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Comparative inhibition by oral bilastine, parenteral dexchlorpheniramine, and a new bilastine parenteral (i.v. and i.m.) formulation of histamine-induced wheal and flare response: A randomised phase I trial

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ABSTRACT

Background: Bilastine is a well-known non-sedating second-generation antihistamine authorised worldwide for the symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria with proven efficacy and good safety and tolerability profile. When the oral route is not suitable or a rapid onset of action is preferred, parenteral formulations represent an effective treatment option. However, the parenteral formulations currently available are sedating antihistamines. The objective of this research was to compare the peripheral anti-H_1 activity of different bilastine formulations (i.v., i.m. and oral) and dexchlorpheniramine among them also versus placebo.

Methods: This was a single-dose, randomized, crossover, double-blind, placebo-controlled, phase I clinical study performed on 25 adult healthy volunteers that compared the peripheral antihistaminic activity of a single dose of bilastine 12 mg i.v., bilastine 12 mg i.m., bilastine 20 mg oral tablets and dexchlorpheniramine 5 mg i.m. among them and versus placebo by inhibiting the histamine-induced wheal and flare (W&F) response. Pharmacokinetics, safety, and tolerability were also evaluated.

Results: All bilastine formulations showed a rapid onset of action (15 min for parenteral and 30 min for the oral formulation), and the maximum effect in both wheal (i.v. 74.44 %; i.m.:74.29 %; oral 70,27 %) and flare area reduction (i.v. and i.m. 80.63 %; oral 77.67 %), was significantly larger compared to dexchlorpheniramine i.m. (25.85 % for wheal and 28.65 % for flare) and placebo (1.35 % for wheal and 4.02 % for flare). A more pronounced reduction in itching score was reached for bilastine oral, followed by i.m. and i.v. formulations. No serious adverse events (SAEs) were reported during the study, and 8 treatment-emergent adverse events (TEAEs) were reported by 5 subjects, all resolved without sequelae. For psychomotor assessments, dexchlorpheniramine i.m. showed a fast onset of drowsiness, as well as decreased attention and coordination when compared to all bilastine formulations and placebo.

Conclusions: All bilastine formulations showed a peripheral H_1-blocking effect inducing a significantly greater inhibition of the wheal and flare response as compared to dexchlorpheniramine i.m. or placebo and provided a greater reduction of the itching sensation score. This study reconfirmed that bilastine has no sedative effect, even in a parenteral formulation. These results suggest that new bilastine parenteral formulation (i.v. or i.m.) may represent a suitable alternative for patients requiring immediate treatment of histamine-mediated type I hypersensitivity reactions, such as acute urticaria, or in those cases where oral administration is not possible.

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1. Introduction

Allergies impact millions of individuals across diverse demographics, and their prevalence is expected to rise in the coming years. Among allergic diseases, urticaria and rhinitis are common health problems causing significant patient burden and disability worldwide. The standard allergy treatment includes pharmacotherapy. Antihistamines are the first-line pharmacological treatment, and second-generation ones are preferred due to the sedative and anticholinergic side effects usually experienced by first-generation ones. Bilastine is a non-sedating second-generation antihistamine indicated worldwide for the symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria in adults, adolescents, and children. According to in vitro and in vivo preclinical studies, the drug is highly selective for histamine H_1-receptors, with little or no affinity for other receptors, including muscarinic and serotonin receptors (Corcóstegui et al., 2006, 2005). In humans, bilastine has proved to be an effective antihistamine, without sedative or cardiotoxic effects, lacking hepatic elimination or interaction with cytochrome P450 (Church, 2011).

Several clinical trials have demonstrated the efficacy of bilastine in the treatment of allergic rhinoconjunctivitis (Bachert et al., 2009; Kuna et al., 2009; Okubo et al., 2017, 2016; Sastre et al., 2012) and chronic urticaria (Hide et al., 2017; Krause et al., 2013; Weller et al., 2018; Yagami et al., 2017; Zuberbier et al., 2010), with a favourable safety profile (Conen et al., 2011; Demonte et al., 2018; García-Gea et al., 2008; Reményi et al., 2018; Valk et al., 2016) and long-term tolerance (Okubo et al., 2017; Sastre et al., 2012). Therefore, bilastine is indicated for the symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria in adults and adolescents aged 12 years and older at a once-daily dose of 20 mg, and for paediatric patients from 2 years old (depending on the regulatory agency), at a once-daily dose of 10 mg (Vozmediano et al., 2019, 2017).

Parenteral administration of medications offers several advantages, particularly when oral or topical routes may not be suitable or ineffective. Specifically, intravenous (i.v.) and intramuscular (i.m.) antihistamine administration may provide a rapid onset of action, making them valuable in the management of acute allergic reactions, exacerbations of chronic reactions, hypersensitivity reactions, or in patients unable to take oral medications. However, there is a need for modern non-sedating antihistamines in parenteral formulations to be used when the oral route is not possible or a fast onset of action is preferred. To address this gap, the availability of bilastine for i.v. and i.m. administration would be a step forward in the treatment of allergic diseases.

2. Methods

The study was conducted at CIM-Sant Pau Institut de Recerca of Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) and received approval from the Ethics Committee for Clinical Research of Fundació de Gestió Sanitària del Hospital de la Santa Creu i Sant Pau and the Spanish Agency of Medicines and Medical Devices (AEMPS/Ministry of Health, EudraCT number: 2019–004,811–29). The study adhered to the ethical principles of the Declaration of Helsinki and complied with the criteria of Good Clinical Practices. Written informed consent was obtained from all participants before study initiation.

