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ORIGINAL RESEARCH

Pharmacokinetics and Safety of a Bilastine Once-Daily, Preservative-Free, Ophthalmic Formulation

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ABSTRACT

Introduction: Bilastine is a second-generation H_1 antihistamine indicated for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. On the basis of the demonstrated efficacy and safety of the oral formulation, a new ophthalmic formulation of bilastine was recently developed. Previous preclinical studies had indicated that bilastine is mainly absorbed by the conjunctiva and shows low plasma concentration. The objective of this study was to evaluate the pharmacokinetics and safety of ophthalmic bilastine (6 mg/mL) after single and multiple dose administration at steady state in healthy adults.

Methods: This was an open-label, single-centre, phase I, bioavailability clinical trial. One drop of the bilastine ophthalmic formulation was administered once daily in each eye of the subjects for 5 days. Bilastine plasma concentrations were measured by HPLC–MS/MS. Adverse drug reactions were recorded for each subject during drug administration and follow-up visits.

Results: Twelve healthy subjects (age 18–55 years) were included in the study. After multiple dose administration, bilastine reached a mean (± SD) maximum blood concentrations of 2682.26 ± 1615.88 pg/mL at a median time of 2.50 h (range 1.25–4.00 h). The half-life of bilastine in plasma was 7.88 ± 6.72 h. Steady state AUC was 19,512.51 ± 9248.76 h·pg/mL. Adverse events were mild and transient, consisting mainly of dysgeusia.

Conclusions: Bilastine once-daily ophthalmic formulation 6 mg/mL is absorbed into the bloodstream in low amounts by the ophthalmic route. The bilastine ophthalmic formulation showed a good safety profile after multiple dose administration.

Keywords: Allergic conjunctivitis; Bilastine; H_1 antihistamine; Ophthalmic formulation; Rhinoconjunctivitis

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Key Summary Points

Why carry out this study?

Allergic conjunctivitis is a highly prevalent disorder of the ocular conjunctive which can greatly affect quality of life.

Bilastine is an efficient and safe antihistamine that has been used to reduce symptoms and signs of allergic conjunctivitis. The pharmacokinetics and safety of a recently developed preservative-free, ophthalmic formulation of bilastine were investigated.

What was learned from the study?

Bilastine once-daily ophthalmic formulation 6 mg/mL is absorbed into the bloodstream in low amounts by the ophthalmic route.

The ophthalmic formulation of bilastine showed a good safety profile after multiple dose administration.

Further controlled clinical trials are warranted to evaluate the efficacy and safety of ophthalmic bilastine in the treatment of allergic conjunctivitis.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14611620.

INTRODUCTION

Allergic conjunctivitis is an highly prevalent IgE-mediated hypersensitivity disorder of the ocular conjunctive [1]. The most frequent ocular symptoms of allergic conjunctivitis are itching, tearing and conjunctival hyperemia, which can greatly affect quality of life [2, 3]. Current treatments for allergic conjunctivitis aim to control and relieve the symptoms and include systemic or topical antihistamines, mast cell stabilizers, dual-action agents, anti-inflammatories and corticosteroids [3]. Systemic antihistamines are especially recommended in the presence of other allergic comorbidities [4, 5]. Topical antihistamines and mast cell stabilizers are usually well tolerated and reduce symptoms and signs of allergic conjunctivitis, but there are limited data on their long-term efficacy [6]. Topical ocular antihistamines constitute the first-line treatment in cases of isolated ocular symptoms. Generally, topical ocular drugs for allergic conjunctivitis are preferred because they act faster and result in higher local bioavailability than systemically administered drugs [5]. Topical eye drops are considered a convenient and safe route of ocular drug administration [7], although special care must be applied in children [8].

Bilastine is a second-generation H_1 antihistamine agent indicated in Europe for adults and adolescents (older than 12 years of age) at a dose of 20 mg once daily, and children (6–11 years, with a body weight of at least 20 kg) at a dose of 10 mg once daily, for symptomatic treatment of allergic rhinoconjunctivitis and urticaria, and in other regulatory agencies for children older than 2 years [9, 10]. In clinical trials, once-daily oral administration of bilastine (20 mg tablets) is effective in controlling the ocular symptoms of allergic rhinoconjunctivitis and it demonstrated an excellent safety profile and long-term tolerance. Moreover, bilastine has also demonstrated efficacy and safety in the treatment of allergic rhinoconjunctivitis and chronic idiopathic urticaria [11–14].

