ORIGINAL ARTICLE

Pharmacokinetics and Safety of Bilastine 10 mg/d in Children Aged 2 to 5 Years With Allergic Rhinoconjunctivitis or Urticaria: A Phase 3 Clinical Trial

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on behalf of the BILA-4021/PED Research Group

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Abstract

Background: Bilastine is a second-generation antihistamine for the symptomatic treatment of allergic rhinoconjunctivitis (ARC) and urticaria in adults, adolescents, and children. The pharmacokinetics and safety of oral bilastine 10 mg/d in children aged 2 to 5 years were evaluated.
Methods: This was a multicenter, open-label clinical trial in children aged 2 to 5 years with seasonal or perennial ARC or urticaria treated once daily with bilastine 10 mg orodispersible tablets. The safety evaluation included treatment-emergent adverse events (TEAEs), vital signs, and physical examination. Pharmacokinetic data were pooled with data from a prior pediatric study, and pharmacokinetic modeling was performed to assess consistency.
Results: A total of 37 children with ARC (81.1%), urticaria (8.1%), or both (10.8%) were included in the study, with a mean (SD) age of 3.7 (1.2) years. The highest plasma concentrations of bilastine were observed 1 hour after administration (634.91 ng/mL). Eight patients (21.6%) experienced 1 TEAE each, none of which was severe. Body weight and age were not covariates of variation in either systemic clearance or the volume of distribution in children aged 2 to 5 years and did not affect the pharmacokinetic parameters of bilastine.
Conclusions: The pharmacokinetics of bilastine was linear and consistent with data from a previous trial, suggesting that a 10-mg dose may be used in children (2 to <12 years). No dose adjustments are deemed necessary. Oral once-daily bilastine 10 mg presented a good safety profile in children aged 2 to 5.

Key words: Children. Young children. Allergic rhinoconjunctivitis. Urticaria. Antihistamine. Bilastine. Pediatric. Nonsedating.

Resumen

Antecedentes: La bilastina es un antihistamínico de segunda generación para el tratamiento sintomático de la rinoconjuntivitis alérgica (RCA) y la urticaria en adultos, adolescentes y niños. Se evaluó la farmacocinética y la seguridad de bilastina oral 10 mg/día en niños de 2 a 5 años.
Métodos: Ensayo clínico multicéntrico, abierto, en niños de 2 a 5 años con RCA estacional o perenne o urticaria tratados una vez al día con bilastina 10 mg en tabletas bucodispersables. La evaluación de seguridad incluyó eventos adversos causados por el tratamiento, signos vitales y exámenes físicos. Los datos farmacocinéticos se combinaron con datos de un estudio pediátrico anterior y se realizaron modelos farmacocinéticos para evaluar su consistencia.
Resultados: Se incluyeron en el estudio un total de 37 niños con RCA (81,1%), urticaria (8,1%) o ambas (10,8%), con una edad media (DE) de 3,7 (1,2) años. Los valores más altos de concentración plasmática de bilastina se observaron 1 hora después de la administración de bilastina (634,91 ng/mL). Ocho sujetos (21,6%) experimentaron un evento adverso cada uno, ninguno grave. El peso corporal o la edad no fueron una covariable de variación ni en el aclaramiento sistémico ni en el volumen de distribución en niños de 2 a 5 años, y se encontró que no afectaba los parámetros farmacocinéticos de bilastina.
Conclusiones: La farmacocinética de bilastina fue lineal y consistente con los datos de un ensayo anterior, lo que sugiere que se puede usar una dosis de 10 mg para toda la población pediátrica (2 a <12 años) y no se consideran necesarios ajustes de dosis. Bilastina oral de 10 mg una vez al día presentó un buen perfil de seguridad en niños de 2 a 5 años.

Palabras clave: Niños. Niños pequeños. Rinoconjuntivitis alérgica. Urticaria. Antihistamínico. Bilastina. Pediátrico. No sedante.

Summary box

- **What do we know about this topic?**
  Bilastine is a second-generation antihistamine authorized for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults, adolescents, and children. However, the pharmacokinetics and safety of oral bilastine 10 mg in children aged 2 to 5 require further research.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  Pharmacokinetic modeling showed that weight and age were not covariates of variation in systemic clearance or volume of distribution in children aged 2 to <12, thus confirming the safety of bilastine 10 mg. Moreover, no dose adjustments are necessary.

Introduction

Allergic rhinoconjunctivitis (ARC) is a common chronic disorder in children, especially in developed countries, and its prevalence has approximately doubled over the past 20 years [1-3]. ARC causes nasal and conjunctival symptoms and general complaints such as fatigue and cough [4-6]. Depending on the type of allergen or allergens involved, ARC can be classified as seasonal ARC (SARC) or perennial ARC (PARC), the former being more common [7]. Urticaria is one of the most common skin diseases and is characterized by the development of wheals (hives), angioedema, or both [8,9]. Urticaria can be classified as acute, when symptoms last ≤6 weeks, or chronic, when these symptoms last longer [10]. Both ARC and urticaria can severely impact the quality of life of patients and caregivers [4,9,11]. First-line treatment of ARC and urticaria includes systemic and topical antihistamines, mast cell stabilizers, anti-inflammatory drugs, and corticosteroids [12-14].