2.1. Study population

Eligible participants were 25 adult healthy volunteers (normal medical records and physical examination at screening, and no clinically significant abnormalities on laboratory tests and serology), with a body mass index (BMI) between $\geq$18.5 and $<$ 28.0 kg/m^2, with induced wheal area values within the reference range in the histamine-induced skin reactivity test, willing to avoid excessive sun exposure or any procedure that could modify the colour of the skin, and with an acceptable psychomotor performance level. Subjects were excluded if they had a history of allergy, idiosyncrasy, or hypersensitivity to investigational products or excipients, were non-responder subjects to histamine, were heavy consumers of stimulating drinks (>5 cups of coffee, tea, chocolate or cola drinks per day), had a past or current history of alcohol dependence (consumption of alcohol >40 g/day for men or >24 g/day for women) or drug abuse in the last five years, were smokers within 6 months before the study, or presented positive dermographism or any other condition that, in the investigator's opinion, may have jeopardised the trial execution.

2.2. Study design

This phase I clinical trial had a crossover, five-arm, randomised, triple-dummy, double-blind and placebo-controlled design to assess antagonist H_1 activity of bilastine 12 mg i.v and i.m. formulation in comparison to dexchlorpheniramine 5 mg i.m., bilastine 20 mg oral formulation and placebo in healthy volunteers.

The treatments evaluated were: (1) bilastine 20 mg as oral formulation (Bilaxten®, FAES Pharma); (2) bilastine 12 mg as i.v. administration; (3) bilastine 12 mg as deltoid i.m. injection; (4) dexchlorpheniramine 5 mg (Polaramine®) as deltoid i.m. injection; and (5) placebo as oral, deltoid i.m. and i.v. formulations. Study treatments were administered as a single dose in the morning at each study period under fasting conditions. Oral treatments were administered with 240 mL of mineral water. Subjects were allocated to each of the following treatment sequences, one per period to complete the five periods: (1) placebo i.m. + bilastine oral + placebo i.v.; (2) bilastine i.m. + placebo oral + placebo i.v.; (3) placebo i.m. + placebo oral + bilastine i.v.; (4) dexchlorpheniramine i.m.+ placebo oral + placebo i.v.; (5) placebo i.m. + placebo oral + placebo i.v. Volunteers received different treatments with only one active formulation administered in each period except one, where the three treatments were placebo formulations. The study design is presented in Fig. 1.

The study comprised three phases: the screening phase, the experimental phase, which comprised five treatment periods separated by a minimum washout of 7 days, and the end of the study phase. Every treatment period encompassed three days: the day before treatment administration, participants were randomised. On day 1, treatments were administered, and study assessments were performed, and on day 2, 24 h post-treatment administration assessments were performed, and participants were discharged. After each washout period, volunteers were admitted to the unit for subsequent treatment periods, following the described treatment sequence and the same assessments as described for the first period were completed.

The primary objective of the study was to compare the peripheral antihistamine activity of i.v., i.m. and oral bilastine formulations, dexchlorpheniramine i.m. and placebo. To this end, the peripheral anti-H_1 activity measured as the percentage (%) of reduction or inhibition of wheal and flare surface areas were obtained through the skin reactivity test at each time point after study drug administration and compared to their corresponding baseline value. The following secondary endpoints were evaluated over the treatment period: (1) the onset of action, defined as the first time point where wheal and flare surface areas show statistically significant differences related to their baseline values; (2) the maximum effect or percentage of reduction of wheal and flare surface areas; (3) the maximum effect time which was the time when the maximum effect was reached; (4) pharmacokinetic parameters; (5) mean change on subjective itching perception relative to baseline values; (6) mean change on subjective drowsiness perception and psychomotor performance at 3 h relative to baseline situation; and (7) safety and tolerability.

2.3. Pharmacodynamic assessments

The skin reactivity test involved the intradermal injection of 0.05 mL of a histamine solution at a concentration of 100 mg/mL in the ventral

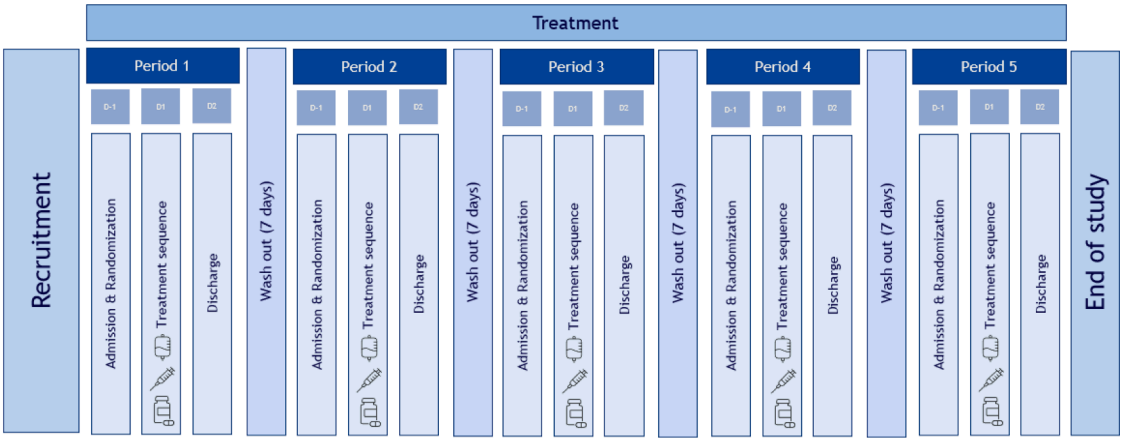

Fig. 1. Flowchart of the study design.

forearm using a tuberculin syringe. Fifteen minutes after the inoculation, the induced wheal and flare surface was measured by drawing the contours with a permanent marker onto a transparent film. The surface areas were quantified using the Visitrak System (Smith & Nephew), which automatically calculates the area in cm^2. Each ventral forearm was divided into six zones based on the proximity to the back (proximal, central, and distal) and external versus internal situations. Ten of the 12 forearm zones were used during each treatment period and for each subject. Basal and 24 h post-treatment histamine inoculations were performed in the same zone due to the time difference between them. To avoid overlap, arms were alternated for successive evaluations.

