

## ARTICLE

# Safety, tolerability, and pharmacokinetics of single and multiple topical ophthalmic administration of imatinib mesylate in healthy subjects

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## Abstract

For the long-term efficacy of dry eye disease treatment, relieving underlying inflammation is necessary. Imatinib mesylate is a novel ophthalmic formulation of imatinib mesylate, which is expected to alleviate inflammation by inhibiting the discoidin domain receptor 1 activity. This study aims to evaluate the safety and pharmacokinetics of imatinib mesylate in healthy subjects. A randomized, double-blind, placebo-controlled study was conducted. In a single ascending dose, 16 subjects received a single eye drop of imatinib mesylate 0.1%, 0.3%, or matching placebo. In the multiple ascending dose (MAD), subjects received multiple eye drops of imatinib mesylate 0.1%, 0.3%, or matching placebo once daily for 7 days. Safety and tolerability were assessed by ophthalmic examination, including the visual analog scale (VAS) to monitor the burning sensation in the eyes. A total of four treatment-emergent adverse events (TEAEs) occurred during the study. All TEAEs were mildly severe with no serious cases. VAS results in the 0.1% MAD group exhibited highest score of two points, whereas it was less than one point in others. Insignificant difference between the imatinib mesylate and placebo groups in the VAS results was seen. After a single dose administration of imatinib mesylate 0.1%, all plasma concentrations were below the lower limit of quantification. The peak plasma concentrations of imatinib were less than 0.54 µg/L in all groups. In conclusion, a single and multiple topical ophthalmic administration of imatinib mesylate was well-tolerated in healthy subjects. Because there was minimal systemic exposure to imatinib, the adverse effect in the body seems to be insignificant.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Given that managing chronic inflammation is crucial in dry eye disease, anti-inflammatory agents are the mainstay of treatment.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

What is the safety, tolerability, and pharmacokinetic profiles of AVI-4015, a novel ophthalmic formulation of imatinib mesylate, in healthy subjects?

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

A single and multiple topical ophthalmic administration of imatinib mesylate were well-tolerated up to 0.3% in healthy subjects, and the systemic exposure of imatinib mesylate was negligible compared to the oral formulation of imatinib.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

This study provides safety and pharmacokinetic information about imatinib mesylate, which will be used for further trial for the treatment of dry eye disease.

## INTRODUCTION

Dry eye disease is a common disorder characterized by ocular fatigue, redness, stinging, or burning sensation in the eyes.<sup>1</sup> Dry eye disease can disrupt everyday activities, leading to poor quality of life.<sup>2</sup> The global prevalence of dry eye disease is estimated to be 5–50%, posing a considerable public health concern.<sup>3</sup> The tear instabilities caused during the disease progression increase tear osmolality and activate stress signaling pathways in the ocular surface epithelium and resident immune cells. During this process, innate inflammatory mediators, such as interleukin 1 $\beta$ , tumor necrosis factor alpha, IL-6, and matrix metalloproteinases-3, cause a further decline in tear function.<sup>4</sup>

Because managing chronic inflammation is crucial in dry eye disease, the mainstay of treatment is anti-inflammatory agents. Replenishing tears are effective only in the early stage, which can just alleviate symptoms.<sup>5</sup> To this date, various anti-inflammatory agents (e.g., corticosteroids, cyclosporin A, lifitegrast, tetracyclines, and autologous serum) have been prescribed for disease-modifying potential.<sup>6–8</sup> However, high treatment failure rate due to intolerance to the medication or lack of efficacy in relieving ocular symptoms has been reported with the agents.<sup>9</sup> Furthermore, only cyclosporin A and lifitegrast have been approved by the US Food and Drug Administration (FDA) for the treatment of dry eye disease, which demands novel treatment options.<sup>10,11</sup>