Bilastine is an effective, well-tolerated, and safe second-generation, nonsedating selective inverse H1 histamine receptor agonist authorized for the treatment of allergic disorders such as ARC and urticaria in adults, adolescents, and children [15,16]. Bilastine has been extensively evaluated in pharmacokinetic, efficacy, and safety studies [17-19], revealing efficacy [20,21] and an excellent safety and tolerability profile [22-26]. In children aged ≥6 years with ARC or urticaria, the safety of oral bilastine has also been extensively evaluated [27-29]. Based on this evidence, oral bilastine is licensed as 20-mg tablets for the symptomatic treatment of ARC and urticaria in adults and adolescents aged ≥12 years [30]. A 10-mg orodispersible tablet and the once-daily 2.5-mg/mL oral solution are also indicated for the pediatric population [16]. The 10-mg daily dose for children aged 6 to 11 years was calculated based on adult data and pharmacokinetic simulations [31], which were confirmed in a clinical pharmacokinetic study (BILA–3009) of children aged 4 to 11 years with ARC or urticaria [31,32]. These analyses were further supported by a pharmacokinetic comparison study after approval of bilastine in children, which showed no significant pharmacokinetic differences between the 10-mg dose in children aged 6 to 11 years and the 20-mg dose in adults [29]. Furthermore, a phase 3, multicenter, double-blind, placebo-controlled clinical trial (BILA–3312) involving 509 children aged 2 to 11 years showed that the safety profile

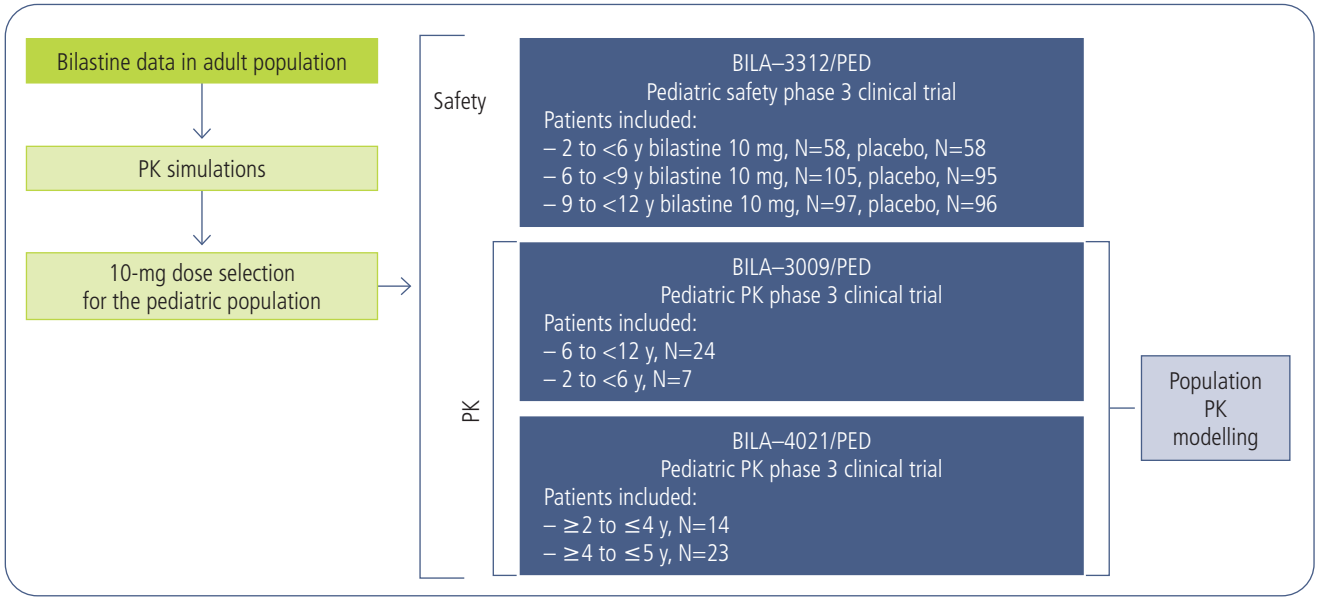

Figure 1. Development of pediatric bilastine, including the present clinical trial (BILA–4021/PED). PK indicates pharmacokinetic.

of once-daily bilastine 10 mg for 12 weeks did not differ from that of placebo [27]. However, the pharmacokinetics of oral bilastine (10 mg/d) has not been thoroughly explored in children aged 2 to 5 years with ARC and/or urticaria, as very few patients below age 6 years were recruited in previous pharmacokinetic studies. For this reason, a multicenter, open-label clinical trial (BILA–4021) was conducted to evaluate the plasma levels and safety of bilastine (10 mg/d) in patients aged 2 to 5 years with SARC/PARC and/or urticaria. The study aimed to provide observations on pharmacokinetics that would make it possible to extend the approved indications down to age 2 years. A summary of the clinical trials related to the development of pediatric bilastine is shown in Figure 1.