2.4. Subjective efficacy assessment

Itching was evaluated using a visual analogue scale (VAS) ranging from 0 (no perception of the symptom) to 100 (the highest perception of the symptom). The skin reactivity test and itching assessments were performed at baseline and after the administration of the treatment sequence at 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 9 h, 12 h and 24 h.

2.5. Safety and tolerability assessments

Drowsiness was measured using a visual analogue scale (VAS) in the same way as the itching score. Other neuropsychologic tests used were: the Digit Symbol Substitution Test to measure speed and visual memory, where subjects match numbers with symbols according to an instruction (Jaeger, 2018; Smith, 2011); the D2 Test of Attention that consists of discriminating characters similar between them in a group of rows promptly and measures selective attention and mind concentration (Sinha et al., 2018); the Grooved Pegboard Test to evaluate eye-hand coordination and motor speed through a test where subjects must fit pegs into the holes as quickly as possible, scores are based on the duration of the task and the number of pegs dropped (Merker and Podell, 2011). Psychomotor performance and drowsiness perception were measured at baseline, 1.5 h and 3 h post-drug administration.

Adverse effects (AEs) occurring after the study treatment administration were recorded spontaneously as they happened or as reported by participants and were considered treatment-emergent AEs (TEAEs). Concomitant medications and (TEAEs) were registered throughout the study. The investigator determined the severity of AEs and their causality. AEs were coded using MedDRA (Medical Dictionary for Regulatory Activities) version 24.0.

Biochemical and haematological laboratory tests and electrocardiogram (ECG) were performed on day 1 and day 2, and vital signs were measured at baseline, 4 h, 9 h and 24 h after treatment sequence administration).

2.6. Statistical analysis

Statistical analyses and randomisation were performed using the software IBM-SPSS (v26.0). Statistical significance was established at $p < 0.05$.

Sample size was calculated considering a variation coefficient of 25 % for the skin reactivity test, results obtained in previous studies, and a significance level of 5 %. A sample size of 22 subjects was estimated to detect a minimum difference of 15 % among treatments with a power of 80 %. However, considering the high risk of dropouts because of the prolonged study duration, the sample size was increased to 25 subjects.

Demographics and safety analyses were based on data from the randomised population who received at least one dose of the study treatment and attended a follow-up visit or safety assessment. Pharmacodynamic outcomes were analysed by considering subjects from the safety population who completed all study phases without major protocol deviations.

Continuous variables were described as the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), and categorical variables by the number (n) and percentage (%) of patients.

Variables obtained in the objective skin reactivity test were expressed in three ways. Firstly, results were shown as direct values to obtain information on the possible effect of the time course. Secondly, numbers were expressed as a percentage of inhibition, using the following formula to calculate the percentage of reduction of wheal and flare areas at each time point relative to baseline values:

$$\%\text{inhibition} = [(\text{baselinevalue} - \text{post} - \text{dosevalue}) \times 100 / \text{baselinevalue}]$$

Thirdly, an area under the curve (AUC) was obtained by converting the inhibition of wheal and flare for each treatment administered at each point. The percentage of reduction of wheal and flare measurements and the AUC were evaluated using an analysis of variance (ANOVA) of repeated measures with Greenhouse-Geiser correction, including the following factors: time, treatment and the interaction between time and treatment. Additionally, an exploratory analysis was performed to obtain additional insights into the impact of time and the interaction between time and treatments. Instead of utilizing the summarized data in AUC, direct values at each time point were examined. When statistically significant differences were detected after adjustment for time, a detailed analysis was conducted by assessing the differences between treatments at each evaluation time and between evaluation times after each treatment using simple-main-effects omnibus tests and pairwise comparisons.

3. Results

3.1. Study population

Of the 25 randomised subjects, 23 completed the study, and 2 discontinued (one due to burning in the arm before any treatment exposition, and one due to personal reasons after completing period 1). Twenty-three subjects were considered for pharmacodynamic and 24 for safety evaluations. Participants' disposition is summarised in Fig. 2.

Demographic data of the 25 subjects are presented in Table 1. Of the randomised patients, 8 % were smokers, 36 % reported alcohol consumption, and 72 % were stimulant drinks consumers within the permitted range to meet the inclusion and exclusion criteria.

3.2. Pharmacodynamic results

3.2.1. Wheal area reduction

Baseline values for the wheal area were similar between all treatments (Greenhouse-Geiser $p = 0.572$). A significant effect of treatment, time, and interaction of treatment and time factors was found after a single treatment dose ($p < 0.001$ for each factor). When considering direct values, all treatments but placebo showed significant differences relative to baseline at each time point over 24 h ($p < 0.001$ for bilastine i.v. and i.m.). The onset of action was rapid (15 min) for all active treatments ($p = 0.012$ for bilastine oral and $p < 0.001$ for the rest). The percentage of inhibition for the wheal area is presented in Fig. 3.

Regarding the primary objective, the reduction in wheal area was significantly higher with bilastine formulations compared to dexchlorpheniramine, starting from 15 min post-administration for the i.v. formulation, 30 min post-administration for the i.m. formulation and from 1 h post-administration for bilastine oral formulation. In the analysis of the differences between treatments, all bilastine formulations showed significant reductions at each time point compared to placebo ($p < 0.01$). Bilastine parenteral formulations showed greater wheal reduction than bilastine oral formulation for the first hour post-administration ($p < 0.02$), whereas bilastine i.v. showed a significant reduction compared to bilastine i.m. initially during 30 min ($p < 0.01$). The maximum wheal reduction effect over 24 h was observed with bilastine i.v. (74.44 %, 4 h post-administration), followed by bilastine i.m. (74.29 %, 12 h post-administration) and bilastine oral (70.27 %, 12 h post-administration). In contrast, dexchlorpheniramine and placebo showed a smaller maximum wheal reduction (25.85 % at 30 min post-administration and 1.35 % at 6 h post-administration, respectively).

