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RESEARCH PAPER

Model Informed Pediatric Development Applied to Bilastine: Ontogenic PK Model Development, Dose Selection for First Time in Children and PK Study Design

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ABSTRACT

Purpose Bilastine is an H_1 antagonist whose pharmacokinetics (PK) and pharmacodynamics (PD) have been resolved in adults with a therapeutic oral dose of 20 mg/day. Bilastine has favorable characteristics for use in pediatrics but the PK/PD and the optimal dose in children had yet to be clinically explored. The purpose is to: (1) Develop an ontogenic predictive model of bilastine PK linked to the PD in adults by integrating current knowledge; (2) Use the model to design a PK study in children; (3) Confirm the selected dose and the study design through the evaluation of model predictability in the first recruited children; (4) Consider for inclusion the group of younger children (< 6 years).

Methods A semi-mechanistic approach was applied to predict bilastine PK in children assuming the same PD as described in adults. The model was used to simulate the time evolution of plasma levels and wheal and flare effects after several doses and design an adaptive PK trial in children that was then confirmed using data from the first recruits by comparing observations with model predictions.

Results PK/PD simulations supported the selection of 10 mg/day in 2 to <12 year olds. Results from the first interim analysis confirmed the model predictions and design hence trial continuation.

Conclusion The model successfully predicted bilastine PK in pediatrics and optimally assisted the selection of the dose and sampling scheme for the trial in children. The selected dose was considered suitable for younger children and the forthcoming safety study in children aged 2 to <12 years.

KEY WORDS bilastine · knowledge integration · Ontogenic model · pediatric drug development · quantitative pharmacology · semiphysiological

ABBREVIATIONS

%	Percentage
ADME	Absorption distribution metabolism excretion
AEs	Adverse Events
AR	Allergic Rhinoconjuctivitis
AUC	Area under the curve
CI	Confidence interval
CL	Clearance
CLr	Renal clearance
CLu	Unbound clearance
Cmax	Maximum plasma concentration
CO	Cardiac output
CYP450	Cytochrome P450
EMA	European medicine agency
F	Bioavailability
FDA	Food and drug administration
fu	Unbound plasma fraction
g/mol	Grams per mol
GFR	Glomerular filtration rate
h	Hour
IC50	Half maximal inhibitory concentration
ICH	International conference on harmonization
Ka	Absorption rate constant
L	Liter
L/h	Liter per hour
Log P	Computational logarithm of the partition coefficient between n-octanol and water
M	Albumin molar concentration
M&S	Modeling & simulation

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mg	Milligram
mg/day	Milligram per day
mg/ml	Milligram per milliliter
MIDD	Model informed drug development
ng.h/ml	Nanogram. hour/ml
ng/ml	Nanogram per milliliter
OATP	Organic anion transporting peptide
PD	Pharmacodynamics
PDCO	Pediatric committee of the EMA
P-gp	P-glycoprotein
PIP	Pediatric investigation plan
PK	Pharmacokinetics
pka	Negative base-10 logarithm of the acid dissociation constant
Q	Distribution or intercompartmental clearance
QD	Once a day (from the Latin quaque die)
SEE	Standard error of estimates
TBW	Total body water
U	Urticaria
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
VPC	Visual predictive check
Vss	Steady state volume of distribution
WT	Body weight
yr	Year
yrs	Years

INTRODUCTION

The profound anatomical, physiological and developmental changes that occur during growth are responsible for differences between children and adults in the ADME processes and overall response to medications. Substantial variation may exist among children of different ages in the capacity to metabolize, absorb, excrete, and transform drugs, and receptors and proteins, among others. It is therefore imperative to account for such differences during pediatric drug development and in specific clinical trials, if needed, to ensure adequate treatment in this vulnerable population (1–3). The main challenges are: 1) to define the first dose in children or an age subset, 2) to find optimal sampling strategies, 3) to choose the appropriate methods for data collection and analysis, 4) to generate knowledge regarding safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of a drug in children, and 5) to determine the right dose and regimen that may differ across ages in the pediatric population. All the above described challenges must be settled entailing minimal risk and burden to each child, especially to those of younger ages, and always guaranteeing a potential benefit for the children (4–7).

One way to overcome the above difficulties is to construct predictive models that integrate the available information about the drug, i.e., implementing the model informed drug development approach (MIDD) in the pediatric development framework (2,3,8). In MIDD, modelling & simulation (M&S) methodologies are applied within a learning and confirming process. First in a learning stage, data integration into a PK or PK/PD model is applied to extrapolate the behavior in children and optimize the design of an upcoming clinical confirmatory study. Then in a confirmatory stage, assumption testing and model confirmation is done with those new data (8–11). The approach also accounts for the logistical limitations related with the performance of clinical trials in children, i.e., study size and the number of blood samples that can be drawn (8,12). Sparse optimal sampling studies, in combination with state of the art bioanalytical and pharmaco-statistical analysis methods, are becoming common because of the ability to adequately characterize the PK while providing convenient schedules with minimal blood draws (8).

The present work concerns the case of MIDD application in pediatric development of the antihistamine bilastine. Bilastine is a non-sedative second generation H_1 receptor antagonist (antihistamine) developed in the dosage form of oral tablets and approved in adults and adolescents for the symptomatic treatment of allergic rhinoconjuctivitis (AR) (seasonal and perennial) and for urticaria (U) (13). In children, AR is currently one of the most common chronic disorders and therefore anti-allergic drugs, particularly the antihistamines and intranasal steroids, are among the most commonly prescribed medications in this population (14). AR has a mean age of onset of 10 years with the highest prevalence observed in school-age children (15,16) and is uncommon in early childhood below the age of 5 (17).

The PK of bilastine has been extensively studied in adults. A MIDD approach was implemented also in adults (including in the model information in the preclinical species and then also the information from special populations) using nonlinear mixed effects modelling that allowed complete characterization of the ADME properties of the drug and the relationship of plasma concentrations with efficacy and safety (9,18). Concretely, a maximum concentration of 1268 ng/ml and exposure of 4799 ng.h/ml were established as a safety threshold derived from the multiple administration of 80 mg daily of bilastine for 7 days. Moreover, the adequacy of a 20 mg/daily dose of bilastine to maintain the antihistamine effect in adults during the dosing interval (24 h) was confirmed by the simulations of the effect-time curves for wheal and flare using the indirect effect PK/PD model. Bilastine showed a linear PK in the dose range 2.5–220 mg/day and no accumulation after multiple dose administration (9,18). Additionally, it is very well tolerated in a wide dose range (2.5–100 mg/day) after multiple dose administration and devoid of sedative and cardiotoxic effects (13,19). Bilastine underwent a well-controlled thorough QT assessment according to ICH E14 guideline (20) and even at supra-therapeutic doses (100 mg) it was not associated with adverse effects on the QTc interval,