Discoidin domain receptor 1 (DDR1) is a novel target of dry eye disease. DDR1 is present in inflammatory cells and corneal epithelial cells and induces cell proliferation and migration.<sup>12</sup> In this regard, inhibition of DDR1 can prevent disease progression to dry eye diseases. Imatinib mesylate, a tyrosine kinase inhibitor, was identified as a potent inhibitor of DDR1 with a half-maximal inhibitory concentration (IC<sub>50</sub>) value of 41 nM.<sup>13–16</sup>

In a preclinical study, topical application of imatinib substantially reduced damage to the ocular surface compared to the control group. Furthermore, imatinib

mesylate reduced the accumulation of inflammatory cells in the corneal epithelium and restored the structure of the conjunctival epithelium, indicating similar or better efficacy than cyclosporine treatment.<sup>17</sup> This study showed the therapeutic potential of imatinib as a treatment for dry eye disease.

Imatinib mesylate was originally approved for the treatment of chronic myeloid leukemia and was used for wider disease subtypes. Although numerous safety data of imatinib for other indications exists currently, no safety data for imatinib as an eye drop is reported.<sup>18(p),19–21</sup> Therefore, in the current study, we aim to evaluate the safety and tolerability, especially for systemic side effects, and pharmacokinetics of a novel ophthalmic formulation of imatinib mesylate in healthy subjects. To our knowledge, this is the first study to administer imatinib mesylate as an ophthalmic formulation in human subjects.

## METHODS

### Subjects

Healthy Korean subjects aged 19–50 years with a body mass index of 18.5–30 kg/m<sup>2</sup> were enrolled. All subjects were confirmed to be healthy based on their medical history, physical and ophthalmologic examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects with a history of or suspected symptoms or diseases of the visual organ were not eligible for the study. Additionally, subjects with corrected vision under 20/40 of Snellen fraction at the screening visit, who underwent ophthalmic surgery, or who started wearing contact lenses within a month before screening were also not eligible.

Written consent was obtained from all the subjects prior to any study-related procedures. This study was performed in accordance with the Declaration of Helsinki and the

Good Clinical Practice guidelines. The study protocol was approved by the Ministry of Food and Drug Safety and the Institutional Review Board of Seoul National University Bundang Hospital (IRB no. B-1911-574-001) and was registered with the Clinical Research Information Service in Korea (KCT0005175).

## Study design

This was a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study (Figure 1). In the SAD cohort, subjects received a single dose of imatinib mesylate in 0.1% and 0.3% eye drops or matching placebo at a ratio of 3:1 once in both eyes. Whereas in the MAD cohort, subjects received multiple doses of imatinib mesylate in 0.1% and 0.3% eye drops or matching placebo at a ratio of 3:1 twice a day for 7 days in both eyes. Blood pharmacokinetic (PK) samples were collected at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 h postdose in the SAD group. Whereas in the MAD group, PK samples were collected at predose on days 1 and 4, and serial samples were taken at the same timepoints as in the SAD group on day 7. Escalation to the next dose level (imatinib mesylate 0.1% to 0.3%) in each group was conducted after the review of blinded safety data until the visit by the safety monitoring committee for safety follow-up.