The pharmacokinetics and pharmacodynamics of orally administered bilastine in children [15–17] and adults [18] have been extensively analysed. After oral administration bilastine is rapidly absorbed, reaching the peak plasma concentration at 1.3 h and a mean bioavailability of 60%, mostly bound to plasma proteins [18, 19]. Bilastine is not significantly metabolized in the liver and approximately 95% is excreted unaltered in either the faeces

(66.5%) or urine (28.3%), with a mean elimination half-life of 12–14.5 h [18, 20].

Pharmacokinetic and pharmacodynamic modelling complemented with non-compartmental analysis showed linear kinetics over a dose range from 2.5 to 220 mg [18]. Additionally, bilastine has been shown to be safe in patients with renal or hepatic impairment and in patients aged 65 years or older [21, 22]. A prolonged duration of action, a property that could derive from its high selectivity and affinity for the H_1 receptor which results in a long residence time at the receptor, has been shown in vitro [23, 24]. However, its interaction with H_1 receptors in the brain is nearly 0%, and thus it can be considered that brain penetration is negligible, unlike most other second-generation H_1 antihistamines [25, 26].

On the basis of the overall superiority of topical to oral administration of treatments for allergic conjunctivitis owing to prompt onset of action and higher effectiveness [3, 27–31], and the demonstrated efficacy and safety of orally administered bilastine, a once-daily, preservative-free, ophthalmic formulation of bilastine was developed. Here, we describe the results from a phase I study carried out to evaluate the pharmacokinetics and safety of ophthalmic bilastine (6 mg/mL) after single and multiple dose administration at steady state in healthy adults.

METHODS

This was an open-label, single-centre, phase I clinical trial to evaluate the relative bioavailability, tolerability and safety of an ophthalmic formulation of bilastine after multiple dose administration to healthy volunteers. The study was carried out at the Hospital Universitario de La Princesa (Madrid, Spain).

All subjects included in the study signed a written informed consent and were free to withdraw the study at any time. The protocol was approved by the Research Ethics Committee of the Hospital Universitario de La Princesa and was conducted in accordance with the ethical principles based on the Declaration of Helsinki and Good Clinical Practice. The study was registered with EudraCT number 2018-001504-11.

Study Population

Subjects were eligible for inclusion in the study if they met the following criteria: age 18–55 years, in good physical and mental health, willing to discontinue wearing contact lenses for at least 72 h prior to and during the study, calculated visual acuity of 0.7 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Exclusion criteria were subjects with body mass index outside the 18.5–30.0 kg/m^2 range, any ocular condition that could affect the subject's safety or trial parameters (such as glaucoma, ocular hypertension, clinically significant blepharitis, follicular conjunctivitis, dry eye, active ocular infection, active allergic conjunctivitis), positive testing for drugs of abuse, tobacco or alcohol consumption, and pregnant or breastfeeding women. Subjects were also excluded if they had signs or symptoms of clinically active allergic conjunctivitis in either eye in the last month, a history of retinal detachment, diabetic retinopathy, active retinal disease, or eye surgery in the previous 3 months. The following medications were not allowed prior to screening and during the whole study: 7 days prior to screening (systemic or ophthalmic H_1 antihistamine, H_1 antihistamine/mast cell stabilizers, H_1 antihistamine–vasoconstrictor drug combinations, or other ophthalmic preparations), 14 days prior to screening (inhaled, ocular, topical or systemic corticosteroids or mast cell stabilizers) and 45 days prior to screening (depocorticosteroids).

Study Design and Procedures

A scheme of the timeline of the study is shown in Fig. 1. Subjects received five doses of the bilastine ophthalmic formulation (one single drop of 6 mg/mL solution/eye, corresponding to 0.42 mg of bilastine) every 24 h for 5 days. The doses were administered by the investigator in the conjunctival sac of both eyes.

