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Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases

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Abstract

Background: Regulations on medicinal products for paediatric use require that pharmacokinetics and safety be characterized specifically in the paediatric population. A previous study established that a 10-mg dose of bilastine in children aged 2 to <12 years provided an equivalent systemic exposure as 20 mg in adults. The current study assessed the safety and tolerability of bilastine 10 mg in children with allergic rhinoconjunctivitis and chronic urticaria.

Methods: In this phase III, multicentre, double-blind study, children were randomized to once-daily treatment with bilastine 10-mg oral dispersible table (n = 260) or placebo (n = 249) for 12 weeks. Safety evaluations included treatment-emergent adverse events (TEAEs), laboratory tests, cardiac safety (ECG recordings) and somnolence/sedation using the Pediatric Sleep Questionnaire (PSQ).

Results: The primary hypothesis of non-inferiority between bilastine 10 mg and placebo was demonstrated on the basis of a near-equivalent proportion of children in each treatment arm without TEAEs during 12 weeks' treatment (31.5 vs. 32.5%). No clinically relevant differences between bilastine 10 mg and placebo were observed from baseline to study end for TEAEs or related TEAEs, ECG parameters and PSQ scores. The majority of TEAEs were mild or moderate in intensity. TEAEs led to discontinuation of two patients treated with bilastine 10 mg and one patient treated with placebo.

Conclusions: Bilastine 10 mg had a safety and tolerability profile similar to that of placebo in children aged 2 to <12 years with allergic rhinoconjunctivitis or chronic urticaria.

Allergic rhinoconjunctivitis and chronic urticaria are common conditions in young children (<12 years) and carry a large burden of disease (1, 2). Allergic symptoms frequently interfere with a child's ability to participate in daily activities and disrupt normal sleeping patterns, causing emotional distress and impacting negatively on learning and cognition (1, 3). This can lead to major dysfunction within the family unit and substantially impair the quality of life of the affected child and other family members.

Second-generation H_1 antihistamines are treatment of choice for allergic rhinoconjunctivitis and chronic urticaria in children (4, 5). Agents currently authorized for use in children aged 2–11 years include cetirizine, desloratadine (1 year of age), levocetirizine, loratadine and rupatadine (6–9). Given the differences between second-generation H_1 antihistamines in terms of their biotransformation, transport and elimination (7), and general age-related differences among children in their ability to absorb, transform, metabolize and excrete medications (10), a need remains for effective options to treat chronic allergic conditions in young children.

Bilastine is a second-generation oral H_1 antihistamine approved for use in several world regions at a once-daily dose of 20 mg for symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and adolescents (≥12 years of age). In these indications, bilastine has been shown to have an efficacy similar to that of other second-generation oral H_1 antihistamines and an excellent safety profile (11–14). To date, there has been no evidence of sedative or cardiotoxic effects

with bilastine in clinical trials or post-marketing experience (15, 16). Bilastine's high selectivity for H_1 receptors (17), limited passage across the blood–brain barrier (18) and negligible metabolism (19) may confer safety and tolerability advantages over other oral second-generation H_1 antihistamines used to treat these conditions.

Although regulations on medicinal products for paediatric use allow for the extrapolation of much of the data generated during studies in adults to paediatric populations, exceptions are pharmacokinetic data (to establish appropriate dosing) and safety data. Previously, a paediatric pharmacokinetic study (protocol BILA-3009/PED – EudraCT No.: 2009-012013-22) established that a 10-mg dose of bilastine in children aged 2 to <12 years provided an equivalent systemic exposure as a 20 mg dose in adults (20). The aim of this study was to assess the safety and tolerability of bilastine 10 mg once daily in children aged 2–11 years with allergic rhinoconjunctivitis or chronic urticaria.

Methods

This phase III, double-blind, randomized, placebo-controlled, parallel-group study was conducted between March 2013 and July 2014 at 20 centres in Argentina, Croatia, Hungary, Poland, Portugal and Spain. Eligibility criteria were boys and girls aged 2–11 years with a documented history of allergic rhinoconjunctivitis or chronic urticaria and with clinical symptoms at study entry. For patients with allergic rhinoconjunctivitis, a positive skin prick test/RAST for at least one allergen was necessary. Results of a 12-lead electrocardiogram (ECG) had to be within acceptable limits, with QTc interval values after Fridericia's correction within normal limits (<440 msec).