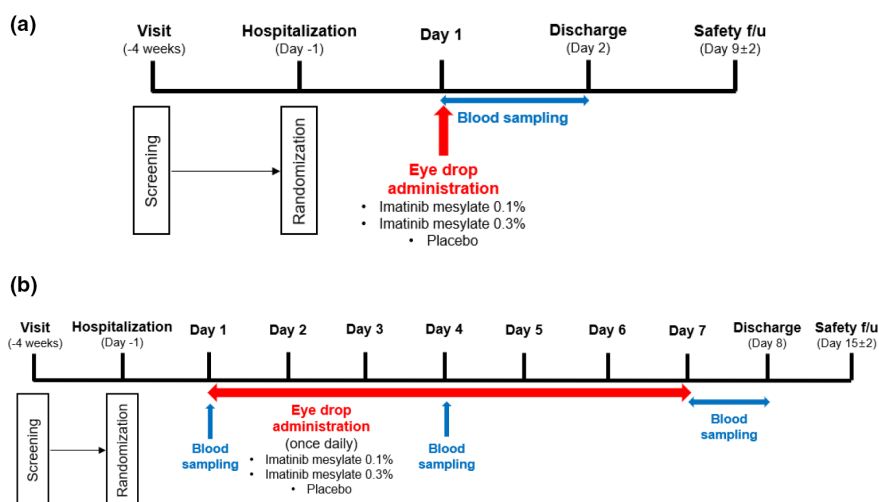
## Safety and tolerability assessment

Safety was evaluated by vital signs, 12-lead ECG, clinical laboratory tests, and physical and ophthalmologic examinations. Ophthalmologic examination included intraocular pressure examination, fundus examination, and slit-lamp microscope examination. In addition, local

irritation and eye congestion were evaluated for each subject using a Likert scale for ophthalmic symptoms. The visual analog scale (VAS) for burning sensation (0: no burning sensation, 10: extreme burning sensation) was evaluated at 0 (predose), 1, 4, 12, and 24 h postdose on day 1, and on follow-up visit in the SAD cohort. In the MAD cohort, VASs were evaluated at 0 (predose), 12, and 24 h postdose on day 1; 0 h (predose) on day 3 and day 5; 0 (predose), 1, 4, 12, and 24 h postdose on day 7; and on the safety follow-up visit (Figure 1).

## Determination of imatinib concentrations

Plasma concentrations of imatinib were determined by high-performance liquid chromatography (ExionLC, AB Sciex, Framingham, MA) and a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS; Triple Quad 5500+; AB Sciex). For sample preparation, 50  $\mu$ l of plasma samples along with 10  $\mu$ l of internal standard (imatinib-d8, 20 ng/ml in 50% acetonitrile) were added to a tube. After adding 1.25 ml of tert-butyl methyl ether, the tube was vortexed for 10 min. The samples were then centrifuged for 5 min at 15,000  $\times$  g at 4°C, and the supernatant was transferred to a new 2 ml tube and solidified with nitrogen gas at 40°C. After mixing the sample with 100  $\mu$ l of 50% acetonitrile, the samples were centrifuged for 5 min at 15,000  $\times$  g, and 2  $\mu$ l of the organic layer was harvested and injected into the LC-MS/MS system after filtration. An analytical column Hecor-A C18 (150\*2.1 mm, 3  $\mu$ m) was used as a stationary phase, and the mobile phase consisted of 0.1% formic acid in 10 mM ammonium acetate and 100% acetonitrile under the gradient condition with a flow rate of 0.3 ml/min. In a multiple reaction monitoring mode, the concentrations of imatinib were determined by computing the peak-area ratios of imatinib to imatinib-d8



**FIGURE 1** Overall study design. (a) Single ascending dose (SAD) and (b) multiple ascending dose (MAD). f/u, follow-up

( $m/z$ : 494.2  $\rightarrow$  394.3 for imatinib,  $m/z$ : 502.3  $\rightarrow$  394.3 for imatinib-d8). The linear calibration curves were established between 0.1 and 10 ng/ml of concentration range, and the correlation coefficient ( $r$ ) of the calibration curve was greater than or equal to 0.9976. The lower limit of quantification for imatinib was 0.1 ng/ml.

## Pharmacokinetic analysis

WinNonlin software version 8.1.1 (Certara, Mountain View, CA, USA) was used for the PK analysis. The PK parameters were calculated using noncompartmental methods. For the areas under the concentration-time curves, the linear trapezoidal summation was used for the ascending concentrations and the log trapezoidal summation was used for the descending concentrations from 0 h to the last measurable time point ( $AUC_{last}$ ) and was extrapolated to infinity ( $AUC_{inf}$ ) using the terminal elimination rate constant obtained by linear regression ( $\lambda_z$ ). After multiple administrations, the area under the plasma concentration-time curve over a dosing interval of 12 h at steady state ( $AUC_{tau,ss}$ ) was calculated. The maximum plasma concentration ( $C_{max}$ ) and time to reach  $C_{max}$  ( $T_{max}$ ) were determined from the observational data. The terminal elimination half-life ( $t_{1/2}$ ) was calculated as the natural logarithm of 2 divided by  $\lambda_z$ . The accumulation ratio (R) was calculated as the mean value of  $AUC_{last}$  on day 7 in the MAD group divided by the mean value of  $AUC_{last}$  on day 1 in the SAD group. For calculating dose-normalized parameters, the imatinib mesylate 0.1% dose group was set to 0.04 mg and 0.3% dose group was set to 0.12 mg, considering the dose contained in one drop ( $\sim 40 \mu\text{l}$ ).

