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ARTICLE

Application of a dual mechanistic approach to support bilastine dose selection for older adults

Chaejin Kim[1]* | Valentina Lo Re[2,3]* | Monica Rodriguez[2] | John C. Lukas[2] | Nerea Leal[2] | Cristina Campo[4] | Aintzane García-Bea[4] | Elena Suarez[3] | Stephan Schmidt[1] | Valvanera Vozmediano[1]

[1]Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, University of Florida, Gainesville, Florida, USA

[2]Drug Modeling & Consulting (DMC), Dynakin, SL, Bilbao, Spain

[3]Department of Pharmacology, Faculty of Medicine and Nursing, University of Basque Country UPV/EHU/ Biocruces Health Research Institute, Bizkaia, Spain

[4]Medical Department, FAES FARMA, S.A, Leioa, Spain

Correspondence
Valvanera Vozmediano, Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, University of Florida, Gainesville, FL 32612, USA.
Email: valva@cop.ufl.edu

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Abstract

The objective of this study was to evaluate bilastine dosing recommendations in older adults and overcome the limitation of insufficient data from phase I studies in this underrepresented population. This was achieved by integrating bilastine physicochemical, in vitro and in vivo data in young adults and the effect of aging in the pharmacology by means of two alternative approaches: a physiologically-based pharmacokinetic (PBPK) model and a semi-mechanistic population pharmacokinetic (Senescence) model. Intestinal apical efflux and basolateral influx transporters were needed in the PBPK model to capture the observations from young adults after single i.v. (10 mg) and p.o. (20 mg) doses, supporting the hypothesis of involvement of gut transporters on secretion. The model was then used to extrapolate the pharmacokinetics (PKs) to elderly subjects considering their specific physiology. Additionally, the Senescence model was develop starting from a published population PK) model, previously applied for pediatrics, and incorporating declining functions on different physiological systems and changes in body composition with aging. Both models were qualified using observed data in a small group of young elderlies ($N = 16$, mean age = 68.69 years). The PBPK model was further used to evaluate the dose in older subjects (mean age = 80 years) via simulation. The PBPK model supported the hypothesis that basolateral influx and apical efflux transporters are involved in bilastine PK. Both, PBPK and Senescence models indicated that a 20 mg q.d. dose is safe and effective for geriatrics of any age. This approach provides an alternative to generate supplementary data to inform dosing recommendations in under-represented groups in clinical trials.

*These authors equally contributed to this research.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Older adults are usually underrepresented in clinical trials limiting the information on pharmacological changes and special dosing needs in this population. New precision medicine tools can help to support dosing recommendations in geriatrics.

WHAT QUESTION DID THIS STUDY ADDRESS?

How to integrate aging-mediated physiological changes in quantitative pharmacology approaches to overcome the lack of sufficient older adults in clinical trials and provide support for precise dosing recommendations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Aging-mediated changes in physiological functions and body composition can be successfully integrated into quantitative strategies to scale the pharmacological knowledge to geriatric patients. This approach provides the mean to rationally improve posological adequacy in this under-represented population.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The present work pioneers the application of quantitative physiological modeling to address the limitations of including older adults in clinical trials and support dosing needs, using bilastine as an example. The application of similar approaches will help to generate pharmacological knowledge and design more efficient dedicated drug development programs for geriatric patients.

INTRODUCTION

Bilastine is a second-generation, H_1 selective antihistamine approved worldwide for the treatment of allergic rhinoconjunctivitis and urticaria in adults and children.[1,2] It has a well-defined therapeutic window and favorable pharmacokinetic (PK) properties, including (1) no significant hepatic metabolism and (2) no significant brain penetration resulting in nonsedative properties and lack of cognitive impairment.[2–4] Regarding the pharmacodynamic (PD) aspects, drug's potency is high, which is compatible with its three and six times higher affinity for the H_1 receptor when compared to cetirizine and fexofenadine, respectively.[5] In addition, bilastine has a very rapid onset (within an hour) and a long duration of action (26 h).[6,7] Aforementioned pharmacological properties are particularly attractive for geriatrics, a population at a higher risk of suffering adverse reactions and drug-drug interactions (DDIs).[8]