highlighting its cardiovascular safety (13,21). Additionally, bilastine appears to have minimal potential for drug-drug interactions given that it is not metabolized in the liver and does not affect CYP450 isoenzymes. However, co-administration of bilastine with either erythromycin, ketoconazole or diltiazem resulted in a significant increase of bilastine AUC and Cmax (compatible with the inhibition of P-glycoprotein and bilastine being a substrate), while the PK parameters of the co-administered drugs remained unaltered in the presence of bilastine (13). The opposite was observed in healthy adults when bilastine was administered together with grapefruit juice (due to the inhibition of OATP and the consequent reduced OATP-mediated uptake of bilastine in the intestine), that lead to reduced Cmax and exposures compared with the drug given alone. These effects of co-administered drugs and grapefruit flavonoids have been attributed to the adjuvant's impact on intestinal p-glycoprotein (P-gp)-mediated efflux (inhibition) and organic anion transporting peptide (OATP)-mediated absorption (reduction), respectively (13).

Bilastine pediatric MIDD was designed to bridge the PK/PD semi-mechanistic model from the adult (9) (which summarizes abovementioned information) into children by scaling the available knowledge in the form of maturation based equations as it is explained in the present publication. The approach was confirmed in a posterior pediatric clinical trial.

METHODS

The main steps followed during the prediction stage of bilastine pediatric drug development are summarized in the diagram presented in Fig. 1.

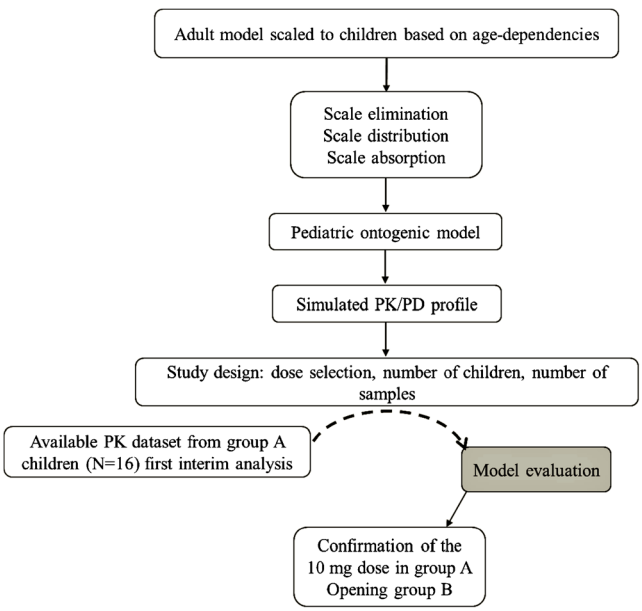


Fig. 1 Overall extrapolation strategy used during bilastine pediatric development.

First Step: Ontogenic Model Development

The starting point was the semi-mechanistic PK/PD model, with no statistically or clinically significant covariates identified, previously developed and qualified for adults. The model allowed for a correct knowledge based approach (9). Preclinical data in several animal species (rat and dog), as well as *in vitro* information was also indirectly used for this purpose in the adult by helping in the investigation (establishment and confirmation of assumptions) of the PK processes (work already published (9)). Then, maturation factors together with ontogenic and PK assumptions, were implemented on the adult model to scale the PK parameters of bilastine for children. (Eqs. 1 to 7 are explained in further detail in Table I). Moreover, the relation between the PK principles and human body function and the comparative physiology of adults and children, which are the basis of the present approach, were obtained from literature and are also shown in Table I. The main pediatric PK parameters were then obtained for the different age groups.

The interpatient variability (modeled as exponential) in all PK parameters as well as the residual variability in the form of proportional error model were assumed to be the same as those estimated in adults. Therefore, similar PK characteristics were assumed between both populations and used as prior information to inform the pediatric model to be confirmed/redefined with the PK clinical data.

The PK ontogenic model was then linked to the PD, which was assumed to be similar to that of adults. The developmental processes related with the PD were considered mature as confirmed with the pediatric literature on the use of similar antihistamines (22–25). In addition, the EMA and FDA guidelines on the clinical development of medicinal products for Allergic Rhino-conjunctivitis, state that in the case of oral applied agents used in this therapeutic area, only PK studies are required for the determination of the effective dose in children older than 2 years of age as the systems are already mature (24,25). The global model proposed on this basis was a 2-compartment PK model linking bilastine plasma concentrations with the inhibitory effect via indirect response model (18).

Second Step: Clinical Study Design in Children: Dose Selection, Sample Size and Sampling Times Selection

The design optimization consisted on selecting the optimal dosing regimen and sampling time points, taking into consideration the typical constraints around studies in children such as the total number of samples, total blood volume, or suitable times when samples can be withdrawn, in order to allow a precise estimation of the PK parameters in this special population.

Table I Semi-Physiological Maturation Equations Used in the Extrapolation of Bilastine PK Parameters to Children from Previous Available Knowledge in the Adult

Parameter	Equations	Comments
Volumes of distribution (V_{ss}, V_c and V_p)	$V_{ss} = TBW \quad (Eq.1)^{\#*}$ $V_c/_F = 0.65 \cdot V_{ss} \quad (Eq.2)^*$ $V_p = V_{ss} - V_c \quad (Eq.3)$	* From a previous study in adults (9) # V_{ss} was converted to V_{ss}/F using a value for F previously estimated in adults. Value for TBW in children of different ages taken from literature (22).
Systemic clearance (CL)	$ratio\frac{CL_u/F}{CL_r} = 17.14 \quad (Eq.4)^*$ $CL_{r\_ch} = \frac{GFR_{ch} \cdot fu_{ch}}{GFR_{ad} \cdot fu_{ad}} \cdot CL_{r_{ad}} (Eq.5)^{\$}$ $fu_{ch} = \frac{1}{1+\frac{M_{ch}}{M_{ad}}\frac{(1-fu_{ad})}{fu_{ad}}} \quad (Eq.6)^{\&}$	* From a previous study in adults (9) $ Renal clearance in children was predicted using Björkman equation (9,23–25). & Unbound fraction was calculated as a function of albumin C_p and assuming that 1) albumin is the main protein to which bilastine binds, 2) the affinity for the protein does not change between adults and children, and 3) binding to albumin is a non saturable process (26).
Distribution clearance (Q)	$ratio\frac{CO}{Q/_F} = 223 \quad (Eq.7)^*$	From a previous study in adults (9,23,24,27)
Absorption rate constant (K_a)	-	Assumed to be equal in adults and pediatrics, as no changes in drug formulation was planned. Possible differences with age regarding affinity for efflux transporters (p-glycoprotein and organic anion-transporting peptides) in the gastrointestinal tract, not accounted for here, do not seem to have significant age effect for this class of drugs (28–31).