## Statistical analysis

SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for the statistical analysis. For the comparison of dose-normalized parameters by dose group, the Mann-Whitney  $U$  test was used, and statistical significance was defined at  $p$  less than 0.05.

## RESULTS

### Subjects

A total of 32 subjects (6 subjects each in the imatinib mesylate 0.1% and 0.3% groups of SAD and MAD cohorts, and 4 subjects in the placebo group in both the SAD and MAD cohorts) were enrolled and completed the study. There were no statistically significant differences in the baseline

demographics and characteristics among the treatment groups (Table 1).

## Safety and tolerability

There were four treatment-emergent adverse events (TEAEs) reported in four subjects. In the SAD group, one TEAE was observed in one subject, whereas in the MAD group, three TEAEs were reported in three subjects (Table 2). The TEAE (arthralgia) that occurred in the SAD cohort was not related to the drug as defined, and the other three TEAEs (neck pain, contusion, and headache) in the MADs were defined as adverse drug reactions. All TEAEs were mild in severity and recovered without any sequelae, and no serious adverse events occurred during the study. No clinically significant changes were observed in clinical laboratory tests, physical examinations, vital signs, and 12-lead ECG results.

There was no significant difference between the imatinib mesylate and placebo groups for both the SAD and MAD groups in ophthalmic examinations. Among the 16 subjects of the SAD group, one subject in the imatinib mesylate 0.1% group responded with a “dry eye symptom” for both eyes receiving one point (some of the time) at day 2, and one subject in the placebo group responded with a “stinging sensation” in the right eye again receiving one point. Both symptoms disappeared at later timepoints. In the MAD group, one subject in the placebo group responded with a “dry eye symptom” for both eyes receiving two points (half of the time) at day 15, and on day 7, one subject in the imatinib mesylate 0.1% group responded with a “blurred vision” symptom for both eyes receiving one point. Both symptoms disappeared at later timepoints. In both the SAD and MAD groups, none of the subjects showed ocular hyperemia in either eye.

As for the intensity of the burning sensation of the eyes evaluated by VAS in the SAD cohort, only two subjects in the imatinib mesylate 0.3% group had a burning sensation of 0.2 points and one point on day 1, and there was no reported burning sensation in the imatinib mesylate 0.1% and placebo groups. In the MAD group, two subjects in the imatinib mesylate 0.1% group, one subject in the imatinib mesylate 0.3% group, and two subjects in the placebo group had symptoms of burning sensation in their eyes. However, most of the burning sensation was within one point and did not last more than 1 day, and only one subject in the imatinib mesylate 0.1% group had two points of burning sensation on day 15 (Table 3).

## Pharmacokinetics

Plasma imatinib concentration was not detected after a single eye drop containing imatinib mesylate 0.1% (Table 4).