Materials and Methods

BILA–4021 was a multicenter, open-label, noncontrolled, phase 3 clinical trial in children aged 2 to 5 years with SARC/PARC or urticaria. The trial was conducted between December 2, 2021 and April 21, 2022 with the participation of 2 clinical trial sites in Lithuania, 1 in Poland, and 4 in Slovakia (Supplementary Materials, Table S1). The trial's primary objective was to collect plasma after administering multiple oral doses of bilastine over a period of 7 (+3) days and obtain bilastine concentration values for the subsequent population-based pharmacokinetic modeling study. This aimed to assess whether children aged 2 to 5 years receiving a once-daily dose of oral bilastine 10 mg achieved plasma values equivalent to those in the older pediatric age range (6 to 11 years) and to establish the suitability of the same dose across the entire pediatric age range (2 to 11 years).

The protocol of the current study and the information included in the written informed consent form were approved by an independent ethics committee before initiation at each center. Written informed consent was received from the patient's legally accepted representative before enrollment in the trial and before the beginning of the study. The trial was conducted in accordance with the Declaration of Helsinki and with the applicable regulatory requirements of the participating countries.

Study Population

The study population comprised boys and girls aged 2 to 5 years with a weight of ≥10 kg and a documented history of mild-to-moderate SARC and/or PARC before or during the first visit and symptomatic ARC (SARC and/or PARC) or urticaria at screening. Patients with ARC had at least 1 documented positive skin prick test result and/or a positive validated IgE test result with at least 1 seasonal and/or perennial allergen in their lifetime before visit 1. Patients were excluded if they had any other known allergy or hypersensitivity to bilastine or its inactive ingredients or if they had taken any of the prohibited medications (depot corticosteroids during the previous 3 months; St John's wort during the previous 15 days; oral corticosteroids or oral antihistamines, antileukotrienes, amoxicillin, benzylpenicillin, macrolide antibiotics, imidazole antifungals, omeprazole, or carbamazepine during the previous 7 days).

Study Design and Measurements

A summary of trial procedures is shown in Supplementary Information Table S2. The trial consisted of a screening period of up to 7 days starting at visit 1, a 1-day baseline period (visit 2), a treatment period of 7 (+3; visit 3) days or 14 (+6) days (visit 4) depending on the investigator's criteria, and a follow-up period of 7 (+3) days (visit 5). At visit 1, informed consents were obtained from the legally accepted representatives, and the screening procedures were performed. At visit 2 (baseline), eligible patients (or their legally accepted representatives) were provided with sufficient 10-mg bilastine orodispersible tablets (Bilaxten, FAES FARMA SA) for a treatment period of 7 (+3) days or 14 (+6) days. Children were to be administered 1 bilastine 10-mg orodispersible tablet daily, at the same time, preferably in the morning, and under fasting conditions (1 hour before or 2 hours after food intake), starting the day after visit 2. Visit 3 had to take place 7 (+3) days after visit 2, and blood sampling was performed during this visit. If, based on his/her criteria and the patient's symptoms, the investigator considered that the patient needed to continue treatment after visit 3, then the patient attended visit 4 at 14 (+6) days after visit 2 (baseline).

To analyze the pharmacokinetic profile of bilastine while keeping the required blood sampling to a minimum, children were allocated to 3 pharmacokinetic sampling groups so that blood samples could be collected at the maximally informative time points, and an acceptable maximum of 3 blood samples per child was not exceeded. Children were randomly assigned to these 3 blood sampling groups at a randomization ratio of 1:1:1 and stratified by age group, with 2 age subgroups defined: children aged ≥2 to <4 years and children aged 4 to ≤5 years. Each pharmacokinetic sampling group included at least 2 patients from each age subgroup. Children in group 1 underwent sampling at 0.5, 2, and 4 hours after intake of bilastine at visit 3; those in group 2 were sampled 24 hours after intake on the day before visit 3 (reflecting the 24-hour timepoint bilastine intake at steady state), and 0.25 hours and 1 hour after intake at visit 3. Finally, children in group 3 underwent sampling 6 and 12 hours after intake of bilastine at visit 3. At visit 3, patients assigned to pharmacokinetic blood sampling group 1 or group 2 took the bilastine tablet at the clinical trial sites, whereas those assigned to group 3 took their bilastine tablet at home, as they did not need to be at the site in the morning. All the clinical trial procedures and standard examinations were chosen so that they did not pose a risk for the patients other than those associated with assessments in daily clinical practice. However, in the case of unusual symptoms or questions, the legally accepted representatives were always requested to contact the investigator and arrange an unscheduled visit if needed.

Adverse events (AEs) were defined as any untoward medical occurrence in a patient to whom a medicinal product was administered and that did not necessarily have a causal relationship with the treatment. For evaluation in this trial, these untoward events were classified as non–treatment-emergent adverse events (untoward event that occurred between the consent signature and the first treatment administration), treatment-emergent adverse events (TEAEs [untoward event happening after the first treatment administration and up to 7

days after the last treatment day]), or serious adverse events (TEAEs considered serious).