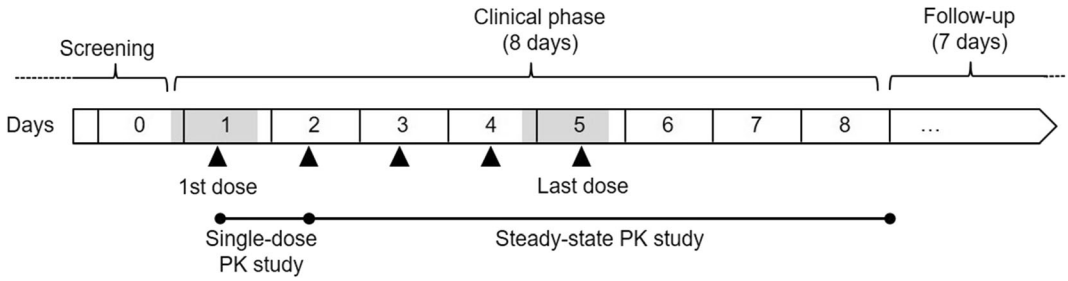

Fig. 1 Design and timeline of the pharmacokinetic study. Shaded boxes indicate in-hospital study periods and black triangles time of ocular administration of bilastine ophthalmic formulation 6 mg/mL. The follow-up phase lasted 1 week after day 8

On days 1 and 5 of the procedure, the subjects remained in-hospital and 5-mL blood samples were drawn at predefined times for pharmacokinetic analysis. On days 2, 3, 4, 6, 7 and 8, and once during follow-up, the subjects attended the hospital once a day for blood sample collection. A complete ophthalmic examination was performed before the first administration of bilastine on day 0 and after the last administration on day 5. It included an assessment of visual acuity, pupil function, extraocular muscle motility, visual fields, intraocular pressure and ophthalmoscopy through a dilated pupil. A full physical examination, including an electrocardiogram (ECG), was performed before day 0, on days 1 and 5, and on the follow-up visit about 1 week after the last bilastine dose.

Bilastine was analysed in an external laboratory using a method validated according to regulatory guidelines [32]. The bilastine quantification method involved a protein precipitation extraction procedure with methanol/acetonitrile (50:50). Bilastine and its corresponding internal standard were measured by reversed-phase high-performance liquid chromatography coupled to a tandem mass spectrometry detector (HPLC–MS/MS) with a lower limit of quantification of 20 pg/mL, validated according to European Medicines Agency (EMA) guidelines.

Pharmacokinetic Analysis: Endpoints and Assessments

For the analysis of the bioavailability after the first dose, the primary endpoint was the area under the curve (AUC_{0-24}) calculated from the plasma concentrations of bilastine. The time to C_{max} (T_{max}) and peak concentration (C_{max}) were also determined.

For the analysis of the bioavailability under steady-state conditions, the primary endpoint was the area under the curve during a dosage interval ($AUC_{0-\tau,ss}$), minimum plasma concentration ($C_{min,ss}$), maximum plasma concentration ($C_{max,ss}$) and time until $C_{max,ss}$ was reached ($T_{max,ss}$) at steady state calculated from the plasma concentrations of bilastine. The plasma concentration previous to the administration of each dose and concentration at the end of the dosing interval ($C_{\tau,ss}$) was also calculated. The percentage fluctuation was computed as $100 \times (C_{max} - C_{min})/C_{avg}$, where C_{min} and C_{max} were obtained between 0 and tau, and C_{avg} was the average concentration during a dosing interval ($AUC_{0-\tau}/\tau$).

The pharmacokinetic data analysis was carried out according to a model-independent approach, following the recommendations of the European and American Regulatory Authorities on investigation of bioavailability and bioequivalence [33–35].

Pharmacokinetic parameters were estimated by noncompartmental analysis using validated WinNonlin Professional 7 software (Pharsight Corporation, NC, USA).

Safety and Tolerability Assessment

In addition to the ophthalmological examination, the safety and tolerability of the bilastine ophthalmic formulation were assessed by clinical evaluation of adverse events (AEs) and other parameters including vital signs, physical examination, ECG and blood and urine tests.