**TABLE 1** Demographic and baseline characteristics in SAD study and MAD study

		<b>Imatinib mesylate 0.1%</b> (N = 6)	<b>Imatinib mesylate 0.3%</b> (N = 6)	<b>Placebo (N = 4)</b>
Single	Age, year	28.8 ± 3.9	25.2 ± 4.4	22.5 ± 1.3
	Male (N, %)	6 (100)	6 (100)	4 (100)
	Height, cm	174.2 ± 4.9	169.6 ± 5.3	172.6 ± 4.2
	Weight, kg	68.9 ± 7.3	68.9 ± 5.1	70.7 ± 7.1
	BMI, kg/m <sup>2</sup>	22.7 ± 1.8	24.0 ± 1.7	23.8 ± 3.4
	Visual acuity, left eye	1.5 ± 0.3	1.5 ± 0.1	1.2 ± 0.2
	Visual acuity, right eye	1.5 ± 0.4	1.3 ± 0.3	1.3 ± 0.3
Multiple	Age, year	29.2 ± 9.9	37.5 ± 5.1	31.8 ± 6.4
	Male (N, %)	6 (100)	6 (100)	4 (100)
	Height, cm	170.9 ± 5.8	172.8 ± 6.9	178.0 ± 1.5
	Weight, kg	66.7 ± 7.3	71.9 ± 8.0	76.0 ± 8.8
	BMI, kg/m <sup>2</sup>	22.8 ± 2.1	24.2 ± 3.7	24.0 ± 2.8
	Visual acuity, left eye	1.2 ± 0.2	1.3 ± 0.3	1.4 ± 0.3
	Visual acuity, right eye	1.3 ± 0.2	1.4 ± 0.2	1.4 ± 0.3

Note: Data are shown as mean ± standard deviation.

Abbreviations: BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose.

**TABLE 2** Summary of the adverse events after single or multiple eye drop administrations of Imatinib mesylate

		<b>Imatinib mesylate 0.1%</b> (N = 6)	<b>Imatinib mesylate 0.3%</b> (N = 6)	<b>Placebo (N = 4)</b>
Single	<b>Musculoskeletal and connective tissue disorders</b>			
	Arthralgia		1 (16.67)	
Multiple	<b>Injury, poisoning, and procedural complications</b>			
	Contusion		1 (16.67)	
	<b>Musculoskeletal and connective tissue disorders</b>			
	Neck pain	1 (16.67)		
	<b>Nervous system disorders</b>			
	Headache			1 (25.0)

Note: Values are presented as number of subjects (percentage of subjects).

The bold values represent 'System Organ Class (SOC)', and the non-bold values represent 'Preferred Term (PT)' of the adverse events.

The mean concentration-time profiles of imatinib mesylate were similar between after a single administration of 0.3% and multiple administrations of 0.1% and 0.3% (Figure 2). Imatinib was absorbed within 1.25 h, reaching  $C_{max}$  of 0.30 µg/L after a single eye drop of imatinib mesylate 0.3%. Imatinib was eliminated with a  $t_{1/2}$  of ~13 h. Imatinib accumulated up to three-fold after multiple administrations for 7 days. The  $T_{max}$  was shortened to less than 1 h at a steady state. Mean  $t_{1/2}$  ranged from 9.1 to 15.5 h, comparable to that after a single eye drop (Table 4). Dose-normalized  $C_{max}$  and  $AUC_{tau}$  did not show a statistically significant difference between the administration groups in the MAD group.

## DISCUSSION

The study showed that imatinib mesylate was well-tolerated up to 0.3% in healthy subjects. Only mild and transient burning sensations were reported after both single and multiple administrations. Ocular hyperemia was not observed in any patient.

The dose strength of imatinib mesylate, in this study, was determined based on preclinical toxicological and pharmacological results. In the dry eye rabbit model, no observed adverse effect level was reported for 3 mg/ml of imatinib mesylate 0.3% administered four times/day. Pharmacologically active dosage for imatinib mesylate

**TABLE 3** Visual analog scale for burning sensation after single or multiple eye drop administrations of imatinib mesylate

		Imatinib mesylate 0.1% (N = 6)	Imatinib mesylate 0.3% (N = 6)	Placebo (N = 4)
Single	Day 1: 0 h, postdose <sup>a</sup>	0.00 ± 0.00	0.40 ± 0.20	0.00 ± 0.00
Multiple	Day 1: 0 h, postdose <sup>a</sup>	0.17 ± 0.41	0.17 ± 0.41	0.25 ± 0.50
	Day 1: 12 h	0.00 ± 0.00	0.17 ± 0.41	0.00 ± 0.00
	Day 2: 0 h, postdose <sup>a</sup>	0.00 ± 0.00	0.00 ± 0.00	0.23 ± 0.45
	Day 3: 0 h, postdose <sup>a</sup>	0.17 ± 0.41	0.00 ± 0.00	0.25 ± 0.50
	Day 15	0.33 ± 0.82	0.00 ± 0.00	0.00 ± 0.00

Note: Data are shown as mean ± standard deviation.