According to the Summary of Product Characteristics of bilastine, no dose adjustment is needed for older adults.[9] However, the dosing recommendation in geriatrics was initially evaluated using data from phase I studies with young adults and a small number ($N = 16$) of older adults (mean age 68.69 years) were included in a conventional population PK (PopPK) analysis.[9,10] This approach may thus not represent the overall geriatric population, which is physiologically diverse due to the heterogeneity of individual aging rate and extent, and the high prevalence of comorbidities/comedications. This situation is frequently encountered in clinical trials despite the efforts from regulatory authorities to include geriatric patients in randomized studies.[11–13] The availability of in silico approaches that integrate aging-mediated changes in physiology with associated effects on drug PKs and PDs, and enhance the understanding of underlying drug and disease mechanisms provide an opportunity to overcome these limitations. Moreover, these approaches may allow the evaluation of comorbidities and DDIs facing the unmet need of appropriate dosing recommendations for geriatrics in the absence of head-to-head clinical trials. In this research, we applied two alternative approaches that integrate physiological characteristics of older adults and the drug properties to characterize the PK and provide dose recommendations. Here, we used bilastine in healthy geriatrics as a case example also motivated by its peculiar secretion involving transporters on the gut wall after i.v. administration. First, we developed a PopPK based semi-mechanistic model, hereafter referred to as Senescence model, by using scaling equations that account for changes on the systemic PK parameters with aging as well as individual subject's demographics. This model is the continuation of a previous model applied to inform bilastine pediatric drug development.[14] Second, we developed a full physiologically-based pharmacokinetic (PBPK) model to evaluate the impact of intestinal transporters on bilastine PKs in adults, which was not possible with the Senescence model, and account for aging-related physiological changes on PK parameters. One remarkable PK feature of bilastine is the high fecal excretion

as an unchanged form after p.o. administration (~ 67% of total dose) and also very likely after i.v. administration (projected for ~ 30% of total dose).[2] Considering that the expected biliary excretion in human is less than 5% and the existing evidences of the drug-intestinal transporter interactions from clinical and in vitro studies, we hypothesize that intestinal transporters play a significant role in both, absorption and secretion.[15] Increasing the knowledge on the involvement of transporters on a drug PKs is crucial to have a deeper understanding of the mechanisms but also to predict the potential for DDIs which is especially important in the polymedicated geriatric population. We first developed the PBPK model in young adults and then, we extrapolated the model to healthy young geriatrics (adults of 65 to 74 years). Finally, both models, Senescence and PBPK, were verified with available data in a limited group of young geriatric volunteers as well as by comparing the predictions with that of a geriatric PopPK model developed using the young geriatrics data. Once this approach was qualified in young geriatric subjects, it was used to evaluate the therapeutic dose in older subjects (>75 years).

METHODS

The overall research strategy is summarized in Figure 1.

Dataset

All the clinical data used in the present study were part of bilastine clinical development and were approved by the corresponding institutional review board (IRB), and conducted in accordance with the principles of the Declaration of Helsinki of 1975 (as revised in 1983).

Young adults bilastine 10 mg i.v. data (BILA-2909/BA)

BILA-2909/BA was designed to investigate bilastine oral bioavailability in humans.[2] It was a randomized, open label, single dose, single center, two-arm crossover-controlled trial under fasting condition. Six male and six female subjects received 20 mg single dose of the p.o. tablet (Bilaxten FAES FARMA) and 10 mg of bilastine i.v. single dose over 5 min. The washout period between the two treatments was of at least 14 days, and the sequence of the treatments was determined by randomization in balanced manner. Subjects aged between 18 ando 24 years (mean 20.8 years), weighed between 50 ando 80.6 kg (mean 65.9 kg), and had body mass index (BMI) between 19.41 ando 25.40 kg/m^2 (mean 22.47 kg/m^2). Detail information can be found in the paper from Sadaba et al. (2013).[2]

Geriatric Bilastine 20 mg p.o. data (BILA/459-05)

BILA/459-05 was an open-label, single-dose, parallel-group study comprising a total of 32 young and elderly subjects. In the present research, data from 16 healthy subjects aged 65 or older (men $n = 8$; women $n = 8$) were used to represent the geriatric population. The elderly subjects were aged between