Exclusion criteria were as follows: hypersensitivity to H_1 antihistamines (including bilastine) or benzimidazoles; any concurrent clinical condition or relevant history of renal, hepatic, gastrointestinal tract, cardiovascular, respiratory, haematological, endocrine or neurological diseases; and clinically relevant abnormal laboratory values indicative of physical illness. Intake of the following medications was not allowed within 7 days (or otherwise noted) prior to randomization: oral corticosteroids; loratadine/desloratadine (10 days) or other systemic antihistamines (3 days); antileukotrienes; delayed-release corticosteroids (3 months); ketotifen (2 weeks); macrolide antibiotics and imidazolic antifungals (systemic); anticholinergics; investigational medication or antibodies. Regularly scheduled immunotherapy was permitted throughout the study except for 24 h before and 24 h after the first dose of study medication.

Six visits were scheduled: screening, baseline, week 4, week 8, week 12 (end of treatment) and a post-treatment follow-up at week 16. Screening assessments included patient history, demographic data, physical examination, 12-lead ECG and a blood sample for laboratory tests. Baseline evaluations included physical examination, 12-lead ECG, adverse events and somnolence/sedation assessment. These same assessments were repeated at weeks 4, 8 and 12, at which times treatment compliance, concomitant medication and the use of rescue medication were also evaluated. Additional activity at week 12 was to take a blood sample for laboratory tests. The safety follow-up at week 16 involved a physical examination, adverse events assessment, somnolence/sedation assessment and recording of concomitant medication. Patients who discontinued the study at any time during the 12-week treatment period were asked to attend an early termination visit in which all activities scheduled for the week 12 visit were conducted.

Study treatments were allocated according to a pre-established randomization list by age strata (2 to <6 years, 6 to <9 years, 9 to <12 years) created by the sponsor, using a random design by blocks. Bilastine and placebo were matched in pharmaceutical form and had identical packaging to maintain blinding.

A bilastine 10-mg oral dispersible tablet (dissolved in water for children 2 to <6 years, and either swallowed or dissolved in water for children aged 6 to <12 years) or placebo was administered once daily in the morning under fasting conditions (1 h before breakfast or two hours after breakfast) for 12 weeks.

To limit the number of dropouts, occasional use of rescue medication was allowed in the form of short-term topical decongestants (eye or nose), corticosteroids or antihistamines for rhinoconjunctivitis, or short-term topical corticosteroids for urticaria.

In accordance with guidance from the Paediatric Committee of the European Medicines Agency, the primary analysis variable was the proportion of children in each treatment group without treatment-emergent adverse events (TEAEs) during the course of the study.

Secondary variables included: the proportion of children with related TEAEs during the course of the study; incidence of TEAEs by System Organ Class and Preferred Term; laboratory blood tests performed at baseline and the end of treatment; assessment of cardiac safety by ECG at each visit; assessment of somnolence/sedation with the Pediatric Sleep Questionnaire (PSQ).

The study was performed in strict compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the most recent revision of the Declaration of Helsinki (Seoul 2008). The study protocol was approved by ethics committees of all participating centres in accordance with local regulatory requirements. Parent(s)/guardian provided written consent for the child to participate in the study.

Statistical analysis

Under the assumption that 80% of patients in each treatment group would experience at least one TEAE during the course of the study, and using a one-sided 0.025 significance level and a 10% delta, it was calculated that 504 patients (252 per treatment group) were required to achieve a power of 80%. Non-inferiority was to be accepted if the upper limit of the two-sided 95% confidence interval (CI) for the difference in the incidence of TEAEs (bilastine minus placebo) was less than 10%.

Statistical analysis was performed using SAS® version 9.2 (Cary, NC, USA).

Statistical significance was assessed for two-sided probability values <0.05 unless otherwise specified (e.g. when checking non-inferiority). Missing values were not considered for statistical calculations, and no imputations were performed to replace missing values. Although the study was not powered for a stratified analysis, descriptive results of TEAEs were provided by age strata.

Quantitative variables were described by the number of subjects, means, standard deviations, maximum and minimum values and quartile values. Qualitative variables were described by frequency and percentage.

The somnolence/sedation questionnaire was assessed by an analysis of covariance (ANCOVA) model, with treatment as the main factor and baseline values as covariates.

Secondary categorical variables were assessed by means of the chi-squared test, or the Fisher's exact test, if applicability conditions were not met.