<sup>a</sup>The 0 h (post-dose) means immediately after eye drop administration.

	Parameter	Imatinib mesylate 0.1% (N = 6)	Imatinib mesylate 0.3% (N = 6)
Single	T <sub>max</sub> , h		1.25 [0.25–2.00]
	C <sub>max</sub> , µg/L		0.30 ± 0.20
	AUC <sub>last</sub> , h·µg/L		2.39 ± 2.94
	AUC <sub>inf</sub> , h·µg/L		5.05 ± 3.73
	t <sub>1/2</sub> , h		12.98 ± 10.68
	CL/F, L/h		34.61 ± 25.76
Multiple	T <sub>max</sub> , h	0.50 [0.25–1.00]	0.38 [0.25–1.00]
	C <sub>max,ss</sub> , µg/L	0.20 ± 0.02	0.50 ± 0.09
	AUC <sub>tau,ss</sub> , h·µg/L	1.60 ± 0.59	4.47 ± 0.88
	t <sub>1/2,ss</sub> , h	9.12 ± 3.33	15.48 ± 5.09
	CL <sub>ss</sub> /F, L/h	27.21 ± 9.13	27.83 ± 6.00
	R <sup>a</sup>		2.93

**TABLE 4** Pharmacokinetic parameters of imatinib mesylate after a single or multiple eye drop administration

Note: Data are shown as mean ± standard deviation, except for T<sub>max</sub>, which is shown as median [minimum–maximum].

Abbreviations: AUC<sub>inf</sub>, area under the plasma concentration-time curve from 0 h to infinity; AUC<sub>last</sub>, area under the plasma concentration-time curve from 0 h to the last measurable time point; AUC<sub>tau,ss</sub>, area under the plasma concentration-time curve for a dosing interval at steady state; CL/F, apparent clearance; CL<sub>ss</sub>/F, apparent clearance at steady state; C<sub>max</sub>, maximal plasma concentration; C<sub>max,ss</sub>, maximal plasma concentration at steady state; R, accumulation ratio; t<sub>1/2</sub>, elimination half-life after a single dose; t<sub>1/2,ss</sub>, elimination half-life at steady state; T<sub>max</sub>, time for maximal plasma concentration.

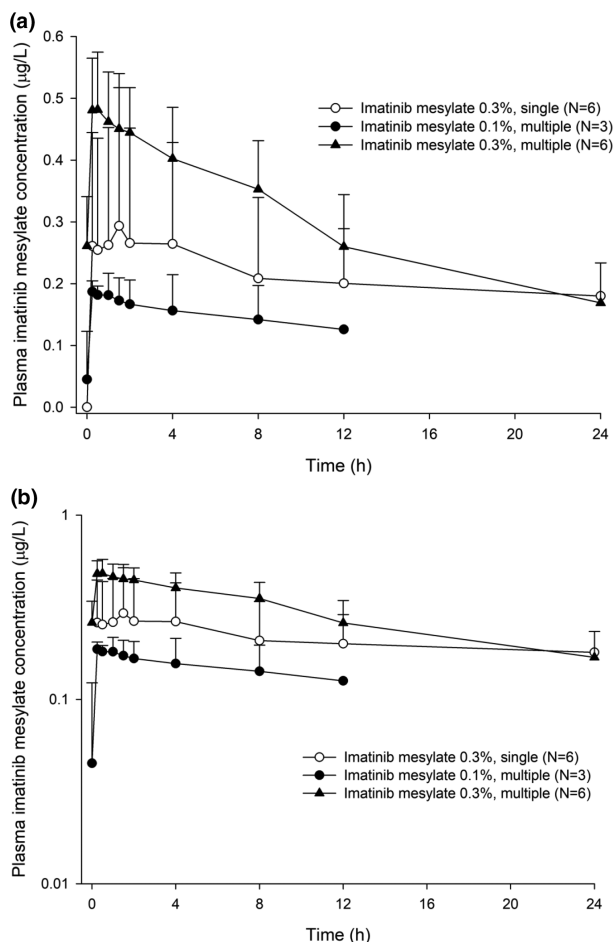
<sup>a</sup>R was calculated as the mean AUC<sub>last</sub> on day 7 divided by the AUC<sub>last</sub> on day 1.