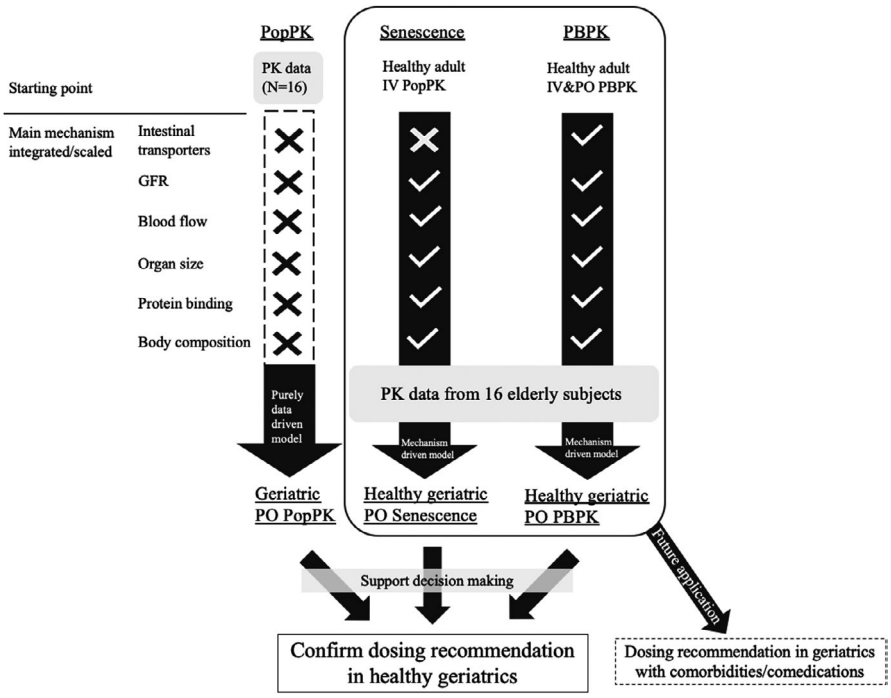

FIGURE 1 Overview of the dual physiologically-based pharmacokinetic model population pharmacokinetic (PBPK-PopPK) model-based approach used to evaluate bilastine dosing recommendation in geriatric subjects. GFR, glomerular filtration rate

65 ando 83 years (mean 68.69 years), weighed between 48.4 ando 85.1 kg (mean 73.06 kg), and had BMI between 21.51 ando 30.15 kg/m^2 (mean 26.33 kg/m^2).

Software used in the analysis

For the Senescence model and the PopPK model, modeling and simulation were performed with NONMEM (version VII; Icon Plc, Dublin, Ireland). Perl-speaks-NONMEM (version 4.6), Pirana (version 2.9.4), and Xpose4 (version 4.7.1) were used for model development and evaluation. For the PBPK model, GastroPlus 9.6 (SimulationsPlus, Inc.) was used for model development and simulation. Data exploration and management and graphics were performed using S-PLUS (version 8.2; TIBCO Software Inc.) and R (version 4.0; R core Team 2019).

Senescence model development

The starting point to build the Senescence model was a published two compartment PopPK model parameterized in terms of absorption rate constant (Ka), volume of the central compartment (Vc), volume of the peripheral compartment (Vp), and intercompartmental clearance (CL/Q).[10] The model was