Throughout the study, subjects were asked about any experienced AEs. Additionally, AEs that were spontaneously notified by the volunteers were also recorded. Causality was determined using the algorithm of the Spanish pharmacovigilance system as definite, probable, possible, conditional and unrelated [36]. Only definite, probable or possible AEs were considered as adverse drug reactions (ADRs) and included in the statistical analysis. Time sequence, intensity and outcome of AEs were also recorded.

Statistical Analysis

Statistical analyses were carried out using SPSS software 15.0 (SPSS Inc., Chicago, Ill, USA). A significance level of $p < 0.05$ was considered statistically significant. All subjects were considered for the pharmacokinetic and safety analysis since all of them accomplished 100% of the study treatment according to protocol. Summary statistics were calculated for demographic and pharmacokinetic parameters, expressed as mean and standard deviation (SD). Owing to the exploratory nature of the study, no formal sample size calculation was performed.

No statistical tests were applied to the data on AEs. Safety and tolerability parameters were evaluated descriptively by analysing the incidence of AEs due to the bilastine ophthalmic formulation. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. Descriptive statistics (N, arithmetic mean, SD and CV) were calculated for blood pressure, heart rate, ECG intervals and laboratory values. No statistical tests were performed on these data since no clinically relevant differences between baseline and post-administration data were detected.

RESULTS

Out of 22 subjects assessed for eligibility, 12 healthy individuals were included in the study, six men with a mean (± SD) age of 26.1 ± 3.8 years and a body mass index of 24.76 ± 4.2 kg/m^2, and six women with a mean (± SD) age of 29.5 ± 8.0 years and a body mass index of 22.2 ± 2.9 kg/m^2. For the total population the mean (± SD) age was 27.8 ± 6.3 years and the body mass index was 23.5 ± 3.8 kg/m^2. All of them completed the clinical trial according to the protocol.

Pharmacokinetic Analysis

The mean plasma concentrations of bilastine up to 24 h after administration are shown in Fig. 2. After a single ophthalmic dose administration, the mean (± SD) $AUC_{0–24}$ of bilastine was 19,537.81 ± 9109.72 h·pg/mL. The maximum mean plasma concentration observed (C_{max}) was 2793.79 ± 1384.40 pg/mL, reached at a median T_{max} of 2.13 h (range 0.25–3.00 h) and with a mean half-life ($T_{1/2}$) of 4.63 ± 1.75 h (Table 1).

For the multiple dose study, bilastine eye drops were administered once daily for 5 days in each eye. The mean concentrations of bilastine at steady state are shown in Fig. 3. In steady-state conditions the mean (± SD) $AUC_{0–\tau,ss}$ of bilastine was 19,512.51 ± 9248.76 h·pg/mL and maximum concentration ($C_{max,ss}$) was 2682.26 ± 1615.88 pg/mL. Both parameters showed high interindividual variability (47.40% and 60.24%, respectively). The minimum concentration at steady state ($C_{min,ss}$) was 54.45 ± 70.42 pg/mL with a interindividual variability of 129.32%. The median time to maximum concentration in steady state ($T_{max,ss}$) was 2.50 h (range 1.25–4.00 h) and the mean half-life ($T_{1/2}$) was 7.88 ± 6.72 h. Fluctuation was 306.16 ± 94.78% and $C_{\tau,ss}$ was 234.10 ± 124.60 pg/mL.

The median terminal half-life was calculated as 4.38 h (range 2.65–9.13 h) on day 1 and 5.42 h (range 2.45–23.24 h) at steady state.