Table 1
Demographic characteristics of randomised subjects.

Parameter	$n = 25$
Age (years), mean ±SD	31.7 ± 8.3
Median (Min, Max)	31 (18, 43)
Sex, No. (%)	
Female	40 %
Male	60 %
BMI (kg/m^2), mean ±SD	24.6 ± 2.4
Median (Min, Max)	25.7 (18.7, 27.7)

SD: Standard deviation; Min: minimum; Max: maximum; BMI: Body Mass Index.

3.2.2. Flare area reduction

Baseline values for the flare area were similar between all treatments (Greenhouse-Geiser $p = 0.860$). Similarly, a significant effect of treatment, time, and interaction of treatment and time factors was found after a single treatment dose ($p < 0.001$ for each factor) for the flare area. When considering direct values, all treatments but placebo showed significant differences relative to baseline over 24 h ($p < 0.0001$ for bilastine i.v. and i.m.; $p < 0.019$ for bilastine oral). The onset of action was rapid, earlier than 30 min for all active treatments, and even faster for all parenteral formulations (15 min post-administration). The percentage of inhibition for the flare area is presented in Fig. 4.

When comparisons with dexchlorpheniramine were made, bilastine i.v. showed significant reduction at each time point ($p < 0.0001$), and bilastine i.m. showed significant difference from 45 min post-administration ($p < 0.0001$) onwards. Bilastine oral formulation also presented a significantly higher flare area reduction compared to dexchlorpheniramine at each time point starting from 45 min post-administration. The pairwise comparisons between treatments showed significant differences compared to placebo for all active treatments at almost all time points, except for bilastine oral at 15 min post-administration and dexchlorpheniramine at 2 h post-administration ($p < 0.05$). Differences between bilastine formulations were found during the initial post-administration period. Specifically, bilastine i.v. demonstrated greater flare reduction compared to bilastine i.m. at 1 h post-administration, and also compared to bilastine oral formulation at 2 h post-administration. The maximum reduction in the flare area over 24 h was higher with bilastine i.m. (80.63 %, 2 h post-administration), bilastine i.v. (80.63 %, 4 h post-administration) and bilastine oral (77.67 %, 4 h post-administration), followed by dexchlorpheniramine (28.65 %, 45 min post-administration) and placebo (4.02 % post-administration).

When the analysis of the treatment effect was performed using the

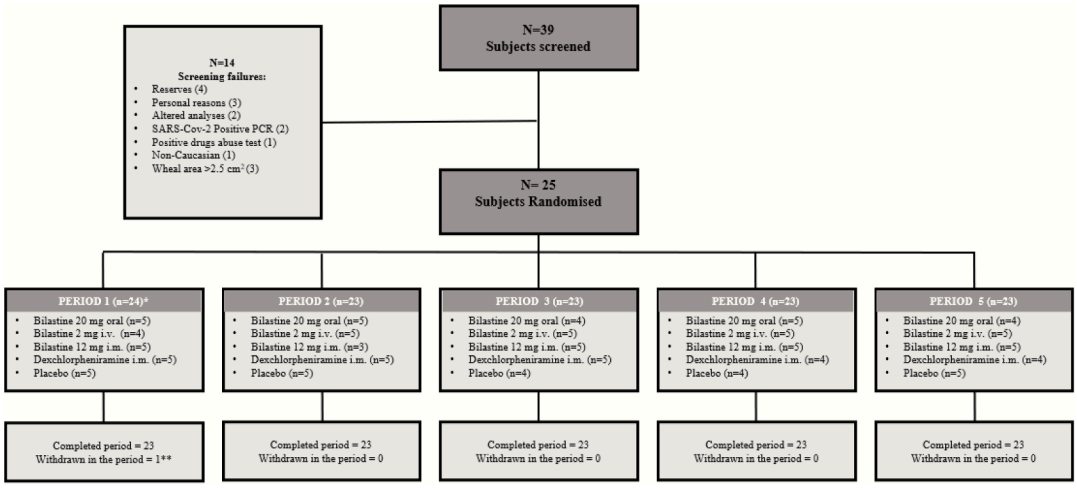

Fig. 2. Disposition of participants.
*1 subject was withdrawn before the first investigational medicinal product administration; ** 1 additional subject was withdrawn after completion of Period 1.