Where *V* Volume of distribution, *ss* Steady state, *c* Central, *p* Peripheral, *F* Bioavailability, *CL* Clearance, *u* Unbound, *r* Renal, *ch* Children, *ad* Adult, *fu* Unbound fraction, *GFR* Glomerular filtration rate, *M* Albumin molar concentration, C_p Plasma concentration, *CO* Cardiac output, *Q* Distribution clearance, K_a Absorption rate constant

Physiological parameters from literature (46–49) = 1 year: TBW = 6.65 L, GFR = 1.62 L/h and CO = 72 L/h; 2 years: TBW = 9.45 L, GFR = 2.45 L/h and CO = 106 L/h; 6 years: TBW = 14.6 L, GFR = 3.64 L/h and CO = 185 L/h; 12 years: TBW = 27.5 L, GFR = 5.55 L/h and CO = 304 L/h; adults: TBW = 42 L, GFR = 8.13 L/h and CO = 336 L/h

Bilastine physicochemical characteristics: Molecular weight = 463.61 g/mol, Log *P* = 2.3 (computational logarithm of the partition coefficient between n-octanol and water), fu_humans = 84–90%, solubility in water = 0.00203 mg/mL, pka (acidic) = 4.4, pka (basic) = 8.78

Dose Selection

Using the PK ontogenic model linked to the PD, different dosing scenarios were simulated considering the efficacy and safety threshold established in adults. Simulations were carried out including the PK variability as well as noise-free (no residual error) predictions. Simulated plasma profiles and wheal and flare effects of bilastine in virtual populations of 1500 children of 2, 6, and 12 years (selected representative ages within the children population) receiving four once daily consecutive oral doses of 5, 10 and 20 mg of the drug. The comparison of the resulting concentration and effect-time profiles (obtained through the integrated PK/PD pediatric model) *versus* the corresponding adult profiles after the therapeutic dose (20 mg) was used to select the appropriate dose for the first PK bilastine trial in this pediatric population subset under the following considerations: (1) achievement of similar wheal and flare profiles predicted in children of different ages (2,6 and 12 years selected as target age groups) to that in the adult after the therapeutic dose (20 mg) accounting for the indirect effect of bilastine and, (2) bilastine plasma concentrations attained in children of 2, 6 and 12 years within the safety threshold pre-stablished from the adult clinical data. In this sense, Cmax and exposure observed in the adult after the dose of 80 mg was conservatively selected as the safety threshold (refer to the introduction for further details).

Sample Size and Sampling Time Selection for the PK Clinical Trial

The sampling scheme was planned based on the simulated PK profiles so that the maximum information could be obtained with the minimum number of blood samples, and thus minimize the burden to participating children. The clinical pediatric PK study was composed of two population groups depending on age. Specifically, group A comprising children from ≥6 up to <12 years was planned to be the starting group in a manner that after a first interim analysis the ontogenic model could be evaluated and the dose readjusted, if needed, for both, the rest of the children of group A, and also group B (children from 2 up to 6 years).

Monte Carlo simulations were performed using the pediatric ontogenic model in virtual populations of 1500 children of 2, 6 and 12 years receiving the selected dose to evaluate the PK profile in each age group (only group A is shown here as an example). The simulated profiles were used to establish a range of time to reach maximum plasma concentrations (tmax values) to guide the sampling schedule around the expected peak. The selection of the sampling times took into consideration that, to completely describe a pharmacokinetic profile, one must obtain the sufficient number of blood samples in the absorption, distribution and elimination phases.

Two different sampling scenarios were then proposed: an extended scenario with a maximum of 6 or 4 samples per child, in older (≥ 6 years) and younger (<6 years), respectively, for those subjects with a catheter inserted in the vein after drug intake, and only one sample (limited scenario) in those subjects without a catheter. This design allowed keeping children, at most, 6 h in the center, while the children with only one sample would come twice to the center, one for drug intake and another one for blood collection at different times. Samples collected in the extensive sampling time groups were aimed to characterize the absorption and early distribution phases, where more variability was expected, and for which nearly equal sampling intervals were selected on the semi-log (for time) plot of the PK profiles (mean and 95% predictive intervals). In the rest of the children the extraction of only one sample in the late distribution and elimination phase was proposed.

The number of children within each group, and the number of samples in each child, was aimed to collect a well distributed number of data which served to characterize bilastine PK in children by confirming the ontogenic model, rather than in strictly statistical methods for sample size calculation. This means that the number of children was empirically selected based on prior information in adults, as well as on similar drugs (26), with a reasonable maximum number of 44 children in total (at least 24 in group A and approximately 20 in group B, to be confirmed depending on the results of the interim analysis).

Simulations were made of the PK profiles for the entire group A pediatric population ($N = 24$) and also split in 2 extensive sampling groups of $N = 6$ patients per group and one single sample group ($N = 12$), extracting from the pediatric population PK parameter distributions. The same process was also performed for the younger group B (< 6 years). A sparse-sampling population PK approach was applied to design the study.

The study was approved by the Pediatric Committee of the EMA (PDCO), and it was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was recorded in the EudraCT database (#2009-012013-22). Parents and children old enough to understand the implications of taking part in the study were given oral and written information on the trial protocol. Parents provided a written consent and children old enough an assent.

Third Step: Clinical Confirmation of the Ontogeny Model Using Data from Children

The proposed PK study was adaptive with at least two planned interim analyses. The aim was to first confirm the dose and study design in a group of older children and to allow eventual inclusion of younger pediatric patients (first interim), and to evaluate the possibility of finalizing the trial based on achievement of stopping rules (second interim). Observations from children recruited for the first interim were used to confirm the assumptions of the ontogenic model, and consequently the validity of the study design, and to safely open the study for the younger children (<6 yrs) and redefine the dose and study design, if needed.

Two M&S based steps were applied to confirm prior knowledge: (Step A) population PK analysis of the actual pediatric observations by nonlinear mixed-effects modelling (see e.g., Karafoulidou et al. (27)) and comparison of model structure with that of the adults including key covariates, and (Step B) visual predictive check (VPC; $N = 1000$) of the ontogenic scaling model to compare the observations with predictions from the actual interim model developed in Step A. The model was considered adequate when the mean pediatric model predictions fell mostly within the 95% CI of the predictions obtained with the prior ontogenic model.

Software Used in the Analysis

Model building and simulations were carried out with the software package NONMEM® (version VI, Icon Plc, Dublin, Ireland). Data exploration, statistical testing external to NONMEM® and graphics were performed using S-PLUS® (version 8.2, TIBCO Software Inc., Palo Alto, CA, USA).