Results

Of 537 children screened, 509 were randomized to either bilastine 10 mg (n = 260) or placebo (n = 249). All randomized patients received study medication and comprised the safety population. Twelve patients in each treatment group were withdrawn before the end of the study (Fig. 1). TEAEs leading to discontinuation were atopic dermatitis (n = 1) and loss of consciousness, dizziness and fatigue (n = 1) in the bilastine 10-mg group and urticaria (n = 1) in the placebo group.

Treatment groups were well matched at baseline for demographic and other characteristics (Table 1). The mean age of the patient sample was 7.5 ± 2.4 years, the proportion of male patients was 62.5%, and 93% of the population were Caucasian. Time since diagnosis was approximately 3.5 years, and the majority of patients had allergic rhinoconjunctivitis.

Compliance, as assessed by tablet count, was 98.5% in the bilastine 10-mg group and 98.6% in the placebo group. Similar proportions of patients in each group required rescue medication (24.6 and 20.1%, respectively).

Safety

Overall, 31.5% of patients (n = 82) in the bilastine 10-mg group and 32.5% of patients (n = 81) in the placebo group were without TEAEs during the course of the study, for a treatment difference of 0.99% (95% CI: −9.10, 7.10) in the primary variable (Fig. 2). No statistically significant differences were found between treatment groups for incidences of TEAEs (Fig. 2) or related TEAEs (Fig. 3) in the population overall or by age subgroup.

The most commonly reported TEAEs (frequency ≥5% in any treatment group) were headache, cough, pharyngitis, allergic conjunctivitis, nasopharyngitis and pyrexia (Table 2). Related TEAEs reported by more than one patient in either the bilastine or placebo group were allergic conjunctivitis (5 vs. 6 events), upper abdominal pain (1 vs. 3 events), vomiting (0 vs. 2 events), rhinitis (3 vs. 4 events), headache (6 vs. 6 events), somnolence (0 vs. 2 events), nasal congestion (0 vs. 2 events), allergic rhinitis (0 vs. 8 events), sneezing (0 vs. 9 events) and urticaria (2 vs. 2 events). The majority of related TEAEs were mild to moderate in intensity (92% for bilastine 10 mg and 86% for placebo). Analysis of TEAEs by System Organ Class (frequency ≥2% in the overall

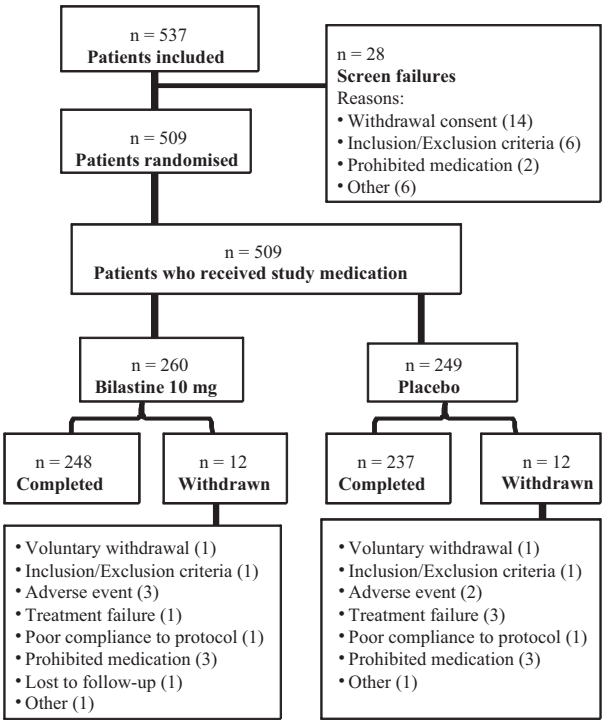

Figure 1 Patient disposition.

Table 1 Demographic and other baseline characteristics: safety population

Variable	Bilastine 10 mg (n = 260)	Placebo (n = 249)
Age (years), mean (SD)	7.5 (2.4)	7.4 (2.5)
Age categories		
2 to <6 years, n (%)	58 (22.3)	58 (23.3)
6 to <9 years, n (%)	105 (40.4)	95 (38.2)
9 to <12 years, n (%)	97 (37.3)	96 (38.6)
Gender (male), n (%)	163 (62.7)	155 (62.2)
Race (Caucasian), n (%)	244 (93.8)	234 (94.0)
Height (cm), mean (SD)	129.1 (15.9)	128.8 (16.8)
Weight (kg), mean (SD)	30.3 (11.5)	30.5 (12.1)
Body mass index (kg/m^2), mean (SD)	17.6 (3.3)	17.7 (3.3)
Time since diagnosis (years), mean (SD)	3.6 (2.5)	3.5 (2.6)
Type of diagnosis		
Allergic rhinoconjunctivitis, n (%)	252 (96.9)	227 (91.2)
Chronic urticaria, n (%)	8 (3.1)	22 (8.8)

SD, standard deviation.