was 0.01% twice a day in a dry keratoconjunctivitis rat model, and 0.1% of imatinib mesylate showed similar efficacy when compared to 0.05% cyclosporin A as a positive control.<sup>17</sup> With these results, clinical doses were set at 0.1% and 0.3% once daily, which is higher than the 0.01% twice daily dose that showed efficacy with no problem in the toxicity test of the preclinical study.

The low incidence of systemic side effects was associated with low systemic exposure to imatinib mesylate. Plasma imatinib concentration was not detected after administration of a single eye drop of imatinib mesylate 0.1% and concentrations were less than 0.3 µg/L of imatinib

mesylate 0.3%. The C<sub>max</sub> was not significantly higher after multiple eye drops (~ 0.5 µg/L) compared to after a single eye drop. Imatinib mesylate accumulated up to three-fold and was eliminated similarly after single and multiple eye drops.

Considering the IC<sub>50</sub> value of imatinib on tumor cells (49.4–296.2 µg/L), the systemic exposure after eye drops was not likely to cause systemic effects.<sup>22,23</sup> The highest exposure after eye drop administration was 0.5 µg/L in the 0.3% MAD group, definitely lower than the systemic IC<sub>50</sub>. In addition, the highest AUC<sub>last</sub> reported in our study was 7.0 µg·h/L, which was clearly lower than



**FIGURE 2** Mean concentration-time profiles of imatinib mesylate after single or multiple administrations. (a) Linear scale and (b) semi-log scale. Error bars denote standard deviation. Concentration data for imatinib mesylate 0.1% cohort was excluded from the figure as no measurable concentration was detected

the tolerable range (20 000–32 640 µg·h/L) in healthy volunteers and patients with chronic myeloid leukemia after oral doses of imatinib.<sup>24,25</sup> Based on these results, the systemic bioavailability of imatinib mesylate as eye drop administration would be negligible compared to oral formulations.

After the administration of imatinib mesylate as ophthalmic formulation, the maximum value of burning sensation as assessed by VAS was two points. This was a very low value compared to the previous ophthalmic formulation study conducted on healthy adults.<sup>26</sup>

This study is a phase I clinical trial conducted in a small number of healthy subjects with a limited dose range that could not be evaluated. The efficacy and safety in patients with dry eye should be further investigated.

In conclusion, a single and multiple topical ophthalmic administration of imatinib mesylate was well-tolerated up to 0.3% in healthy subjects, and the systemic exposure to imatinib mesylate as ophthalmic formulation was negligible compared to the oral formulation of imatinib.

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## CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

## AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. H.C.K., J.H.L., J.C.Y., and J.Y.C. designed the research. J.Y.N. and J.Y.C., performed the research. J.Y.N., K.Y.H., and J.Y.C. analyzed the data.