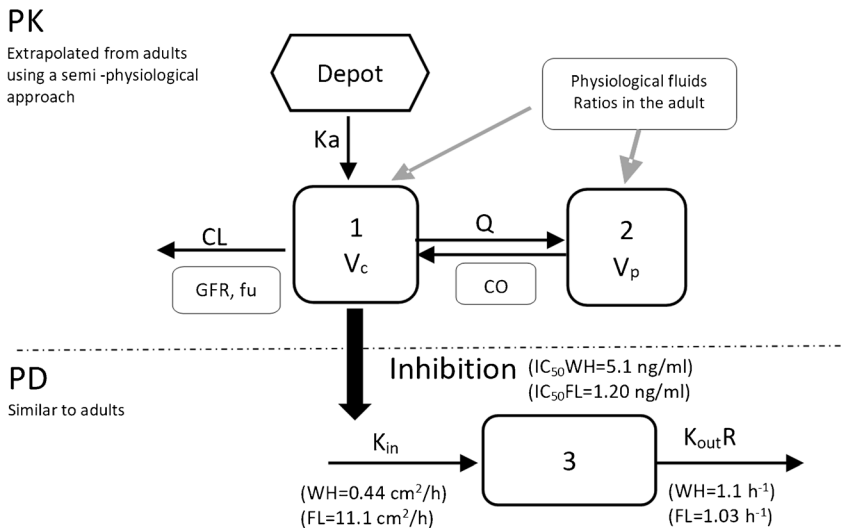


Fig. 2 Pharmacokinetic/pharmacodynamics semi-mechanistic model developed for bilastine in children from data in the adult and ontogenic based factors correcting the differences in the parameters derived from children growth and maturation. PK = Pharmacokinetics; PD = Pharmacodynamics; Ka = First order absorption rate; CL = systemic clearance; Vc = Central volume of drug distribution – compartment no. 1; Q = Inter-compartmental clearance; Vp = Peripheral volume of distribution – compartment no. 2; GFR = Glomerular Filtration Rate; fu = unbound drug fraction; CO = Cardiac output; IC_{50} = Inhibitory concentration where 50% of the maximum inhibition factor is attained; WH = Wheal allergic response effect; FL = Flare allergic response effect; Kin = Allergic response induction (in compartment no. 3) secondary to H_1 stimulation; Allergic response fade-out (stimulus elimination); "Inhibition" = Bilastine blockage of H_1 stimulation.

RESULTS

The ontogenic model developed by scaling bilastine PK in children linked to the PD from the adult and used to optimize the population design for the PK pediatric clinical trial is presented in Fig. 2.

The assumptions and ontogenic equations considered to translate the PK model from adults to pediatrics are detailed in Table I. Bilastine volumes of distribution (central (Vc) and peripheral (Vp) were scaled from the adult considering the differences in the physiological water and the ratios between the PK volumes (9,28). Additionally, considering that bilastine clearance (CL) is mainly by renal glomerular filtration, as it is not affected by hepatic metabolism or any other active transport in the kidney, CL was extrapolated by means of a function which incorporates age-related changes in the glomerular filtration rate (GFR) and in drug unbound fraction (fu) (9,29–31). Inter-compartmental clearance (Q), was extrapolated as a proportion of the cardiac output (CO) by age (9,28). This is justified by the fact that Q ultimately depends on blood perfusion (32,33). No ontogenic effect on bilastine bioavailability (F) was considered since active transporters in the intestine (P-gp and OATP) reach adult levels and expression by approximately the age of 2 years (34–36). The mean PK parameters of bilastine in pediatrics scaled by considering the above dependencies are summarized in Table II.

Simulations performed with the PK/PD model to select the optimal pediatric dose are presented in Fig. 3. As shown in this figure (top panel), the dose of 10 mg/day was able to maintain bilastine wheal and flare effects during the entire dosing interval in a comparable way to adults.

Note that the difference in the PK profiles between the age groups is not directly translated with the PD profiles, compatible with the indirect nature of the PK/PD relationship for bilastine. The indirect response simulation of the effect *versus* time profile facilitated the comparison across age groups and

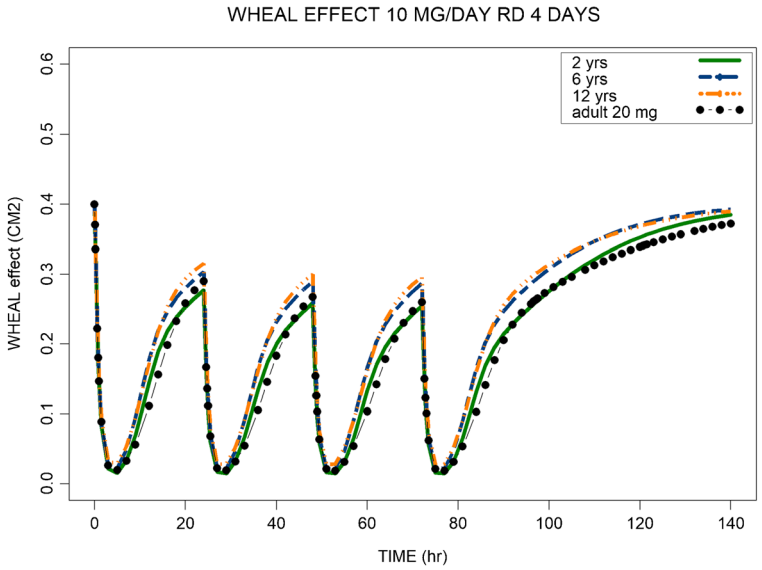
Table II Mean PK Parameters of Bilastine Predicted in Children Using a Semi-Physiological Approach. The PK Parameters Estimated *via* Direct Modelling of Observations in the Adult are Listed for Comparison

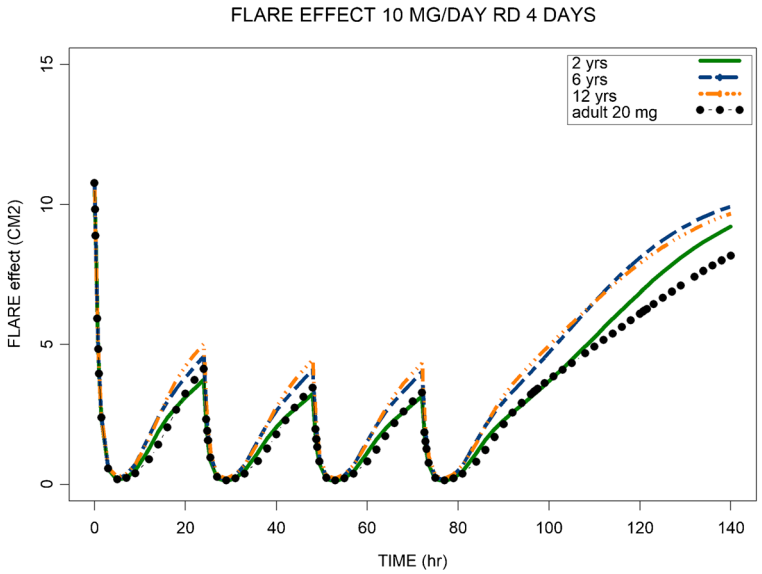
PK parameters	2 yrs	6 yrs	12 yrs	Adult *Obs.*
CLr (L/h)	2.63	4.00	5.97	8.13** (pred)
CL/F (L/h)	6.29	9.67	14.2	18.7
V_{ss}/F (L)	20.5	31.7	59.8	91.8
V_c/F (L)	13.3	20.6	38.9	60.4
V_p/F (L)	7.20	11.1	20.9	31.4
Q/F (L/h)	0.475	0.830	1.36	1.51
*Ka (h^{-1})	1.28	1.28	1.28	1.28