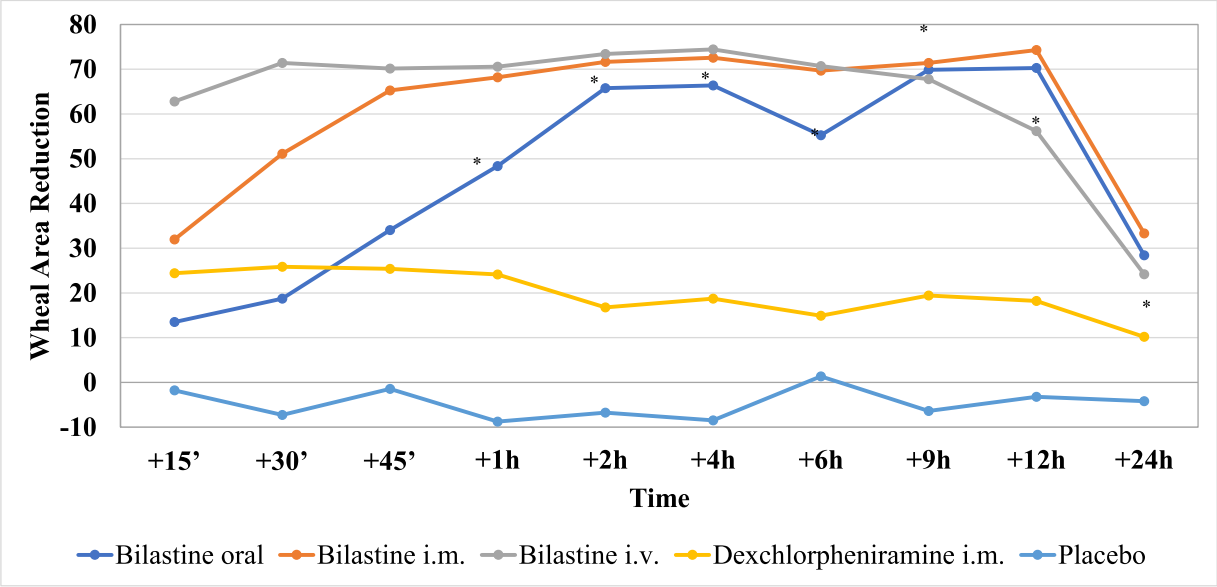

Fig. 3. Percentage of wheal area reduction from baseline.
The graph shows the percentage of wheal area inhibition at every study time point for each study treatment. P-values below 0.05 of bilastine compared to dexchlorpheniramine are highlighted using (*).

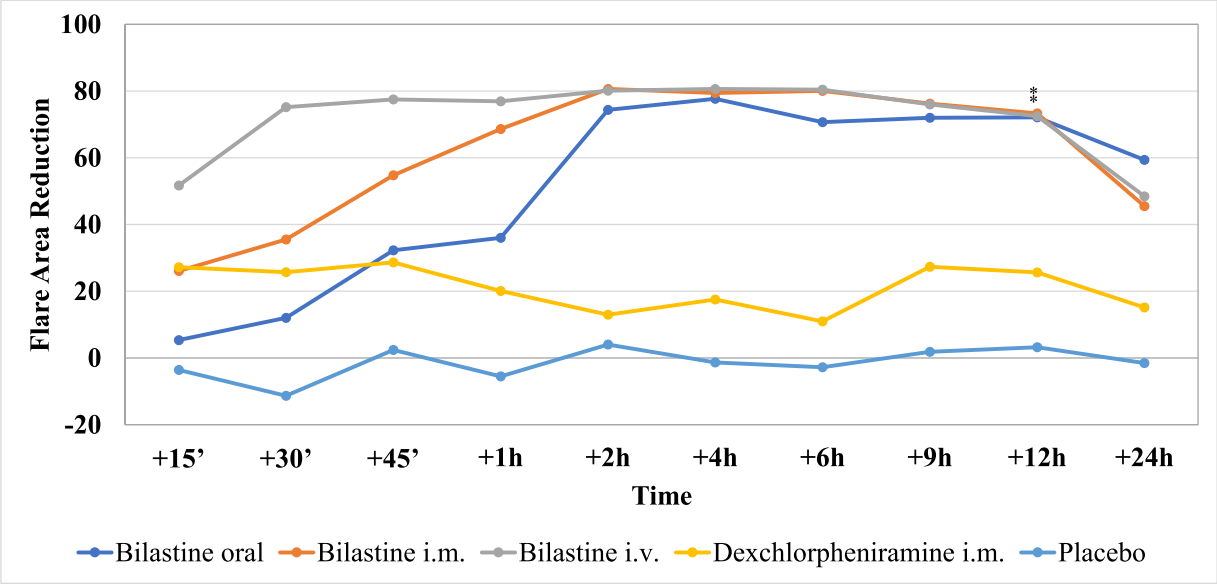

Fig. 4. Percentage of flare area reduction from baseline.
The graph shows the calculated percentage of inhibition of the flare area at every study time point for each study treatment. P-values below 0.05 of bilastine compared to dexchlorpheniramine are highlighted using (*).

mean AUC_{0-24} values for the wheal area, all active treatments showed a significant difference compared to placebo ($p < 0.001$). Moreover, the AUC values of all bilastine formulations were significantly greater than dexchlorpheniramine ($p < 0.001$) and bilastine i.v. was significantly higher than bilastine i.m. ($p = 0.014$) (Table 2).

For the flare area, all bilastine formulations were greater than dexchlorpheniramine AUC, showing significant differences for bilastine i.v. and bilastine oral ($p < 0.001$) (Table 2). Also, statistically significant differences were found between placebo and all active treatments. ($p < 0.005$).

3.2.3. *Itching perception*

When the itching perception was analysed, significant effects of the treatment ($p = 0.012$) and time factors ($p = 0.014$) were found after a single treatment dose. Subjects in active treatment arms showed significant reductions in itching perception scores versus baseline at some time points during the study. Itching reduction was statistically significant 15 min after the administration of dexchlorpheniramine and 2 h after the administration of parenteral formulations of bilastine. Oral bilastine achieved significant reduction from baseline at 4 h post-administration and had the most prolonged duration of the effect, with significant differences from 4 h post-administration to 9 h post-administration. The greatest decrease in itching score from baseline was observed with bilastine oral (10.18 mm at 4 h post-administration), bilastine i.m. (9.82 mm at 2 h post-administration), and bilastine i.v. (8 mm at 2 h post-administration), followed by dexchlorpheniramine (8.18

Table 2
Calculated AUC_{0-24} values for wheal and flare area.

