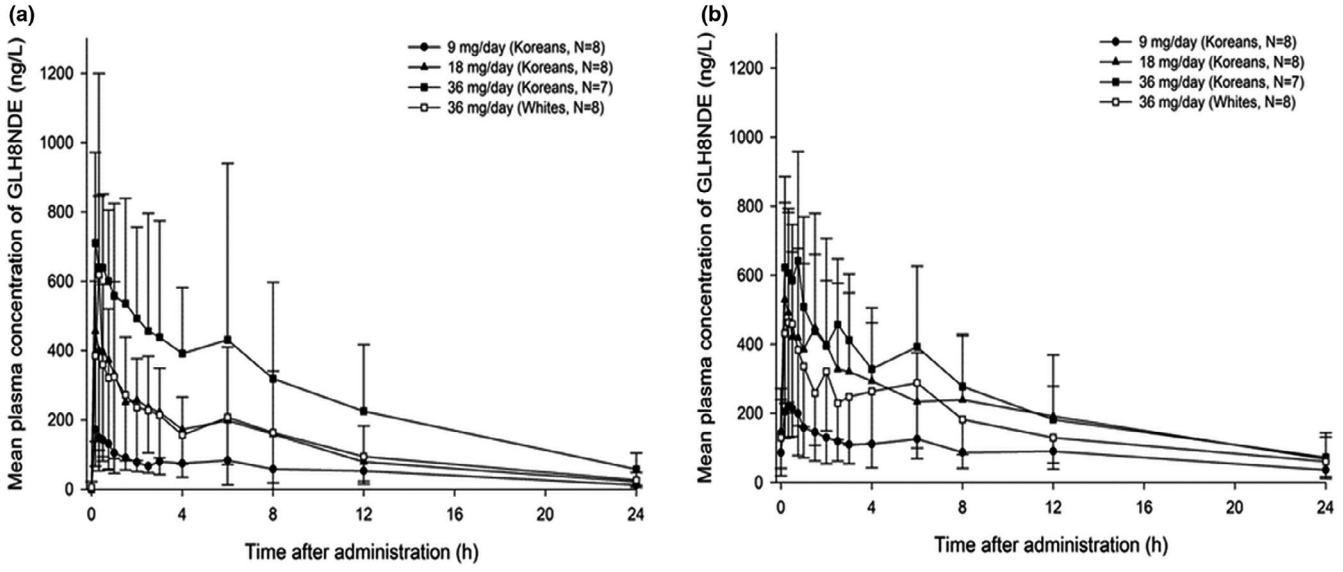

FIGURE 3 Mean plasma concentration-time profiles of GLH8NDE after a single-day (a) and multiple-day (b) administrations. The error bars denote the SDs

to GLH8NDE as measured by AUC_{last} after single-day administration of the same dose was 109% higher in Koreans than in Whites (Table 3).

TEAEs after administration of GLH8NDE, particularly ocular ones such as eye irritation and conjunctival hyperemia, were more frequently reported in its two lower dose groups (i.e., 9 and 18 mg/day), than in the highest dose group (Table 2). This result is difficult to explain by a specific mechanism, although we may postulate that the general air condition such as humidity was worse during the period when subjects in cohort A were confined to the Clinical Trial Center than during the other periods. Overall, however, the proportions of subject experiencing TEAEs were comparable between GLH8NDE and placebo. Future clinical trials are warranted to better investigate the tolerability profiles of GLH8NDE in humans and its concentration-dependent nature.