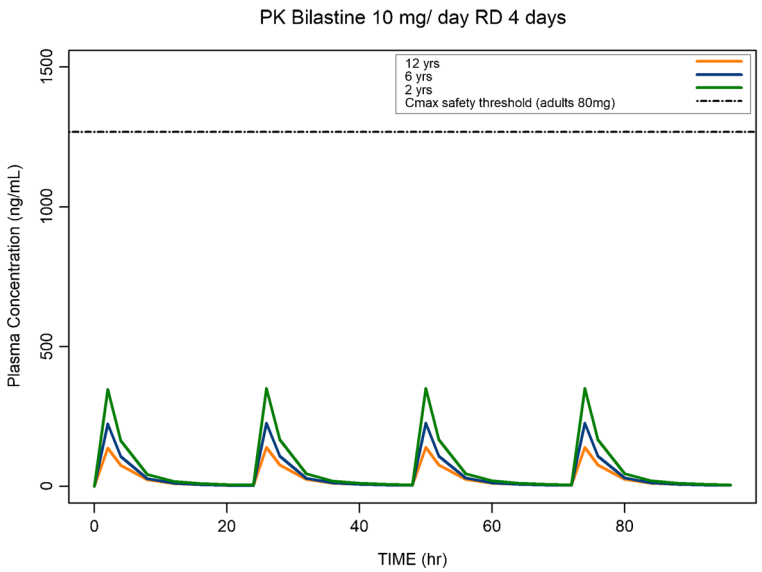
*Same as in adults

**Predicted in adults (9)

Fig. 3 Top and middle panel: Simulated temporal evolution of the wheal (left) and flare (right) effects after a repeated daily dose of 10 mg of bilastine during 4 consecutive days in children of 2 (green), 6 (blue) and 12 (red) years and in adults (dotted black) after the therapeutic dose (20 mg). Bottom panel: Simulated temporal evolution of mean plasma concentrations of bilastine in infants and children of different ages after the same dosing regimen. The horizontal line mark the safety threshold. RD = Repeated dosing.







allowed to confirm the suitability of the 10 mg dose in the entire pediatric group, with efficacy exposures comparable across age groups.

Moreover, and as shown in the bottom panel of the same figure, and considering the wide safety margin of bilastine, plasma levels achieved with either of the simulated doses were far from producing toxicity in children (only 10 mg shown here). In this sense, Cmax and exposure observed in the adult after the dose of 80 mg was conservatively selected as safety threshold (Cmax of 1268 ng/mL and exposure of 4799 ng.h/mL). The comparison of the predicted exposures in children of 2 years of age (youngest group of intended population) after the 10 mg dose *versus* the adult exposure after 80 mg was only used for safety purposes as the efficacy conclusions were drawn comparing the PK exposures with the 20 mg dose in the adults as well as through simulation of the wheal and flare effects (see Fig. 2 top panel).

In addition, as shown in Fig. 4, the simulated exposure in 2 year old patients receiving 10 mg of bilastine once a day was predicted to be approximately 1450 ng.h/mL (corresponding to the AUC calculated with the ontogenic PK parameters in 2 year old children). This level was substantially lower than the safety threshold stablished in adults (AUC = 4799 ng h/mL).

Furthermore, Cmax values observed in adult healthy volunteers receiving a dose of bilastine of 80 mg/day (1268 ng/mL) was around 3-fold greater than the mean predicted value in children of 2 years of age receiving 10 mg/day of bilastine. It was therefore concluded, that 10 mg daily dose in children of 2 years of age is a safe dose that can be safely used to start the trial in the pediatric population intended for bilastine, and to be revised in the first interim analysis.

Bilastine simulated plasma profiles after 10 mg/day in representative ages were also used to design the PK pediatric study. Simulations performed in 1500 replicates from the children population showed an expected tmax range of 0.8 to 2 h, with median of 1.2 h and standard deviation of 0.2 (results not shown). Figure 5 (top panel) depicts the simulations performed at the fourteen selected sampling times to adequately describe the complete bilastine plasma profile in children considering the high variability in the absorption process and therefore with a rich sampling in this region of the curve with the combination of data from all the children (n = 24), as well as the three sparse sampling groups proposed (bottom panel) of 6 samples in the two extensive groups (N = 6 per group) and only one sample in the remaining children (N = 12). The same process was then repeated for the younger group of children (< 6 yrs) limiting the extensive group to 4

Fig. 4 Comparison of bilastine plasma profiles in children of 2 years where the solid lines and blue shaded area correspond to the predictions with the ontogenic model. The horizontal dotted line represents the safety threshold calculated from the adult after the 80 mg dose.