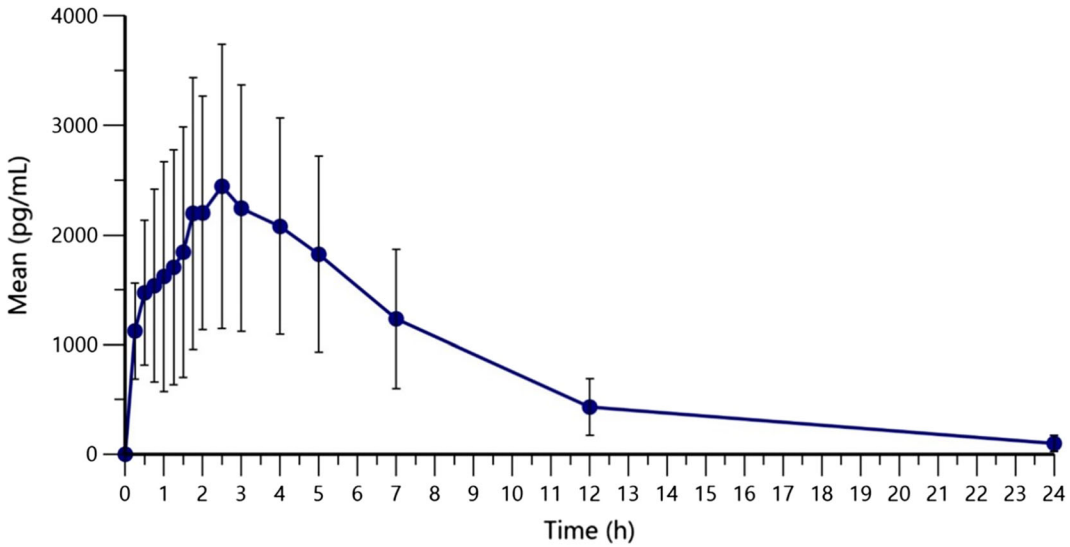

Fig. 2 Bilastine plasma concentrations (pg mL^{-1}) after single administration of one drop of 6 mg/mL per eye. Means (standard deviation) are shown

Table 1 Summary of pharmacokinetic parameters of ophthalmic bilastine (6 mg/mL) in plasma

Parameter N = 12	**Mean ± SD**
AUC_{0-24} (h·pg/mL), mean ± SD*	19,537.81 ± 9109.72
C_{max} (pg/mL), mean ± SD*	2793.79 ± 1384.40
$AUC_{0-\tau,ss}$ (h·pg/mL), mean ± SD	19,512.51 ± 9248.76
$C_{max,ss}$ (pg/mL), mean ± SD	2682.26 ± 1615.88
$C_{min,ss}$ (pg/mL), mean ± SD	54.45 ± 70.42
T_{max} (h), median (range)*	2.13 (0.25–3.00)
$T_{max,ss}$ (h), median (range)	2.50 (1.25–4.00)
$T_{1/2,ss}$ (h), mean ± SD	7.88 ± 6.72
$T_{1/2,ss}$ (h), median (range)	5.42 (2.45–23.24 h)

AUC_{0-24} area under the curve from time 0 to 24 h after drug administration, $AUC_{0-\tau,ss}$ area under the curve from time 0 to tau in steady state, C_{max} maximum concentration in plasma, $C_{max,ss}$ maximum concentration in steady state, C_{min} minimum concentration in steady state, T_{max} time to maximum concentration in plasma, $T_{max,ss}$ time to maximum concentration in steady state, $T_{1/2,ss}$ half-life in steady state
*Calculated after first dose

Safety and Tolerability Assessment

During the study nine subjects reported a total of 43 AEs that were considered as adverse drug reactions (ADRs) since they were definitively, probably or possibly related to the study drug (Table 2). The most frequent ADRs were dysgeusia in eight subjects, and blurred vision reported by a single subject. No serious or life-threatening AEs were reported during the study, no AEs caused premature termination of the study and all were resolved by the end of the