Statistical Analysis

This trial was designed to achieve sufficiently high bilastine plasma concentrations and thus estimate the pharmacokinetic parameters of oral bilastine in children aged 2 to 5 years using a population-based approach. With the selection of 24 pediatric patients providing a maximum of 3 samples each and divided into 3 groups with distinct sampling schemes, there was a good balance between the anticipated precision of the population pharmacokinetic parameters to be estimated and the data to be collected in the clinical setting.

TEAEs, vital signs, and physical examination findings were analyzed and reported descriptively. The incidence of TEAEs is presented according to the Medical Dictionary for Regulatory Activities primary system organ class and preferred terms. Additionally, TEAEs were summarized by intensity (severity), seriousness, and relationship to treatment with bilastine. The number and percentage of patients with normal and abnormal physical examination findings, as well as vital sign values, including assessment of clinical significance, were also described.

Modeling

The plasma concentration results of this clinical trial were incorporated into the population pharmacokinetic model for bilastine in children aged 2 to <12 years that had been previously created with data from the previous pediatric pharmacokinetic study (BILA–3009) [29,31]. This pharmacokinetic model was run using NONMEM© v.7.3 (ICON plc) with the NMTRAN preprocessor and PREDPP routines and subsequent Bayesian estimation of individual pharmacokinetic parameters (FOCE/POSTHOC in NONMEM®). Two compartment and 1-compartment models were tested initially for comparison, with random effects on clearance and the first order absorption rate constant. The half-life of oral bilastine was calculated as ln [2]/[clearance/steady-state volume of distribution]. Preliminary multiple correlations among individual pharmacokinetic parameters and potential covariates (ie, demographic data) were determined using scatter matrix plots and locally estimated scatterplot smoothing or locally weighted scatterplot smoothing regressions. The primary covariates available were body weight, age, and sex.

Results

A total of 39 children were enrolled in this trial (Figure 2), although 1 was considered a screening failure due to ineligibility. Another child withdrew after randomization and before treatment started. Thirty-eight children were randomized to pharmacokinetic blood sampling groups, and 37 children had at least 1 intake of bilastine and were included in the safety set. Only 1 patient (2.7%) out of these