	Wheal			Flare		
	Mean	SEM	CI	Mean	SEM	CI
Bilastine oral	79,402.54	6450.83	66,024.21-92,780.87	95,494.04	4535.92	86,087.12 – 104,900.95
Bilastine i.v.	88,660.47	3142.38	82,143.57-95,177.36	96,212.37	2946.96	90,100.74 – 102,323.99
Bilastine i.m.	78,046.04	4994.003	67,689.11-88,402.96	98,651.66	3482.10	91,430.22 – 105,873.09
Dexchlorpheniramine i.m.	23,389.44	6012.62	10,920.03-35,858.84	28,804.14	5254.26	17,907.48 – 39,700.80
Placebo	−6023.85	6301.24	−19,091.83-7044.13	624.25	9396.33	−18,862.54 – 20,111.04

SEM: Standard error of the mean; CI: Confidence interval; i.v..: intravenous; i.m.: intramuscular.

mm at 24 h post-administration) and placebo (6.7 mm at 4 h post-administration). Significant differences emerged between bilastine formulations and dexchlorpheniramine when treatments were compared from 2 h to 6 h post-administration, except for bilastine oral formulation which showed a significant itching decrease from 2 h to 12 h post-administration. Results are shown in Fig. 5.

3.2.4. Safety results

In regard to psychomotor performance, drowsiness showed a significant effect on the time factor ($p = 0.001$) and the treatment factor ($p = 0.042$). Dexchlorpheniramine i.m. showed consistently higher scores compared to baseline at all evaluation times, whereas bilastine oral, i.v., and placebo showed significant increases at 3 h post-administration. Notably, bilastine i.m. did not show significant differences at any time when evaluated. The maximum drowsiness score and the first onset of action were found with dexchlorpheniramine (31.04 at 1.5 h post-administration), followed by bilastine i.v. (23.70 at 3 h post-administration), bilastine i.m. (17.35 at 3 h post-administration) and placebo (17.26 at 3 h post-administration). Oral bilastine achieved a lower score than the placebo, with the lowest score recorded at 1.5 h post-administration (13.61) (Table 3). Dexchlorpheniramine arm showed higher scores than baseline at all evaluation times ($p \leq 0.001$). In contrast, significant differences were observed with bilastine oral ($p = 0.028$), i.v. ($p = 0.020$) and placebo ($p = 0.036$) at 3 h post-administration. When comparing treatments, significant differences relative to baseline values were found with lower scores for bilastine oral compared to dexchlorpheniramine at 1.5 h ($p = 0.042$) and 3 h post-administration ($p = 0.025$), and dexchlorpheniramine and placebo at 1.5 h post-administration ($p = 0.018$).

Table 3
Drowsiness measured using a Visual Analog Scale (VAS).

	Baseline	1.5 h	p-value	3 h	p-value
Bilastine oral	6.70	13.83	0.057	13.61	**0.028**
Bilastine i.m.	11.39	14.30	0.514	17.35	0.203
Bilastine i.v.	10.48	16.48	0.146	23.70	**0.020**
Dexchlorpheniramine i.m.	7.04	31.04	**0.001**	28.57	**0.001**
Placebo	7.74	15.22	0.058	17.26	**0.036**

i.v.: intravenous; i.m.: intramuscular; significant values are highlighted.

A significant effect of the time factor was seen in all psychomotor tests (Grooved Pegboard Test $p = 0.007$, D2 attention test $p < 0.001$ and Digit Symbol Substitution Test $p = 0.031$). A significant effect in treatment interaction and time was found after a single treatment dose in the Grooved Pegboard Test and the D2 attention test ($p = 0.03$). The treatment factor was only significant in the case of the Grooved Pegboard Test ($p = 0.045$).

The longest time to complete the Groove Pegboard test (slower motor speed) was observed with dexchlorpheniramine followed by bilastine i.

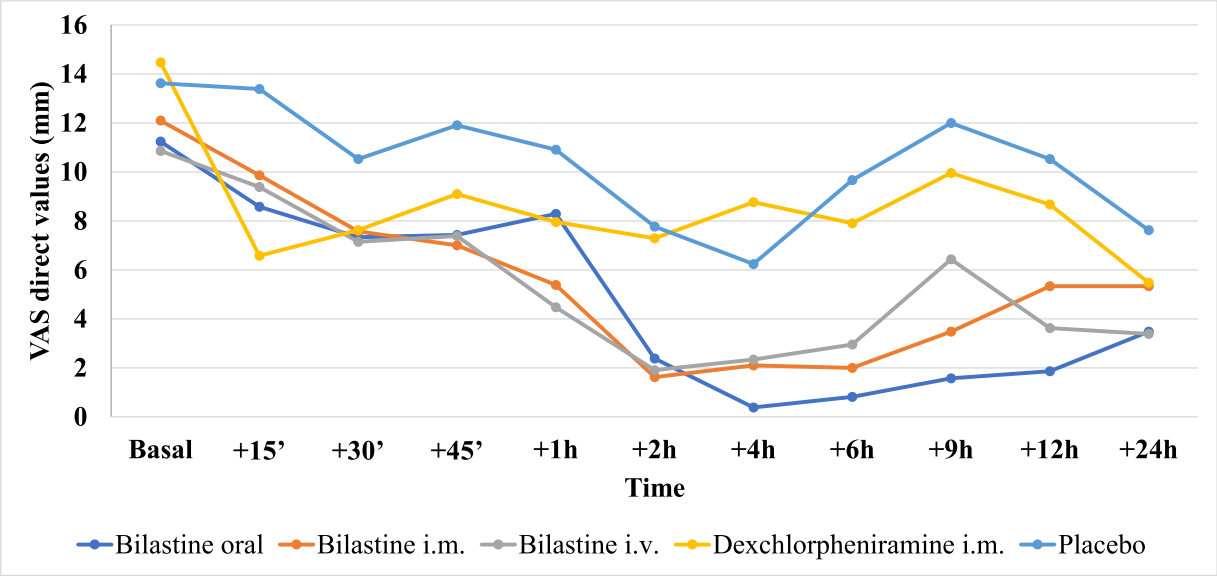

Fig. 5. Itching perception measured with the Visual Analog Scale (VAS).
The graph shows direct values of itching scores (VAS values measured in mm) at every study timepoint for each study treatment. P-values below 0.05 of bilastine compared to dexchlorpheniramine are highlighted using (*).

m., bilastine oral, placebo and bilastine i.v., in that order (Table 4).