TABLE 1 Main assumption and conclusion from the Senescence and PBPK models

Main assumptions	Justification	Approach to assess the impact	Conclusion
Senescence			
Changes in the PK as a consequence of aging related changes in albumin, GFR, CO, TBW, and TBF	Known processes involved in bilastine's PK that was also successfully used previously for pediatrics	Comparison of individual parameters predicted with the senescence model compared to EBE from a PopPK model	Individual predictions within the two-fold and less than 30% prediction error in the case of mean parameters (Senescence vs. geriatric popPK). The equation used to predict bilastine CL successfully tested CLr in patients with renal dysfunction.[32] Miss-predictions on CL/F attributable to (1) use of mean F from young adults, and (2) possible changes in F with aging not considered in the model.
F mean in young subjects similar to that in older adults			
PBPK			
Apical and basolateral transporters involved in bilastine secretion and absorption	Only 66% of the drug recovered in urine after i.v. but CLr is the main elimination pathway.[19] Amount recovered in urine after oral: ~42%[19] DDI and in vitro studies evidenced the influence of transporters at an intestinal level	Compare predictions and observations before and after the inclusion of transporters for iv and oral. Comparison with the mass balance results.	Apical and basolateral transporters needed to predict bilastine PK profile after i.v. and p.o. administration. After i.v. administration, only 74% of the drug predicted to be systemically available (in line with observed 66% recovery in urine) and the rest secreted to the GI track by active transporters. After p.o., only about 42.3% predicted to be systemically available; and 40% recovered in urine. This is in line with drug's renal CL and amount recovered in urine in the BA study (42%).[19] These results are also in line with the radio-labeled mass balance study.[20] Bilastine is eliminated by renal filtration in the kidneys. Decrease in renal CL in subjects with renal impairment was proportional to the decrease in the GFR.
Renal CL main route of elimination of bilastine	Mass balance study[19,20]	Comparison of urine recovery in the mass balance studies with the PBPK mass balance	Bilastine plasma concentrations were well predicted in geriatric subjects without the inclusion of aging related changes on drug transporters
No impact of aging on drug transporters	Not enough evidence to inform possible changes	Application of the model to predict the PK in older subjects and comparison with observations	

Abbreviations: BA, bioavailability; CL, clearance; CL/F, total apparent clearance; CLr, renal clearance; CO, cardiac output; DDI, drug-drug interaction; EBE, empirical Bayes estimate; F, bioavailability; GFR, glomerular filtration rate; GI, gastrointestinal; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; TBF, total body fat; TBW, total body water.

developed and qualified using p.o. data from 310 healthy adult volunteers in NONMEM (first order conditional estimation [FOCE] method) using nonlinear mixed effects (NLME) and standard procedures for population analysis.[10,16,17] Following a previous application of this approach to predict bilastine's PKs in pediatrics, a comprehensive literature search was carried out to design and/or extract appropriate mathematical equations for scaling Vc, Vp, clearance (CL), and Q with respect to age, sex, weight, height, and change of physiological factors with aging. The final equations integrated in the Senescence model are depicted in Table 1. Due to the difficulty of inferring a mathematical function to account for the aging effects on Ka, individual values of this parameter were directly borrowed from the geriatric PopPK model described below (see section "Geriatric population pharmacokinetics model development"). We also considered that the bioavailability (F) of the 20 mg bilastine p.o. dose was 61% (i.e., invariant regardless of aging and demographics).[2]

The Senescence model was then used along with subject specific demographics of elderly subjects ($N = 16$; BILA/459-05) to simulate the individual PK after 20 mg of p.o. bilastine. Simulations were then compared with those from the geriatric PopPK model (section "Geriatric population pharmacokinetics model development") developed using data from the same subjects. Specifically, predicted individual PK parameters (Vci, Vpi, CLi, and Qi) using the Senescence model and divided by a mean F of 61% were compared with the individual parameters estimates from the geriatric PopPK model. The Senescence model was considered appropriate when the ratio between the parameters estimated for each individual from both models was less than two fold.

Geriatric population pharmacokinetics model development

The geriatric PopPK model was developed with data from 16 elderly subjects from study BILA/459-05 using NLME and standard procedures for population analysis.[10,16,17] The purpose of developing the geriatric PopPK model was to estimate a Ka to inform the Senescence model but also to use it as a reference for comparison. Further information on the model development and qualification can be found in section 2 of the supplementary material.