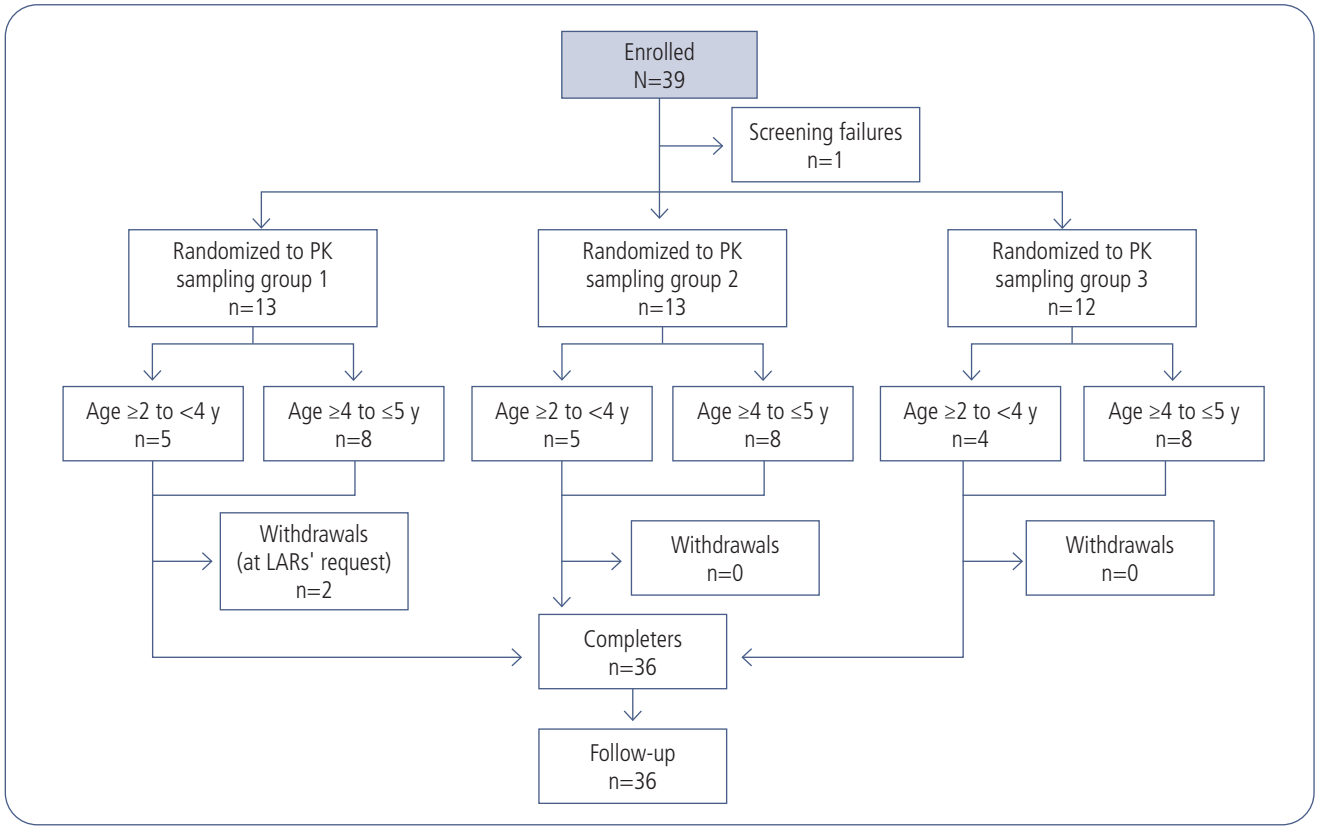

Figure 2. Patient disposition in the BILA-4021/PED trial. PK indicates pharmacokinetic; LAR, legally accepted representative.

37 children discontinued prematurely at the legally accepted representative's request. The remaining 36 patients completed at least a 7-day treatment period and had, as intended, a minimum of 1 pharmacokinetic blood sample taken. The demographic and clinical characteristics of the patients are shown in Table 1. The mean (SD) age was 3.7 (1.2) years and 70.3% were boys. Seventeen children had PARC (45.9%), 1 had SARC (2.7%), and 12 had a combination of PARC and SARC (32.4%). Three children (8.1%) had urticaria and 4 (10.8%) had combined urticaria and ARC.

Table 1. Demographic and Clinical Data of the Study Population.

Variable	N=37
Mean (SD) age, y	3.7 (1.2)
Age categories, No. (%)	
≥2 to <4 y	14 (37.8)
≥4 to ≤5 y	23 (62.2)
Sex (male), No. (%)	26 (70.3)
Mean (SD) weight, kg	19.2 (5.4)
Mean (SD) height, cm	107.4 (10.5)
Patients with only urticaria, No. (%)	
Chronic urticaria	2 (5.4)
Acute urticaria	1 (2.7)
Patients with only ARC, No. (%)	
PAR	17 (45.9)
SAR	1 (2.7)
PAR and SAR	12 (32.4)
Patients with ARC and urticaria, No. (%)	
Chronic urticaria and SAR	1 (2.7)
Acute urticaria and SAR	2 (5.4)
Acute urticaria and PAR	1 (2.7)
Types of allergens in patients with ARC, No. (%)	
Mites (PAR)	27 (79.4)
Tree pollen (SAR)	12 (35.3)
Pet (PAR)	7 (20.6)
Grass pollen (SAR)	6 (17.6)
Fungus (PAR)	5 (14.7)
Other (SAR and PAR)[a]	7 (20.6)
Patients with concomitant medication, No. (%)	24 (64.9)
Salbutamol	11 (29.7)
Fluticasone propionate	9 (24.3)
Nasal preparations[b]	10 (27.0)
Other[c]	11 (29.7)

Abbreviations: ARC, allergic rhinoconjunctivitis; PAR, perennial allergic rhinoconjunctivitis; SAR, seasonal allergic rhinoconjunctivitis.
[a]Grain/legumes (SAR), animals (PAR), feathers (PAR), food (PAR), and unclassified.
[b]Mometasone furoate, fluticasone propionate, or mometasone.
[c]Inosine pranobex (antiviral), bacterial lysate nos, dermatological preparations, vitamins, and not available.

Demographic data were comparable among all the pharmacokinetic groups. The highest bilastine plasma concentration values were observed at 0.5 hours (583.35 ng/mL), 1 hour (634.91 ng/mL), and 2 hours (375.81 ng/mL) after the intake of a daily 10-mg dose of bilastine. Individual values decreased to below 100 ng/mL at 4, 6, and 12 hours after intake except for 1 patient with 154.20 ng/mL after 4 hours.

Safety of Bilastine in Children

The mean overall duration of treatment in this trial was 15.4 days (range, 8-20 days). Eight patients (21.6%) experienced 1 TEAE each, and only 1 of those TEAEs, fatigue, was categorized as being possibly related to the treatment. Five out of 8 TEAEs (13.5%) were infections or infestations, which required medication in 4 cases (10.8%). There was no association between somnolence and any of the TEAEs. No deaths, serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation of the trial were observed during the treatment period (Table 2). No abnormalities in heart rate were observed during the trial. Normal body temperature values were reported for all patients except 1 who developed urinary tract infection and in whom the increase in body temperature was considered to be clinically significant at visit 4.

Abnormal physical examination findings at baseline were observed for the eyes, nose, skin, and general appearance, and the number of abnormal findings decreased slightly during the trial. Reported abnormal findings at baseline concerning the eyes, nose, and skin were assumed in most cases to be related to the underlying diagnoses of ARC and/or urticaria. No clinically significant changes from normal at baseline to abnormal

Table 2. Safety of Oral Bilastine (10 mg).