In the D2 attention test, dexchlorpheniramine did not experience a significant increase in scores related to baseline at any evaluation time, whereas other treatments showed a significant increase versus baseline. The maximum score when evaluating the total effectiveness (TOT) was found with placebo, followed by bilastine i.v., bilastine oral, bilastine i.m., and finally dexchlorpheniramine (Table 5). When comparing treatments, only bilastine i.v. and placebo showed a significant difference compared to dexchlorpheniramine ($p = 0.003$ and $p = 0.014$ for bilastine i.v. at 1.5 and 3 h post-administration; $p = 0.009$ and $p = 0.005$ for placebo at 1.5 and 3 h post-administration).

In the digit symbol substitution test, no treatment showed statistically significant differences versus baseline values at any evaluation time, and no significant differences between treatments were found. Detailed results for the tests can be found in Table 6.

Eight (8) TEAEs were reported in five subjects throughout the follow-up across the treatment groups: one event of headache and one of diarrhoea in two subjects treated with placebo, one event of mild dizziness in a patient treated with bilastine i.m., and one event of toothache not related to bilastine i.v. that required concomitant medication. Another subject reported events of headache, aphonia and oropharyngeal pain with bilastine oral formulation and another event of headache with dexchlorpheniramine i.m., all were of moderate intensity but required concomitant medication. No serious AEs or deaths were reported during the study. No significant alteration in vital signs, laboratory results, or ECG readings was detected throughout the study.

4. Discussion

This phase I clinical trial assessed the peripheral H_1-antihistamine pharmacodynamic effect, the psychomotor profiles, and the safety of a single dose of three bilastine formulations (i.v., i.m., oral) compared to placebo and the first-generation antihistamine dexchlorpheniramine for the first time. The results related to pharmacokinetics are not addressed in this article, since we have chosen to focus the analysis on pharmacodynamic (Wheal and Flare area reduction) aspects.

This trial, aimed at studying pharmacodynamic effects of 12 mg of parenteral bilastine formulations was developed in response to the demand for alternative parenteral drugs with reduced drowsiness and a better safety profile than current options (Cardona et al., 2020; Jones et al., 2008; Simons, 2004).

In the present study, all active treatments reduced wheal and flare areas compared to placebo at all time points. In particular, bilastine formulations showed significantly higher peripheral antihistamine activity in terms of wheal reduction compared to dexchlorpheniramine and placebo. In addition, bilastine oral showed similar results to those previously reported (Coimbra et al., 2022; García-Gea et al., 2008). All bilastine forms, especially bilastine i.v. and bilastine i.m., showed the most significant inhibition above the 60 % of the wheal area at 15 min and 45 min, respectively, meaning a rapid onset of action and a sustained effect during at least 24 h with minimal variation (<10 %) from 2 h on. Remarkably, bilastine oral also presented a sustainable effect from 2 h on, comparable to its parenteral formulations, with a maximum wheal area reduction of over 60 %. The onset of action was also similar to parenteral formulations, especially compared to dexchlorpheniramine, despite the oral administration. In contrast, dexchlorpheniramine could not show inhibition percentages above 25 % of the affected surface at any time, meaning that the effect was poorer and less extended than bilastine formulations.

Concerning flare area reduction, results were in line with wheal area data. Bilastine formulations showed significantly higher peripheral antihistamine activity in flare area reduction at most of the time points compared to dexchlorpheniramine and placebo. Hence, significant differences versus placebo were observed in all active treatments. The onset of action for the flare area reduction was 15 mins for parenteral treatments and 30 min for bilastine oral, which was expected with the tested pharmaceutical forms, meaning a rapid onset of action. Notably, maximum flare area reduction was similar between bilastine formulations and significantly higher than dexchlorpheniramine and placebo. Nevertheless, the time to reach maximum flare area reduction in the bilastine group was 2 h post-administration with i.m. formulation and 4 h post-administration with both i.v. and oral formulation (i.v. 80.63 %, i.m. 80.63 %, oral 77.67 %), remaining with minimal variations (<10 %) until the end of the study period when percentages decreased. It should be noted that >50 % of flare area reduction could be observed at the time of the onset of action (15 min post-administration of bilastine i.v. formulation). On the other hand, the time to achieve maximum flare area reduction in the dexchlorpheniramine group was 45 min post-administration, yet this reduction remained below 30 %.

Although dexchlorpheniramine was associated with a rapid decline of the subjective itching sensation, the different bilastine formulations showed a constant and pronounced reduction of the itching sensation during the first hour's post-administration, meaning that subjects treated with bilastine formulations felt less itching than subjects in the dexchlorpheniramine or placebo groups.

Expectedly, wheal and flare reductions differ among bilastine formulations during the initial period post-administration due to the distinct administration routes according to the respective pharmaceutical forms. However, no differences were found at any time point when comparing the subjective sensation of itching following the administration of the different bilastine formulations. Considering all these data, all three bilastine formulations showed a similar efficacy profile.

The safety and tolerability profile of bilastine in the pharmaceutical forms tested were favourable. No notable or consistent changes were observed in ECG, vital signs, and laboratory tests, with values outside the normal range without clinical significance. No serious AEs or deaths were identified during the study period. This safety profile is also consistent with previous reports (Coimbra et al., 2022; García-Gea et al., 2008).

Table 4
Grooved Pegboard Test values obtained in three hours.

	Baseline	1.5 h	p-value	3 h	p-value
Bilastine oral	74.70	71.57	**0.018**	72.87	0.314
Bilastine i.m.	74.91	70.91	**0.008**	73.48	0.488
Bilastine i.v.	75.30	70.87	**0.009**	71.35	**0.022**
Dexchlorpheniramine i.m.	74.83	76.00	0.503	76.91	0.277
Placebo	75.83	72.00	**0.007**	69.44	**0.000**

i.v.: intravenous; i.m.: intramuscular; significant values are highlighted.