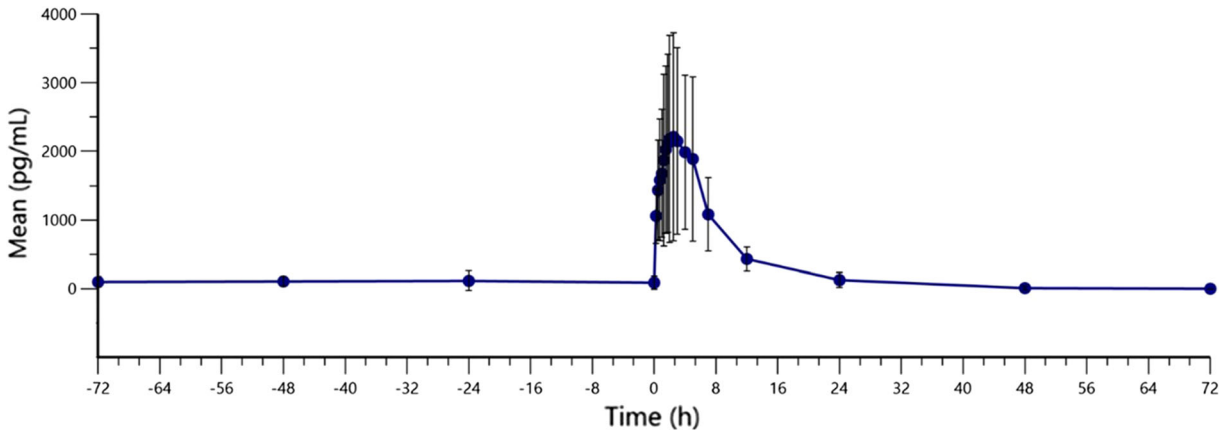

Fig. 3 Bilastine plasma concentrations (pg mL^{-1}) after multiple administration of eye drops. Means (standard deviation) are shown spanning from day 2 of administration to 72 h post-dose of day 5 of administration

Table 2 Adverse drug reactions (ADR) reported in the study

ADR	Number of ADR/number of subjects
Dysgeusia	33/8
Blurred vision	4/1
Abnormal sensation in eye	2/2
Photophobia	2/1
Headache	1/1
Throat irritation	1/1
Total number of ADRs/number of subjects with any ADR	43/9

trial. The complete ophthalmological examination performed on days 0 and 5 reported normal results and no abnormalities with clinical relevance.

DISCUSSION

In this study the pharmacokinetic parameters of a novel ophthalmic formulation of bilastine were investigated in healthy subjects. The results showed that bilastine ophthalmic formulation 6 mg/mL is absorbed via the ocular route and reaches the bloodstream. Reported adverse events during the study were mild or moderate, suggesting this route of administration is safe and well tolerated.

In this pharmacokinetic study a dose of one drop of 35 µl in each eye every 24 h was chosen because it is the dose confirmed in previous dose-finding and efficacy clinical trials. As the ophthalmic formulation has 6 mg/mL, the total dose received by the subjects was 0.42 mg every day, much lower than the therapeutic 20 mg/day oral dose. As steady-state concentrations were achieved by the third day of once-a-day oral dosing [9, 18], and achievement of steady state is assessed by comparing at least three pre-dose concentrations of the drug, in this study we administered five ophthalmic doses in 5 days. After administration of a drop containing 0.42 mg of bilastine dose by the ophthalmic route, bilastine was absorbed into the bloodstream, reaching maximum blood

levels within 2.50 (1.25–4.00) h after administration at steady state, slightly later than when orally administered (approximately 1.3 h) [18, 19].

In our study very low levels of bilastine were detected in plasma (C_{max} 2.79 ng/mL), which is justified because after topical ocular administration bilastine must overcome several ocular natural tissue barriers such as the cornea, the conjunctiva and other related tissues before reaching the bloodstream. This is consistent with a previous preclinical animal study, which found a C_{max} of 6.10 ng/mL in plasma after a single topical ocular administration of 6 mg/mL (0.6%) of the bilastine ophthalmic formulation in each eye to male Dutch-Belted rabbits (unpublished data). This low but detectable level of bilastine in plasma suggested, in addition to the nasolacrimal route, a bulbar–stromal conjunctival route of drug absorption. In that animal study, although bilastine was distributed predominantly in the conjunctiva and cornea, consistent with administration site, the highest concentration of bilastine was observed in the conjunctiva, the intended target organ. Lower concentrations of bilastine were found in the iris/ciliary body and retina/choroid, and even lower in the aqueous humour, vitreous humour and crystalline lens. The preferential distribution of bilastine in conjunctiva may have been determined by its high molecular weight (463.6 g/mol) and high polar surface area (67.6 $Å^2$). Further, bilastine presented an elevated conjunctiva/cornea AUC ratio (5.7), higher than for other antihistamines [37], and a high conjunctiva/plasma AUC ratio (> 800). The reduced but detectable levels of bilastine in plasma of rabbits reinforces the idea of the bulbar–stromal conjunctival route. Besides, despite the obvious differences between preclinical and clinical studies, the low levels of bilastine in plasma are comparable to those detected in the present study after a single topical administration of 6 mg/mL of the ophthalmic bilastine formulation in healthy volunteers. In contrast, the C_{max} of bilastine in plasma after oral administration of a single dose of 20 mg ranges from 182.4 to 256.6 ng/mL [20]. Also, in this study the half-life after ocular administration (7.88 ± 6.72 h) was slightly lower than that observed after oral administration (9–15 h) [18, 19].