Variable	N=37
Mean (SD) overall treatment period, d	15.4 (3.7)
Mean (SD) completion period, d[a]	8.8 (2.2)
TEAEs, No. (%)	8 (21.6)
Nonserious TEAE	8 (21.6)
Serious TEAE	0
Related TEAE	1 (2.7)
TEAEs requiring medication	4 (10.8)
TEAEs leading to discontinuation	0
Incidence of TEAEs, No. (%)	
COVID-19	1 (2.7)
Upper respiratory tract infection	1 (2.7)
Urinary tract infection	1 (2.7)
Varicella	1 (2.7)
Viral infection	1 (2.7)
Fatigue	1 (2.7)
Injection site hematoma	1 (2.7)
Vomiting following administration of medication	1 (2.7)

Abbreviations: TEAE, treatment-emergent adverse event
[a]Period from the date of first intake of bilastine to visit 3.

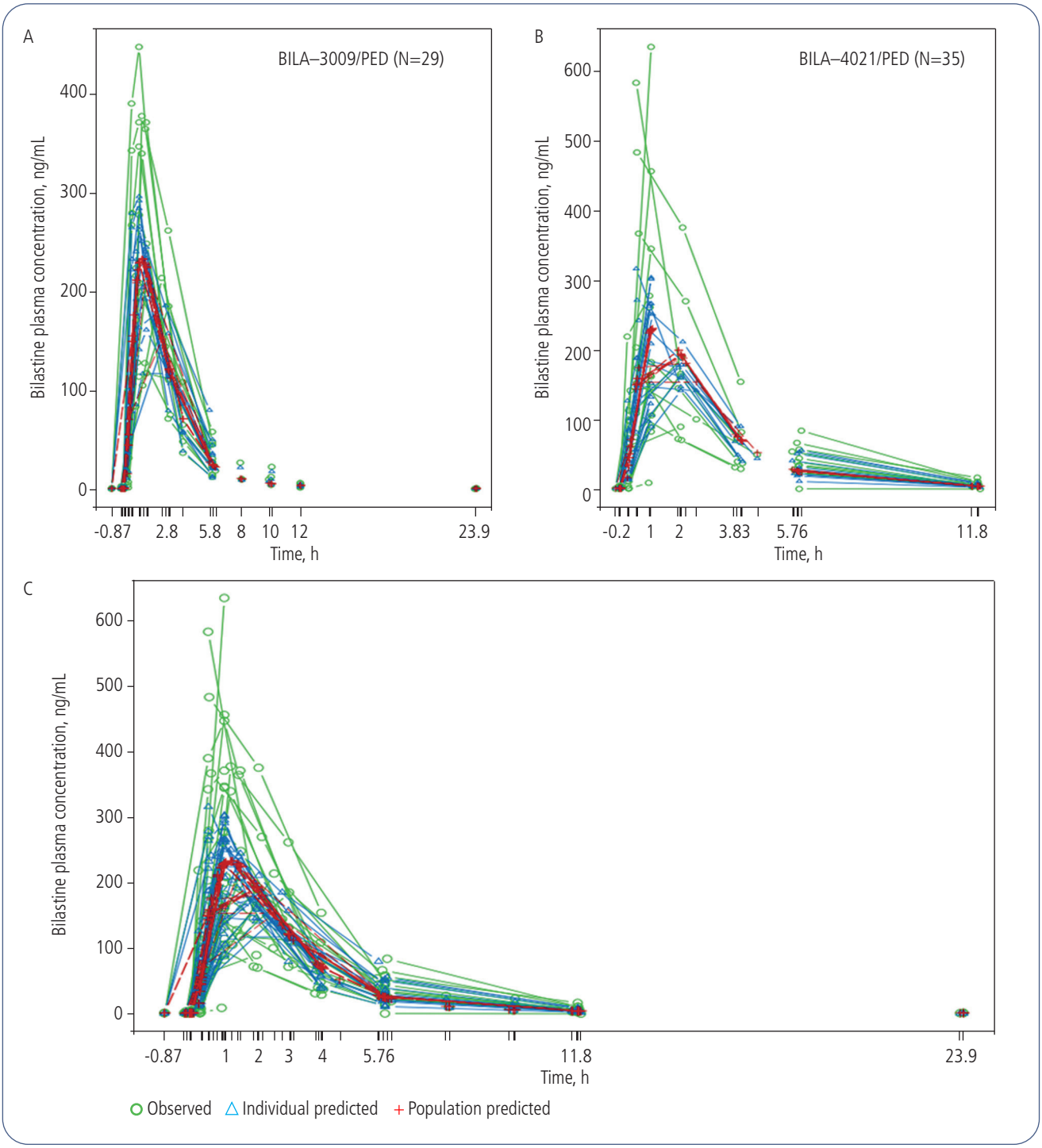

Figure 3. Comparison of observed and predicted bilastine pharmacokinetic profiles on a time-after-dose scale (day 7 of QD 10 mg bilastine po). A, BILA–3009/PED study. B, Present study (BILA–4021/PED). C, Combined dataset.

were observed at visit 3 or visit 4 for any parameter, and only 1 change from normal at baseline to abnormal (not clinically significant) was observed at visit 4 for eye parameters. The evaluation of TEAEs, physical examinations, and measurement of vital signs did not reveal any safety concerns.