Physiologically-based pharmacokinetic model development

The PBPK model was developed using i.v. and p.o. data from healthy young adults participating in study BILA-2909/BA, which contains plasma concentration and mass balance (cumulative urine excretion) data using GastroPlus 9.6. A key characteristic of the PBPK model is that it considers intestinal transporters. The evaluation of the influence of transporters on secretion and absorption was performed in a step-wise fashion: first, the influence of transporters on bilastine's secretion was evaluated using the i.v. data; second, the need of inclusion of additional transporters involved in the absorption was evaluated using the p.o. data. Based on the evidence from in vitro and clinical data, we introduced an apical efflux transporter, which represents the P-glycoprotein (P-gp). However, due to its location in the apical membrane it was not able to account for the secretion after the i.v. administration, suggesting the need of an additional transporter on the basolateral membrane. The values for maximum value (V_{max}) and kinetic metabolite (Km) were not available from in vitro studies and were thus incorporated in the model using a sensitivity analysis to fit the PK data (Figure S7). After the inclusion of transporters, the PBPK model was further qualified using external data from 12 clinical trials after single and/or multiple p.o. doses in the range between 5 mg and 220 mg per day (Table S4).[10,18] Moreover, the mean area under the curve (AUC) and maximum plasma concentration (C_{max}) values from observations and predictions were also compared (Figure S4 and S5). The model was considered appropriate when the ratio of the PK parameters from mean of observations and mean of predictions was less than twofold. Furthermore, multiple dose of 20 mg p.o. q.d. scenario was simulated, and it compared with observations for additional verification of the PBPK model (Figure S6 and Table S5).[10,18] Available mass-balance data were also used for verification (Figures S8 and S9).[19,20] The PBPK model was then extrapolated to healthy geriatrics. Virtual geriatric subjects were generated using GastroPlus 9.6 built-in Population Estimates for Age-Related (PEAR) Physiology program[21] at mean age of 70 (age range of 65–75 years with 50% men) and at mean age of 80 (age range of 75–85 years with 50% men). Based on age-related information, whole-body tissue estimates are calculated for weight, volume, and perfusion for each tissue and recalculate drug distribution to each specific organ in the model as well as elimination. The age-related population data in GastroPlus comes from the National Health and Nutrition Examination Survey (NHANES) from 11,039 Americans (50% male and female subjects; 1–85 years old). The model predictions ($N = 1500$) in young elderly subjects were visually verified with the observations before proceeding with the extrapolation to the older group.

Evaluation of the suitability of bilastine 20 mg q.d. oral dose in geriatrics

To test whether bilastine 20 mg q.d. p.o. dose is also appropriate for the overall group of geriatrics, simulated PK profiles from the Senescence ($N = 16$), geriatric PopPK ($N = 1500$), and

TABLE 2 Senescence model scaling equations used in the extrapolation of bilastine PK parameters to elderly

Parameter	Equation and/or reference	PK related parameters	Equation to scale intravenous PK in elderly
CSHA (g/L)	$\text{CHSA} = -0.0709 \times \text{Age(yr)} + 47.7$ Eq. 1[27]	fu	$\text{fu ger} = \frac{1}{1 + \frac{\text{CHSAger} \times (1 - \text{fuad})}{\text{CHSAad} \times \text{fuad}}}$ Eq. 2[33]
GFR (L/h)	$\text{GFR(ml/min/100 g kidney)} = 26.6 \times \left(1 - \frac{0.9 \times (\text{Age(yr)} - 30)^{1.5}}{\text{TA}_{50}{}^{1.5} + (\text{Age(yr)} - 30)^{1.5}}\right)$ Where TA_{50}:54 (male), 59 (female) Eq. 3[25] The GFR equation and relevant age and sex dependent kidney weight is obtained from Schlender et al. 2016	CLr (L/h)	$\text{CLr}_{\text{ger}} = \frac{\text{GFRger} \times \text{fu}_{\text{ger}}}{\text{GFRad} \times \text{fu}_{\text{ad}}} \times \text{CLr}_{\text{ad}}$ Eq. 4 $\text{ratio}\frac{\text{CL}}{\text{CLr}}$ Eq. 5[34,35]
CO (L/h)	$\text{CO} = 159 \times \text{BSA}\left(\text{m}^2\right) - 1.56 \times \text{Age(yr)} + 114$ Eq. 6[27]		$\text{ratio}\frac{\text{CO}}{\text{Q}_{iv}}\text{male} = 348.62$ Eq. 8[14]
BSA (m^2)	$\text{BSA} = 0.007184 \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}$ Eq. 7[36]	Q (L/h)	$\text{ratio}\frac{\text{CO}}{\text{Q}_{iv}}\text{female} = 315.04$ Eq. 9[14]
TBW (L) TBF (kg)	$\text{TBW}_{\text{male}} = 1.203 + 0.176 \times \text{weight (kg)} + 0.449 \times S^2/\text{Res}$ Where $\frac{S^2}{\text{Res}}$ (age groups 60 − 69.9) = 67.0, (age groups 70 − 79.9) = 64.3 Eq. 10[37] $\text{TBW}_{\text{female}} = 3.747 + 0.113 \times \text{weight (kg)} + 0.45 \times S^2/\text{Res}$ Where S^2/Res (age groups 60 − 69.9) = 46.2, (age groups 70 − 79.9) = 45.2 Eq. 11[37] $\text{TBF (kg)} = 0.68 \times \text{weight (kg)} - 0.56 \times \text{height (cm)} + 6.1 \times \text{Sex} + 65$Where male = 0, female = 1 Eq. 12[27]	Vss, Vc and Vp (L)	Vss iv ≅ TBW + TBF Eq. 13 Vc iv = 0.65 × Vss iv Eq. 14 Vp iv = Vss iv − Vc iv Eq. 15
		k_a	The constant of absorption was taken from the Geriatric PopPK model