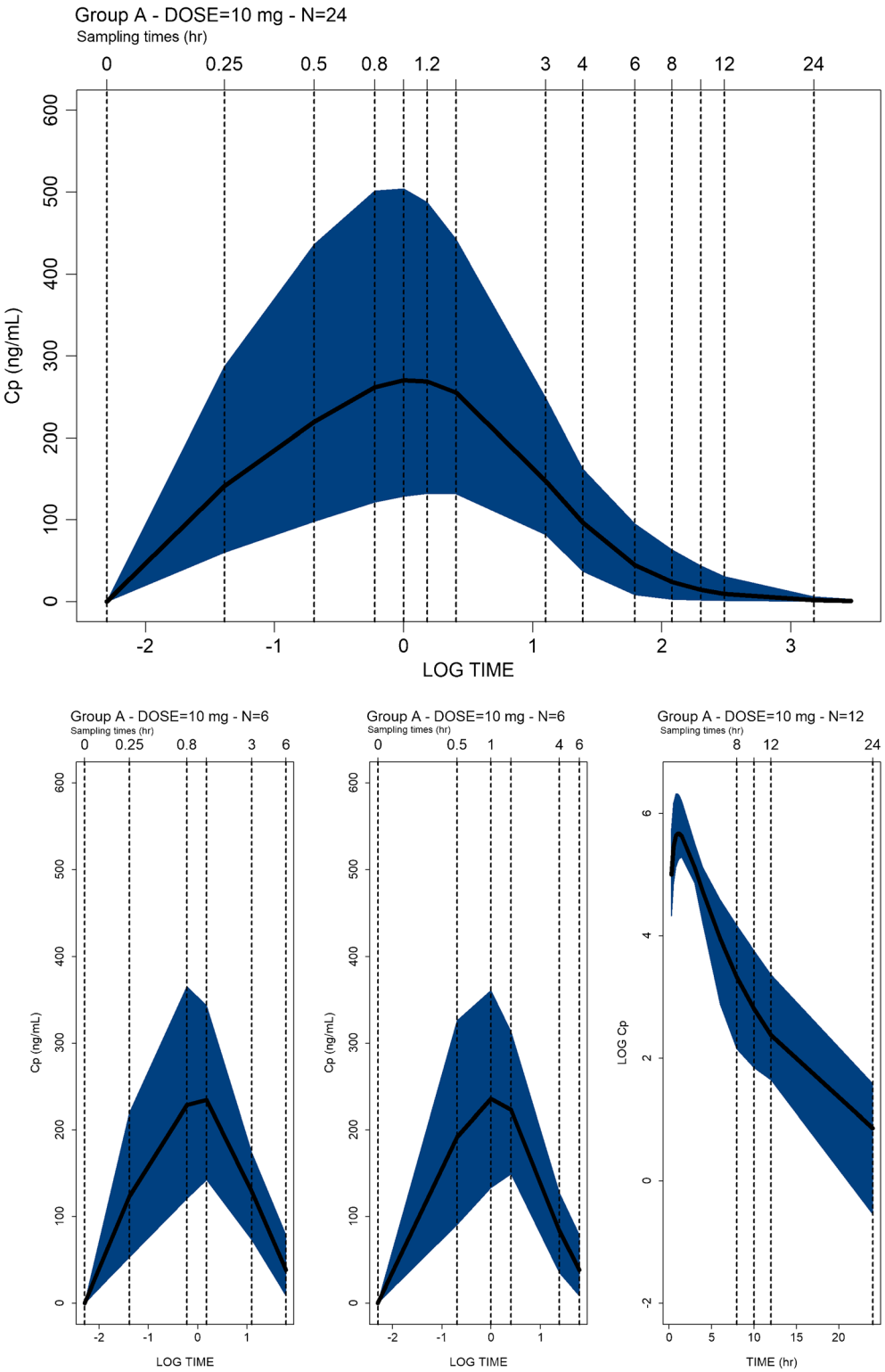


Fig. 5 Plot of predicted bilastine oral PK in a simulated population of 24 children from group A (top panel), and also split in three sparse sampling groups on 6 children in the extensive group and 12 children with only one sample (bottom panel) receiving 10 mg. Blue shaded areas represent the 95% confidence interval of model predictions. Vertical dotted lines mark the sampling times selected in the study design. Simulations presented in Log- time for better visualization of the selected times in absorption phase except for the children in the group with only one sample that is presented in Log-Concentration for a better visualization of the late distribution and elimination phases.

samples, but only the simulations in the older group are presented here as an example. Table III reports the proposed study design in both groups A and B, with a total of 128 samples and establishing a maximum total number of 44 children to be confirmed/redefined with the results of the interim analyses.

The pediatric PK clinical trial was then initiated and a first interim analysis was performed with a data set from children of group A (≥ 6 yrs) consisting of 65 bilastine plasma observations: 60 assessments from 11 children with an intensive sampling scheme of 6 samples per child and 1 sample from the five remaining children. One subject was

Table III PK Study Design for Group A (6 to <12 years) and Group B (2 to <6 years)

Group A (6 to < 12 yrs)		
N total (24)	Sampling times (h)	M Total (84)
A1, A2, A3* (2)	Predose***, 0.25, 0.8, 1.2, 3, 6	36
A1, A2, A3* (2)	Predose***, 0.5, 1.0, 1.5, 4, 6	36
A1, A2, A3 ** (1)	8	3
A1, A2, A3 ** (1)	10	3
A1, A2, A3 ** (1))	12	3
A1, A2, A3 ** (1)	24	3
Group B (2 to < 6 yrs)		
N total (20)	Sampling times (h)	M Total (44)
B1, B2**** (2)	Predose***, 0.25, 1.5, 6	16
B1, B2**** (2)	Predose***, 0.5, 1.0, 3	16
B1, B2***** (2)	8	4
B1, B2***** (2)	10	4
B1, B2***** (2)	12	4

Subgroups defined by age within GROUP A: A1 [≥6 to <8 yrs], A2 [≥8 to <10 yrs], and A3 [≥10 to <12 yrs] Subgroups defined by age within GROUP B: B1 [≥2 to <4 yrs], and B2 [≥4 to <6 yrs]

N Total number of children, *M* Total sampling number

*There are two children of each subgroup (A1, A2, and A3) and six samples from each child

**There is one child of each subgroup (A1, A2 and A3) and one sample from each child

***Sampling time at 24 h corresponds to predose extraction

****There are two children of each subgroup (B1 and B2) and four samples from each child

*****There are two children from each subgroup (B1 and B2) and one sample from each child

Table IV PK Bi-Compartmental Parameters Estimates from the Final Mixed Effects Model for the Interim Pediatric Dataset (N = 15 Patients) Including a Power of Covariate Relation for Mean-Weighted Age (Age/9) on Systemic Clearance and Mean-Weighted Body Weight (WT/40) on Central Volume of Distribution with Power Exponents Alpha and Beta, Respectively. (The SEE% for the Parameter Inter-Individual Standard Deviations are Those for the Variance)

Parameter	Estimated	SEE (%)
Ka (h^{-1})	1.28	NA
CL_{base} (L/h)	13.3	8.5
Vc_{base} (L)	18.7	18
Q (L/h)	2.63	18.3
Vp (L)	17.1	11.6
Tlag (h)	0.179	28.6
Alpha	0.602	55.8
Beta	1	NA
ωCL (%)	23	53
ωVc (%)	61	47
σPK (%)	38	34

removed from the modelled dataset as it had a deviation to the clinical protocol that could affect the PK and was causing instability during the analysis.

The final population PK model parameters estimated for the first interim pediatric dataset (N = 15) are listed in Table IV. Covariate predictors were built for weighted age (Age/9) and body weight (WT/40) on CL and Vc, respectively, as power exponent relations as follows,

$$\frac{CL}{F} = CL_{base} \cdot \left(\frac{Age}{9}\right)^{alpha} \tag{8}$$

$$\frac{Vc}{F} = Vc_{base} \cdot \left(\frac{Weight}{30}\right)^{beta} \tag{9}$$

Where, CL and Vc are the typical value for clearance and central volume slopes, respectively as listed in Table IV and alpha and beta the corresponding exponents. CLi and Vci are the parameters individualized by the corresponding covariate.