Table 5
D2 attention test values obtained in three hours.

	Baseline	1.5 h	p-value	3 h	p-value
Bilastine oral	516.17	538.13	**0.002**	555.96	**0.000**
Bilastine i.m.	518.57	536.17	**0.029**	545.13	**0.003**
Bilastine i.v.	522.65	556.57	**0.000**	558.52	**0.000**
Dexchlorpheniramine i.m.	517.26	512.09	0.452	521.87	0.574
Placebo	524.78	548.70	**0.000**	564.30	**0.000**

i.v.: intravenous; i.m.: intramuscular; significant values are highlighted.

Table 6
Digit symbol substitution test values obtained in three hours.

	Baseline	1.5 h	p-value	3 h	p-value
Bilastine oral	99.01	98.03	0.065	98.64	0.377
Bilastine i.m.	98.32	97.51	0.222	98.88	0.444
Bilastine i.v.	98.27	98.06	0.731	98.26	0.970
Dexchlorpheniramine i.m.	98.94	98.22	**0.052**	97.62	**0.065**
Placebo	99.17	98.54	0.171	98.29	0.097

i.v.: intravenous; i.m.: intramuscular; significant values are highlighted.

Regarding psychomotor evaluations, drowsiness perception increased from baseline in all participants. Still, the increase lasted longer in participants treated with dexchlorpheniramine than those treated with bilastine and placebo. This may suggest that when higher scores are present, activities requiring attention and alertness, such as driving or operating machinery, should be avoided. In statistical terms, i.m. bilastine group subjects did not show significant differences from baseline in drowsiness perception at any point in time. It is worth mentioning that subjective items could present some bias, as observed by the unexpected significant increase in the placebo values at 3 h post-administration.

Other psychomotor evaluations depicted similar favourable results regarding adverse effects of bilastine formulations. Subjects treated with dexchlorpheniramine performed worse in the digital symbol substitution test, showing a significant reduction in the scores at both evaluation times, which indicates difficulties in tasks that require attention and quick response, such as working in demanding environments or making decisions. In parallel, only subjects treated with dexchlorpheniramine showed a reduction in the D2 test of attention associated with difficulties in concentration during prolonged activities, such as studying or working on projects. Whereas, bilastine and placebo arms significantly increased the score in the D2 test. Similar results were observed with the Grooved Pegboard Test since dexchlorpheniramine was the only treatment group showing an increase in the scores over time that may translate into challenges in performing tasks that require manual precision, such as writing, sewing, or manual dexterity-related activities. In this test, bilastine i.v. performed significantly better, followed by placebo, bilastine oral and bilastine i.m. Taking together, dexchlorpheniramine decreased attention and coordination when compared to bilastine formulations and placebo. Of note, some of the performed tests can have a bias, as patients are repeatedly asked to complete them, and therefore, they can be unwillingly trained. Notwithstanding, these results are aligned with previous publications about the non-sedating effects with minimal adverse effects on the psychomotor performance of bilastine (García-Gea et al., 2008; Montoro et al., 2011).

Although the limitations commented on previously related to some subjective measures used to assess the sedative effects of tested treatments, the wheal and flare areas reduction methodology used in this study is well documented, and the study design was chosen to minimise interindividual variability. This is evidenced by the similar baseline values for the wheal and flare areas, which represent comparable conditions for each treatment period.

5. Conclusions

In the landscape of antihistamine therapies, the study of parenteral formulations represents a significant advancement in managing allergic conditions. Integrating rapid-acting and effective parenteral antihistamines without sedative effects offers clear advantages for patients suffering from acute allergic manifestations that demand a rapid and efficacious response.

In this clinical trial, all active treatments showed a significant peripheral H_1-blocking effect. Bilastine i.v., bilastine i.m. and bilastine oral formulation induced the highest percentage of wheal and flare area reduction from baseline. Bilastine i.v. and i.m. exhibited a rapid onset of action and a sustained effect over a 24 h period, exceeding that of dexchlorpheniramine. Moreover, bilastine i.v. and i.m. exhibited fewer sedative effects and had a good safety and tolerability profile. Oral bilastine depicted similar results to parenteral forms of bilastine in terms of onset of action and antihistamine effect. Thus, parenteral bilastine forms seem to be an appropriate treatment for patients requiring a parenteral formulation for the treatment of histamine-mediated type I hypersensitivity reactions.

CRediT authorship contribution statement

Jimena Coimbra: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Montserrat Puntes:** Writing – review & editing, Investigation. **Pol Molina:** Writing – review & editing, Investigation. **Ignasi Gich:** Writing – review & editing, Investigation, Formal analysis. **Rosa Antonijoan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Inmaculada Gilaberte:** Writing – original draft. **Paula Arranz:** Writing – original draft. **Carlos Sánchez:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

IG, PA and CS are employees of FAES FARMA. The other authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Ethics approval

The study was conducted at CIM-Sant Pau, Institut de Recerca of Hospital de la Santa Creu i Sant Pau (Barcelona, Spain) after receiving approval from the Ethics Committee of the hospital and the Spanish Agency of Medicines and Medical Devices (AEMPS) and was conducted in accordance with the ethical principles based on the Declaration of Helsinki of 1964, and its later amendments.

Consent to participate

All participants provided written informed consent.

Author contributions

Rosa Antonijoan and Jimena Coimbra contributed to the study's conception and design. All the authors conducted the research and investigation process. Data analysis was performed by Ignasi Gich. Rosa Antonijoan, Jimena Coimbra, Inmaculada Gilaberte, Paula Arranz and Carlos Sánchez drafted the manuscript. All authors read and approved the final manuscript.

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