Pharmacokinetic Modeling

These plasma concentration results obtained in children aged 2 to 5 years were used to enhance the previously generated population pharmacokinetic model, by combining the dataset from this study with that of the previous pediatric

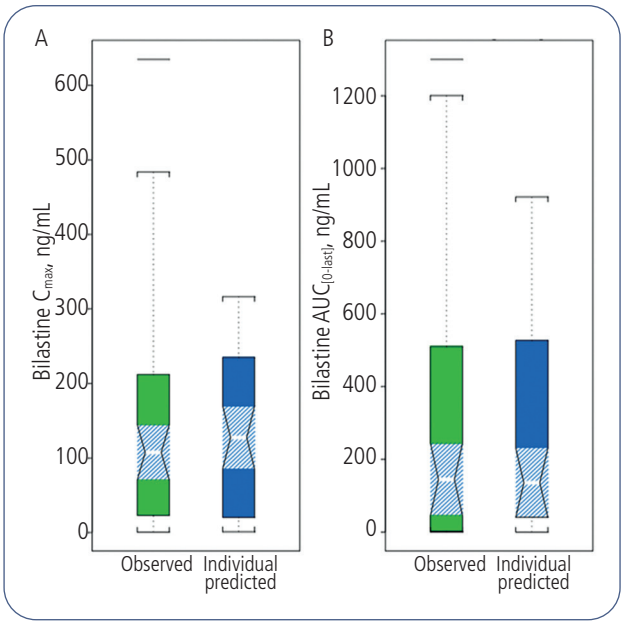

Figure 4. Comparison of noncompartmental analysis metrics calculated using the observed and individual predicted bilastine pharmacokinetics (combined BILA–3009/PED and BILA–4021/PED). A, C_{max}. B, $AUC_{[0\text{-}last]}$. The boxes contain the median (white line), with dashed notches marking the 95%CI of the median. The box covers the center half of the data, displaying, approximately, the first quartile, the median, and third quartile. The whiskers are values near 1.5 × the box span (upper – lower edge of the box). In a skewed distribution, such as that shown, the lower whisker is also the minimum value. The upper straight lines are outliers (values beyond 1.5 × the box span), and the last line is the maximum value.

pharmacokinetic study, which included 31 children (BILA–3009) [29,31]. The combined studies resulted in a total of 64 children with measured plasma bilastine concentrations for analysis. The mean (SD) age of this pooled population was 5.5 (2.6) years, the mean weight was 23.3 (7.5) kg, and 43 (67.2%) were male. A display of the pharmacokinetic model fit is shown in Figure 3. The observed clearance of bilastine was 12.7 L/h and the half-life was 2.2 hours. A comparison of the observed versus the predicted bilastine noncompartmental analysis metrics C_{max} and $AUC_{[0\text{-}last]}$ at steady state (day 7) is shown in Figure 4.

The relationship between clearance of bilastine and body weight and age is shown in Figure 5. The graph shows no apparent slopes for any of the covariates. The Pearson correlation between clearance and weight and age was r=0.15 and r=0.09, respectively.

Discussion

The aim of this multiple-dose pediatric trial with bilastine conducted in children aged 2 to 5 years with SARC/PARC and/or urticaria was to obtain pharmacokinetic data and safety and tolerability data. Subsequently, a population-based pharmacokinetic model was developed by combining these results with data from a previous pediatric open-label noncontrolled pharmacokinetic study with the aim of characterizing the pharmacokinetics of once-daily oral bilastine (10 mg/d) in children aged 2 to 5 years and quantifying the contribution of relevant covariates to the random variability