Figure 6 shows the VPC performed to validate the model developed during the first interim analysis were the orange lines and the blue area represent the mean and 95% confidence interval of the model predictions calculated for the children with the population model (only children with extensive sampling scheme are shown) and the red dotted lines correspond to the individual observations.

In addition, Fig. 7 shows the simulations performed using the ontogenic PK model for each individual child where the black lines and the blue shaded area represent the mean and 95% confidence interval of model predictions and the red dots are the individual observations from the pediatric clinical trial. Comparison of predicted bilastine PK exposures after 10 mg in children with the ontogenic model (employed for study design purposes) and with the model developed in the first interim analysis from the pediatric observations (clinical trial BILA/3009-PED, EudraCT number 2009-012013-22) was performed to ensure the adequacy of the selected pediatric dose (Table V). Predicted exposures using both methods were very similar confirming the assumptions used during ontogenic model development, and well within the established efficacy and safety thresholds.

Based on above results the study design was considered adequate to assess the PK in pediatrics confirming the validity of the predictive ontogenic model and its assumptions, and no adaptation was required for continuation, including dose selection.

DISCUSSION

Drug dosing in children is still largely empirical with the regimen usually derived *via* simple linear body weight

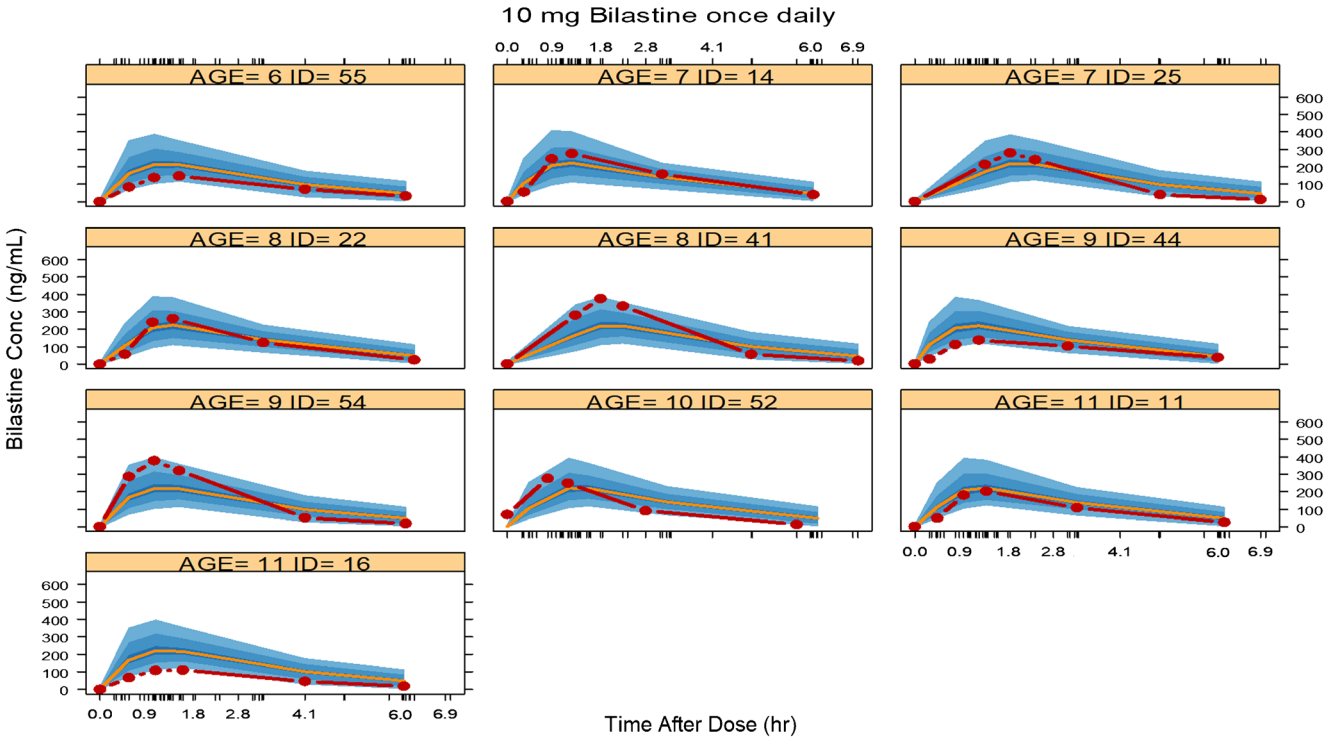


Fig. 6 PK predictive intervals (mean, 95% CI) in a population of children subjects ($n = 1000$) after the administration of 10 mg multiple dose of bilastine. The orange solid lines represent the population PK mean response and the blue area represents the CI range estimated for children. Red lines are the mean individual predictions (per individual children) from the model developed in children after the first interim analysis. Only children with extensive sampling are shown.