Multiple peaks were observed in the PK profile of GLH8NDE ~ 3 and 6 h after administration (Figure S1). Those multiple peaks were probably caused by the enterohepatic recirculation of GLH8NDE. In a preclinical study with rats, 36.5% of GLH8NDE were excreted from the bile after single i.v. injection. Assuming the excretory routes of GLH8NDE in humans are similar to those in rats, we hypothesize that those multiple peaks in the PK profiles of GLH8NDE may reflect its enterohepatic recirculation. Furthermore, when eye drops are administered into the eyes, several routes of absorption are possible. Absorption occurs initially through the cornea, conjunctiva, and nasal mucosa. On the other hand, up to 80% of the topically administered eye drops can spread across the hyper-vascularized nasopharyngeal mucosa and then move into the systemic circulation, which can also cause the delayed additional absorption presented by multiple peaks.[25–27]

The systemic exposure to GLH8NDE as measured by AUC_{last} after single-day administration of the same dose was 109% higher in Koreans than in Whites (Table 3). Genetic, physiological, and anatomic factors may explain the difference in the systemic exposure to GLH8NDE between the ethnic groups. We propose that anatomic differences might have resulted in the difference in the systemic exposure to GLH8NDE between Asians and Whites. Generally, Asians have higher epithelial permeability in the eyes by higher shear stress and shallower anterior chamber.[28–30] Higher epithelial permeability in Asians could lead to a lower volume of aqueous humor and, therefore, higher intraocular concentrations of GLH8NDE in Koreans. Furthermore, tear films are known to act as a barrier for instilled drugs causing reduced penetration of the drugs into intraocular tissues.[31] Asians are reported to have relatively instable tear films, which are likely to function as a weaker barrier on the ocular surface.[28] The weak barrier by lack of stability in tear films might allow more penetration of GLH8NDE into the eyes, causing the higher intraocular concentrations of GLH8NDE in Koreans. Higher intraocular concentrations of GLH8NDE may help its diffusion through several systemic absorption routes, such as local blood capillaries at cul-de-sac or nasal cavity, resulting in a higher exposure to GLH8NDE in Koreans than in Whites. In addition, Asians have more melanin distribution in the eyes than Whites.[32,33] Melanin pigments in the eyes can affect the PK of an ocular drug. For example, the transscleral delivery of celecoxib into the vitreous body and retina was significantly lower in pigmented rats than in nonpigmented rats, which was hypothesized by the binding of celecoxib to melanin.[34–36] Therefore, we postulate that the lower transscleral delivery of GLH8NDE in Koreans than in Whites could lead to more drug to be absorbed systemically, resulting in higher exposure to GLH8NDE in Koreans than in Whites.

This study had a couple of limitations. Application of our results to patients with DED might be limited because this study was conducted in healthy subjects. Because patients with DED have different eye conditions and sensitivity than healthy subjects, the ophthalmic tolerability of GLH8NDE shown in this study may not be fully extrapolated to patients with DED.[37] However, given the relatively low absorption of GLH8NDE,[14] the systemic tolerability concern may be minimal. Furthermore, given that only healthy subjects were enrolled, this study was limited in showing any difference between GLH8NDE and placebo in TBUT's change from baseline. In this sense, it was still interesting to note that a couple of GLH8NDE doses numerically increased TBUT from baseline in both eyes, whereas placebo-treated subjects consistently did not show any change in TBUT from baseline. The sample size was also small. Another limitation of this study was the information on iris color was not available. The PK profile of an ophthalmic drug could be affected by eye pigments.[34,35] The effect of eye pigments or iris color on the PK of GLH8NDE should be investigated in future studies. Nevertheless, this study provides a potential for GLH8NDE that could be further developed as a useful treatment option for patients with DED. Identifying a possible ethnic sensitivity in exposure to GLH8NDE is another important finding out of this study.

In conclusion, GLH8NDE was safe and well-tolerated in healthy Korean and White male adults over the dose range of 9–36 mg per day after single- and multiple-day administrations. GLH8NDE was absorbed fast after ocular administration. The systemic exposure to GLH8NDE as measured by AUC_{last} after single-day administration of the same dose was 109% higher in Koreans compared to Whites. Further clinical development for GLH8NDE is warranted.

CONFLICT OF INTEREST

J.S.P. and E.K. are employees of GL PharmTech Corporation. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.J. and H.L. wrote the manuscript. X.J. and H.L. designed the research. J.J., X.J., K.Y.H., I.J., A.H., K.H.P., and H.L. performed the research. J.J., K.Y.H., J.S.P., E.K., J.L., and H.L. analyzed data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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