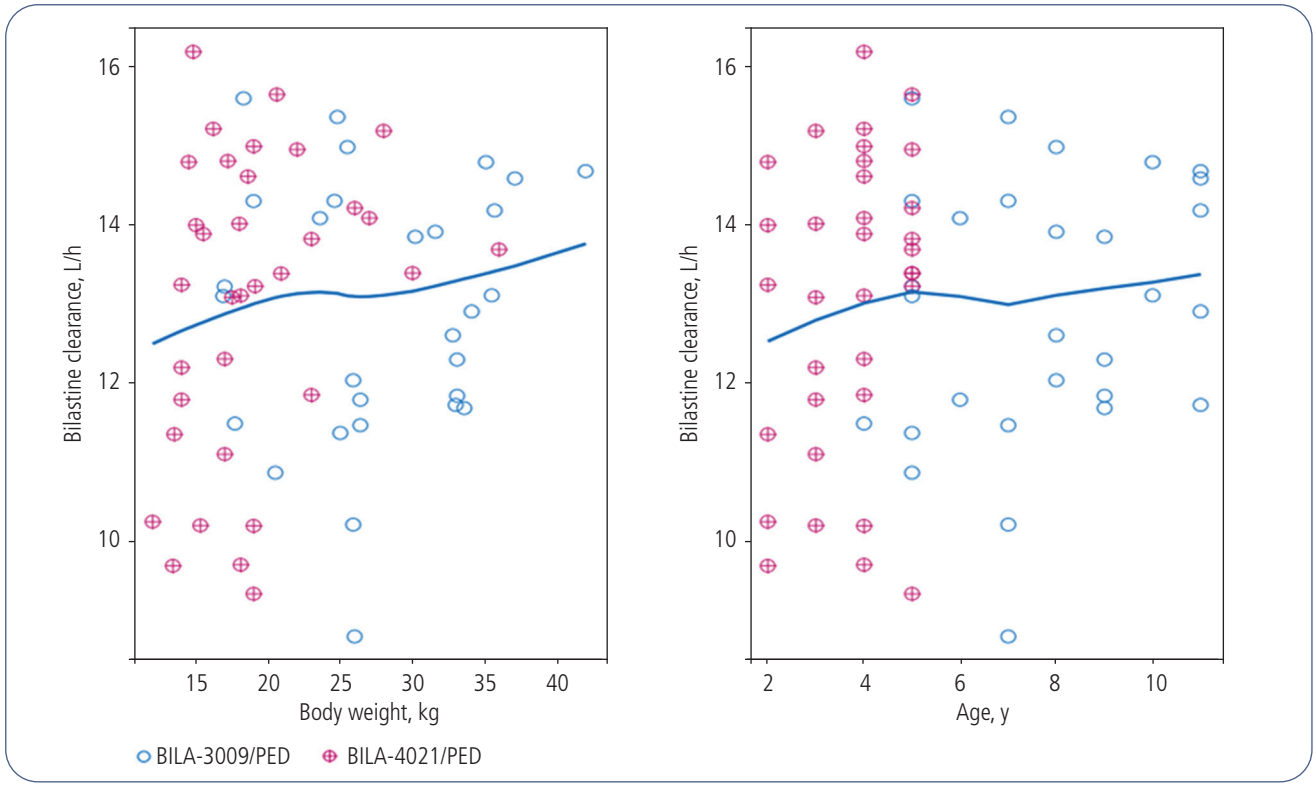

Figure 5. Relationship between systemic clearance and covariates weight and age in the pediatric population in the previous study (BILA–3009/PED, blue circles) and the present study (BILA–4021/PED, red symbols). Ages span from 2 to <12 years and the weight range is 12-42 kg (median of 21 kg). The solid blue lines represent the lowest fits.

of the pharmacokinetic parameters. The overall conclusions of the pharmacokinetic model are that the pharmacokinetic parameters of a once-daily oral dose of bilastine 10 mg in children aged 2 to 5 years do not differ from those observed in a group of children aged 2 to 12 years with ARC or urticaria and that the dose is safe and well tolerated in this population.

Consistent with previous studies, the pharmacokinetics of bilastine did not demonstrate significant structural complexity. Representation was optimized using a 2-compartment model with first-order absorption and a lag time. The same 2-compartment model best describes bilastine pharmacokinetics in adults [17]. The estimated oral clearance of bilastine in the population-based pharmacokinetic model for children aged 2 to <12 years (12.6 L/h) was comparable to the estimated clearance found in the pharmacokinetic study for children aged 6 to <12 years with a body weight of at least 20 kg (12.2 L/h). Covariate analysis showed that age was not a significant predictor of the variation/absence of variation in clearance or volume of distribution. The pharmacokinetic modeling study showed that body weight and age were not covariates of variation in either systemic clearance or volume of distribution in children aged 2 to <12 years. The combined results suggest that the pharmacokinetics of bilastine is not age-dependent in children with ARC or urticaria, as reported in earlier studies [29,31,32]. These results support the suitability of the pediatric dose of bilastine 10 mg for children with ARC and urticaria aged 2 to <12 years.

In terms of safety, in our study (BILA–4021), a total of 8 (21.6%) children experienced 1 nonserious TEAE each, and only 1 TEAE, fatigue, was classed as possibly related to bilastine. Analysis of heart rate, body temperature, and physical examination findings revealed no safety concerns. No abnormal heart rate values were observed, and only 1 case of abnormal body temperature was recorded during the trial. Our results further corroborate the safety of bilastine 10 mg in children aged <6 years, consistent with the results of previous trials [27,29].

Conclusions

The results of this clinical trial show that the same once-daily oral dose of bilastine 10 mg may be used for the whole pediatric subset (2 to <12 years) without dose adjustments. It also confirmed data observed in a previous safety study [27], indicating that even in the youngest age range (children aged <6 years), the 10-mg dose of bilastine demonstrated a favorable safety profile for the treatment of ARC and urticaria.

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Conflicts of Interest

Itziar Martín, Carlos Sánchez, Inmaculada Gilaberte, and Paula Arranz are full-time employees of FAES FARMA. The remaining authors declare that they have no conflicts of interest.

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