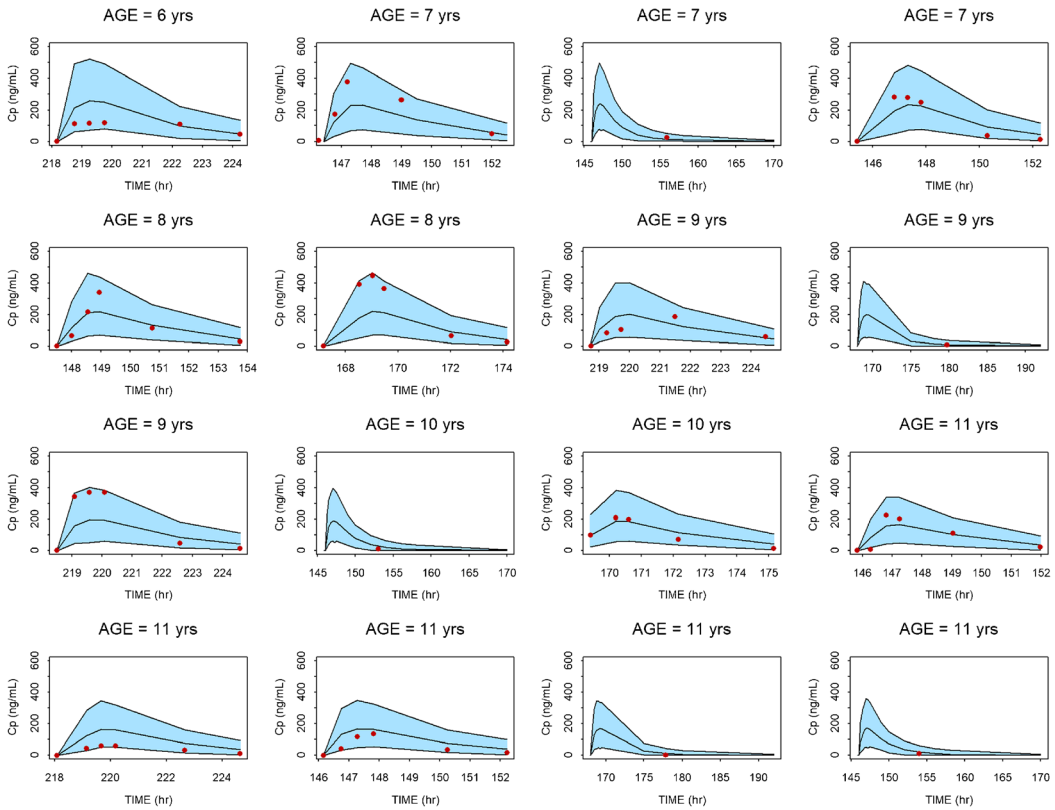


Fig. 7 PK predictive intervals (mean, 95% CI) in a population of children subjects ($n = 1000$) after the administration of 10 mg multiple dose of bilastine using the ontogenic PK model *versus* the observation in children. The black solid lines and shaded area represent the population PK mean response and the CI range estimated for children. Red dots are the individual observations from the pediatric clinical trial.

Table V Comparison of Bilastine Exposures in Children of 2, 4 and 6 yrs. After 10 mg and in the Adult after 20 mg Predicted Using the Clearance from the Ontogenic Model Used to Design the Study, and the Model Developed with the Data from the First Interim Analysis

$AUC_{0-\infty}$ (ng.h/ml)	2 yrs	4 yrs	6 yrs	Adult after 20 mg
First interim analysis predictions Mean	1792	1181	925	991
Ontogenic model Mean (95% CI)	1450 (341–3569)	1154 (262–2821)	1137 (253–2801)	1070

Safety threshold: 4799 ng.h/ml

relationships from the adult regimens. This paradigm is worrisome for the pediatrician, for the regulator and also for the pharmaceutical industry (2) because maturation changes are in general non-lineal processes (37). Thus, dose calculation from simpler principles may lead to infra- or supra- dosing. The matter is complex because performing dose-finding trials in children is not always ethical or feasible, particularly for lower ages. Importantly, it is in this last group that dosing may fail the most if maturation processes are not considered.

Advances in quantitative pharmacology can contribute to the resolution of the problem. The use of mathematical models incorporating maturation factors together with detailed understanding of the drug's PK/PD in adults as well as the use of standardized simulation techniques allow to predict the actual useful dose across different age groups (8). The combined methods are included under the MIDD initiative (38). Regulatory agencies for the marketing authorization of a new chemical entity - liable to be used in children – now require a rational dose recommendation in pediatrics as well as presentation of a viable pediatric investigation plan (PIP) (2,7,39).

In the present work MIDD type methods were applied for calculating the optimal oral dose of bilastine to be used in pediatrics. First was the integration of prior knowledge on the drug, preclinical and clinical, physiological and pharmacological as well as information *in vitro* (9). This integration, viewed as translational development, goes beyond the need to extrapolate and constitutes the scientific solution to the inefficiency in drug development being also the best manner to avoid failures in later phases or post marketing (8,9,40–42). Clearly, decisions on the trade-off between method applicability and complexity, depend on the strategic significance of such development and potential resource constraints.

The semi-mechanistic method proposed here utilizes information on ontogeny and physiology that already exists in the public domain so the task is connecting them to the kinetics of the specific product. In the present experience, the physiology underlying bilastine ADME (PK) parameters were resolved and linked in age group scaled ratios. Based on the published information on the use of similar antihistamines in pediatrics as well as the EMA and FDA guidelines (22–25), the PD of bilastine was considered already mature by the age of two years and the safety and efficacy thresholds considered to be equivalent to that in the adult. The fact that bilastine has straightforward non-saturable (linear) kinetics across a wide range of doses facilitated the exercise (18).

The PK/PD model was then successfully used to select the dose of bilastine to be used in children and optimally design a PK clinical trial *via* simulations. Population model-based methods applying the estimated variability in adults to children and addressing residual and inter-subject variabilities separately were used. The 10 mg/daily showed to be adequate to maintain wheal and flare effect during the entire dose interval (24 h) in children from 2 to <12 years, and therefore initially selected for the trial. The fact that only one dose was appropriate for the entire population was in accordance with the implied physiological process on bilastine PK/PD. By the age of 2 years (corresponding to the younger applicable age in the present project), the majority of the physiological processes contributing to bilastine plasma concentration and effect profiles are almost mature and only slight differences were expected derived from these small differences in the ontogeny. For example, bilastine clearance related mainly with the GFR is very similar across groups when corrected by the body weight. It is important to consider that the number of filtering nephrons in the children of 2 years of age is similar to adults considering that at 36 weeks of gestation nephrogenesis is complete and no new nephrons are formed. Renal tubular growth contributes exclusively to the large increase in renal mass from 36 weeks gestation to adulthood (43). This conclusion was also supported by the fact that for similar drugs as fexofenadine (similar PK behavior and same therapeutic class) a unique dose has been demonstrated to be adequate, and therefore approved, for the entire pediatric subset (from 2 years up to 11 years) in USA (44,45). Moreover, the wide therapeutic index of bilastine supported the possibility of using a unique dose for the entire pediatric population subset. Finally, the pediatric clinical trial intended to first study 6 to 12 year olds and then to extend to younger than 6 years would guarantee the adequacy of the dose as readjustments were approved if necessary, i.e., if strong age dependence existed in the PK parameters.

Confirmation of the above came at the first interim analysis with PK observations from the first group of children (>6 years), where a population PK model was developed (same structure as in adults) and contrasted with the ontogenic model. Simulation-based comparisons confirmed the scaling method, and the subsequent study design (including the

appropriateness of the 10 mg dose). The trial proceeded according to the plan derived from the ontogenic model in continuing recruitment of additional and younger patients.

CONCLUSION

The experience with bilastine points out the utility of pharmacology-enhanced modelling techniques when integrating knowledge on drugs as well as the use of simulation to quantify concerns, answer questions and facilitate decision on new drugs while optimizing testing in humans. The potential is undisputed in pediatric testing more so when development in adults is completed. From a clinical perspective, the use of M&S can aid in optimizing trials by minimizing sample size and risk simultaneously in a rational and quantifiable manner. The methods eventually aid to minimize failure risk and performance of unnecessary trials, thus reducing burden to this vulnerable population subset (risk) and optimizing efficacy and safety (benefit).

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