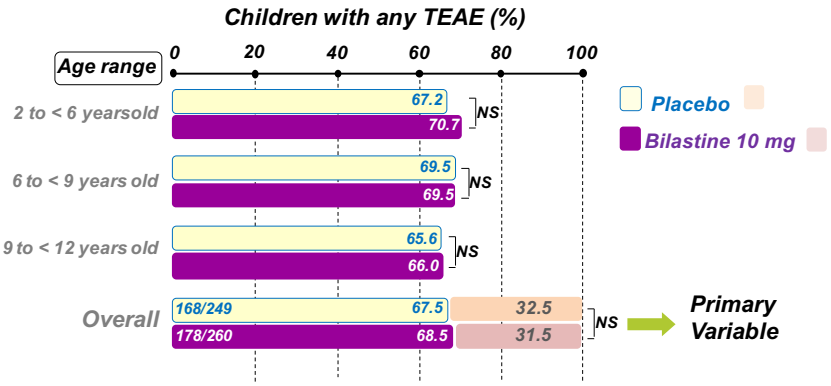

Figure 2 Children (%) with any treatment-emergent adverse event (TEAE) in the population overall and by age range.

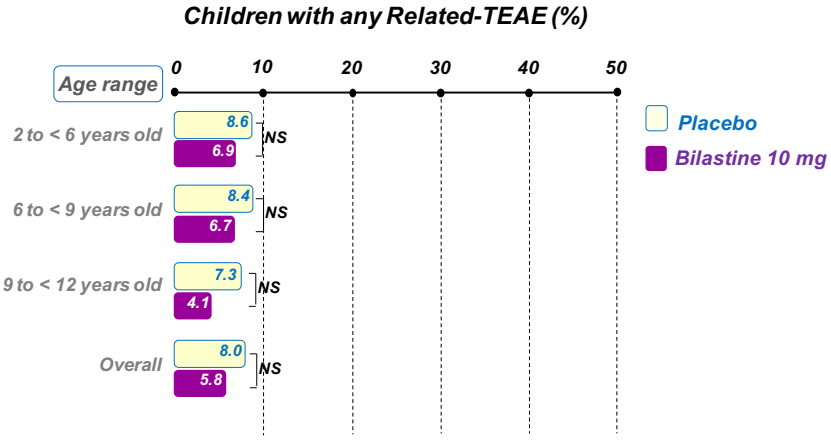

Figure 3 Children (%) with any related treatment-emergent adverse event (TEAE) in the population overall or by age range.

population) showed no statistically significant differences between treatment groups according to body system.

There were no deaths during the study. Of 14 serious TEAEs reported in 11 patients (two events in two patients treated with bilastine 10 mg, 12 events in nine patients treated with placebo), none was considered to be related to treatment.

There were no clinically and/or statistically relevant differences between bilastine 10 mg and placebo for vital signs (systolic and diastolic blood pressure, heart rate and body temperature), clinical laboratory values (except for one patient with elevated transaminases at screening who was withdrawn from the study after one dose of bilastine 10 mg), ECG parameters or physical examination.

PSQ scores for somnolence/sedation decreased slightly from baseline to week 12 in both the bilastine 10-mg and placebo groups (Fig. 4). Between-group differences were not statistically significant for the total score or for scores in the individual domains.

Discussion

Given the difficulties and ethical considerations associated with performing clinical trials in children (21), a common approach has been to utilize data generated in adults and adjust the dose according to a child's weight. However, as children have developmental and physiological characteristics distinct from adults and respond differently to medications (10), this practice is now considered to be wholly inappropriate. In recent times, legislation has been enacted to encourage the development of medicines for children and to improve information about the use of medicines in children (21, 22). As part of the bilastine Paediatric Investigation Plan submitted to the European Medicines Agency (EMA), this phase III, multicentre, double-blind, randomized study was undertaken to assess the safety and tolerability of bilastine 10-mg oral dispersible tablet administered once daily for 12 weeks in children aged 2–11 years with allergic rhinoconjunctivitis or chronic urticaria.