In this pharmacokinetics study the median T_{max} of bilastine after single dose administration was 2.13 h, which is comparable to that found for ophthalmic formulations of olopatadine (0.5–2 h), epinastine (2 h), ketotifen (2–4 h) or azelastine (5.3 h) [38]. Ophthalmic bilastine presented a considerably longer half-life, 7.88 h, than ophthalmic olapatadine 0.77%, which had a half-life of 3.40 h [39]. The study in rabbits had shown that the long half-life of bilastine was also observed in conjunctiva 24 h after a single bilateral topical administration, similar to a study of 0.77% olapatadine in rabbits [37].

Ocular administration of antihistamines or mast cell-stabilizing agents rarely leads to systemic side effects, but in some occasions a dry mouth feeling, nausea, headache or drowsiness have been observed [8]. Given the previous safety profile of orally administered bilastine and the compared low dose administered in this study, no safety concerns were expected. No ocular toxicity was detected in animal studies performed with this new ophthalmic formulation (unpublished data). Moreover, in a previous dose-finding pharmacodynamic study with the ophthalmic formulation no safety issues were identified (ClinicalTrials.gov identifier NCT03231969). In this study bilastine ophthalmic formulation 6 mg/mL showed a good tolerability and safety profile after an ophthalmic multiple dose administration. Ophthalmic exploration (visual acuity, pupil function, extraocular muscle motility, visual fields, intraocular pressure and ophthalmoscopy) performed before and at the end of the treatment were normal, with no changes versus baseline. No serious adverse events were reported. Taste discomfort alterations were the most frequent adverse events and they were mild and transient. No previous study had found dysgeusia associated with bilastine [15, 23, 40], although there are some reports of dysgeusia caused by H_1 antihistamines azelastine and emedastine [41].

It has been estimated that allergic conjunctivitis is often underdiagnosed and undertreated, as only about 10% of patients with

allergic conjunctivitis seek medical treatment [3]. Allergic conjunctivitis is often treated in the context of comorbid rhinitis, but ocular symptoms without nasal involvement occur in 5–6% of patients with allergy [42, 43]. When ocular symptoms are not adequately treated, they can substantially contribute to the burden of the disease for patients with allergy. For these reasons, the recently developed preservative-free ophthalmic formulation of bilastine could become a welcome innovation in the therapeutic arsenal available for the management of allergic conjunctivitis.

As with any clinical study, there are some limitations of the study that should considered in the interpretation of the results. The subjects included in the study were healthy with an age range of 20–44 years, and a wider age range would have been desirable. However, the selection of healthy participants is characteristic for this type of study. Ongoing clinical studies testing the efficacy and safety of bilastine 6 mg/mL in the treatment of patients with allergic conjunctivitis are addressing this issue specifically.

CONCLUSIONS

This pharmacokinetic study showed that bilastine ophthalmic formulation 6 mg/mL presents low levels of plasmatic absorption and concentration. The study also showed that the bilastine ophthalmic formulation was safe and well tolerated in healthy subjects after multiple dose administration. These results suggest that the efficacy of the bilastine ophthalmic formulation for the treatment of allergic conjunctivitis may be related to tissue local permanence and direct effect on the tissue target.

Current controlled clinical trials are warranted to evaluate the efficacy and safety of ophthalmic bilastine in the treatment of allergic conjunctivitis.

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Vilchez, and Gina Mejía-Abril declare that they have nothing to disclose. Gonzalo Hernández, Paula Arranz, Lorena Elgezabal, and Nieves Fernández are employees of FAES FARMA SA (Spain)

Compliance with Ethics Guidelines. All subjects included in the study signed a written informed consent and were free to withdraw the study at any time. The protocol was approved by the Research Ethics Committee of the Hospital Universitario de La Princesa and was conducted in accordance with the ethical principles based on the Declaration of Helsinki of 1964, and its later amendments.

Data Availability. The data that support the findings of this study are available on request from the corresponding author.

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