## REFERENCES

1. Belmonte C, Nichols JJ, Cox SM, et al. TFOS DEWS II pain and sensation report. *Ocul Surf.* 2017;15(3):404-437.
2. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol vis Sci.* 2012;53(9):5722-5727.
3. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf.* 2017;15(3):334-365.
4. Pflugfelder SC, de Paiva CS. The pathophysiology of dry eye disease: what we know and future directions for research. *Ophthalmology.* 2017;124(11S):S4-S13.
5. Yagci A, Gurdal C. The role and treatment of inflammation in dry eye disease. *Int Ophthalmol.* 2014;34(6):1291-1301.
6. Findlay Q, Reid K. Dry eye disease: when to treat and when to refer. *Aust Prescr.* 2018;41(5):160-163.
7. Pflugfelder SC. Anti-inflammatory therapy of dry eye. *Ocul Surf.* 2003;1(1):31-36.
8. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628.
9. Williamson JF, Huynh K, Weaver MA, Davis RM. Perceptions of dry eye disease management in current clinical practice. *Eye Contact Lens.* 2014;40(2):111-115.
10. FDA drug label\_Xiidra (lifitegrast ophthalmic solution) [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/208073s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208073s000lbl.pdf). Accessed May 7, 2021.
11. FDA drug label\_Restasis (cyclosporine) [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/050790s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050790s020lbl.pdf). Accessed May 7, 2021.
12. Vogel WF, Abdulhussein R, Ford CE. Sensing extracellular matrix: An update on discoidin domain receptor function. *Cell Signal.* 2006;18(8):1108-1116.
13. Canning P, Tan L, Chu K, Lee SW, Gray NS, Bullock AN. Structural mechanisms determining inhibition of the collagen receptor DDR1 by selective and multi-targeted type II kinase inhibitors. *J Mol Biol.* 2014;426(13):2457-2470.
14. Borza CM, Pozzi A. Discoidin domain receptors in disease. *Matrix Biol.* 2014;34:185-192.
15. Mohan RR, Mohan RR, Wilson SE. Discoidin domain receptor (DDR) 1 and 2: collagen-activated tyrosine kinase receptors in the cornea. *Exp Eye Res.* 2001;72(1):87-92.
16. Azizi G, Mirshafiey A. Imatinib mesylate: an innovation in treatment of autoimmune diseases. *Recent Pat Inflamm Allergy Drug Discov.* 2013;7(3):259-267.
17. Baek YY, Sung B, Choi JS, et al. In Vivo Efficacy of Imatinib Mesylate, a Tyrosine Kinase Inhibitor, in the Treatment of

- Chemically Induced Dry Eye in Animal Models. *Transl vis Sci Technol.* 2021;10(11):14.
18. El Bairi K, Trapani D, Petrillo A, et al. Repurposing anticancer drugs for the management of COVID-19. *Eur J Cancer.* 2020;141:40-61.
  19. Rizzo AN, Aman J, van Nieuw Amerongen GP, Dudek SM. Targeting Abl kinases to regulate vascular leak during sepsis and acute respiratory distress syndrome. *Arterioscler Thromb Vasc Biol.* 2015;35(5):1071-1079.
  20. Wahlgren N, Thorén M, Höjeberg B, et al. Randomized assessment of imatinib in patients with acute ischaemic stroke treated with intravenous thrombolysis. *J Intern Med.* 2017;281(3):273-283.
  21. Eklund KK, Joensuu H. Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases. *Ann Med.* 2003;35(5):362-367.
  22. Yao JC, Zhang JX, Rashid A, et al. Clinical and in vitro studies of imatinib in advanced carcinoid tumors. *Clin Cancer Res.* 2007;13(1):234-240.
  23. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Ziegler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood.* 2000;96(3):925-932.
  24. Peng B, Dutreix C, Mehring G, et al. Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol.* 2004;44(2):158-162.
  25. Peng B, Hayes M, Resta D, et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. *J Clin Oncol.* 2004;22(5):935-942.
  26. Benitez-Del-Castillo JM, Moreno-Montañés J, Jiménez-Alfaro I, et al. Safety and efficacy clinical trials for SYL1001, a novel short interfering RNA for the treatment of dry eye disease. *Invest Ophthalmol Vis Sci.* 2016;57(14):6447-6454.

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