The primary hypothesis of non-inferiority of bilastine 10 mg with respect to placebo was demonstrated on the basis of a near equivalent proportion of children in each treatment arm without TEAEs during 12 weeks' treatment (31.5% vs. 32.5%). Results for the primary analysis variable were supported by all secondary safety variables. No meaningful differences between treatment groups were observed from baseline to study end for TEAEs or related TEAEs, vital signs, ECG parameters and somnolence/sedation scores. The safety and tolerability profiles of bilastine 10 mg and placebo were

Table 2 Most frequent treatment-emergent adverse events (≥5% frequency); safety population

Adverse event	Bilastine 10 mg (n = 260) Events/Patients (%)	Placebo (n = 249) Events/Patients (%)
Headache	48/30 (11.5)	45/26 (10.4)
Cough	29/23 (8.8)	32/22 (8.8)
Pharyngitis	27/25 (9.6)	18/16 (6.4)
Allergic conjunctivitis	25/24 (9.2)	21/19 (7.6)
Nasopharyngitis	38/24 (9.2)	19/17 (6.8)
Pyrexia	16/16 (6.2)	38/23 (9.2)
Allergic rhinitis	20/13 (5.0)	28/21 (8.4)
Bronchitis	12/10 (3.8)	15/14 (5.6)
Viral infection	12/10 (3.8)	18/16 (6.4)

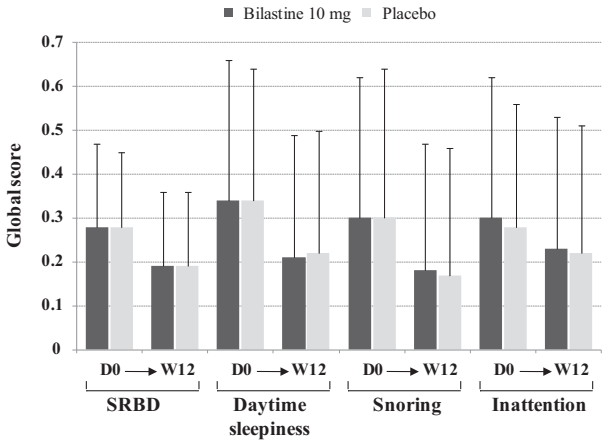

Figure 4 Assessment of somnolence/sedation from baseline (D0) to week 12 (W12) according to global scores on the four domains of the Pediatric Sleep Questionnaire: sleeping-related breathing disorder (SRBD), daytime sleepiness, snoring and inattention.

similar across all three age strata (2 to <6 years, 6 to <9 years and 9 to <12 years) and across a range of different climates in participating countries from the Northern and Southern Hemispheres.

The 12-week study duration was in accordance with EMA guidelines for clinical development of medicinal products for treatment of allergic rhinoconjunctivitis in children. Bilastine thus joins cetirizine (23), levocetirizine (24, 25) and loratadine (26) as second-generation H_1 antihistamines approved for use in paediatric patients for which long-term safety data are available.

In terms of limitations, for safety and regulatory reasons, the bilastine dose was set at 10 mg once daily including in children with chronic urticaria. As such, no information was obtained on dose escalation in young children. Greater efficacy with fourfold updosing of bilastine (i.e. 80 mg), without an increase in sedation, has been demonstrated in adults with cold contact urticaria (27); whether the same holds true for young children remains to be determined. The hypothesis of non-inferiority between bilastine and placebo was based on the assumption that 80% of patients would experience at least one TEAE during the 12-week treatment period. Although only 70% of patients experienced a TEAE, the low attrition rate meant that the sample size was still sufficient to confirm non-inferiority between bilastine 10 mg and placebo.

Conclusions

On the basis of a confirmed primary hypothesis of non-inferiority between bilastine 10 mg and placebo with respect to the proportion of children without TEAEs, and the similar safety and tolerability profile of bilastine 10 mg and placebo, bilastine 10 mg can be considered a suitable treatment option for children aged 2–11 years with allergic rhinoconjunctivitis or chronic urticaria.

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Conflicts of interest

Román Valiente is a fulltime employee of FAES FARMA S. A. The remaining authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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