Note: Reference Adult body composition parameter: (adult of reference were considered aged 30–50 years).

CO adult man = 352.11, CO adult woman = 318.19[27]; GFR adult man = 113.03, GFR adult woman = 99.66[25] ; fu adult = 0.13[10]; CHSA adult = 44.86.[27]

Abbreviations: V, Volume of distribution; ss, steady state; c, Central; p, Peripheral; F, bioavailability; CL, clearance; r, renal; ad, adult; fu, unbound fraction; GFR, glomerular filtration rate; CHSA, albumin molar concentration; Cp, plasma concentration; CO, cardiac output; Q, intercompartmental clearance; TBW, total body water; TBF, total body fat; k_a, absorption rate constant.

TABLE 3 Summary of bilastine pharmacokinetic parameters in elderly subjects

Senescence model (20 mg p.o.) $F = 61\%$		Geriatric PopPK model (20 mg p.o.)	
Parameter	**Mean of individual subjects' predicted parameters**	**Parameter**	**Mean of individual subjects' predicted parameters**
Vc/F (L)	66.88	Vc/F (L)	77.44
Vp/F (L)	36.01	Vp/F (L)	37.62
CL/F (L/h)	12.78	CL/F (L/h)	18.04
Q/F (L/h)	1.40	Q/F (L/h)	1.57
Ka (1/h)	1.28	Ka (1/h)	1.28
CV (%) Ka	24.67	CV (%) Ka	24.67
CV (%) CL	8.91	CV (%) CL	26.26
CV (%) Vc	10.33	CV (%) Vc	30.50
CV (%) Q	8.51	CV (%) Q	29.22
CV (%) Vp	10.33	CV (%) Vp	38.17

Note: (Left) Mean and CV of individual predicted parameters with the Senescence model in subjects ($N = 16$) from study BILA/459-05; (right) Mean and CV of individual Bayesian estimates with the geriatric popPK model using data from BILA/459-05 ($N = 16$).

Abbreviations: CL, clearance; CL/F, total apparent clearance; CV, coefficient of variation; Ka, absorption rate constant; PopPK, population pharmacokinetic; Q/F, intercompartmental clearance; Vc, central compartment; Vp, peripheral compartment.

PBPK ($N = 1500$; mean age of 70) models were compared with that of young adults PopPK model ($N = 5000$).[10] We compared predicted C_{max} and AUC values as well as visually check the plasma concentration profiles focusing on whether the overall predictions from the three geriatric models were within 95% confidence interval (CI) of young adults PopPK model. PBPK simulated results at mean age of 80 were further compared with that of young adults PopPK model to evaluate whether bilastine 20 mg q.d. is also appropriate in the older geriatric age.

RESULTS

Figure 1 summarizes the different approaches combined in this analysis with a highlight of the main mechanisms on bilastine PK investigated and/or supported by each of these analyses. Moreover, Table 1 summarizes the main assumptions and conclusions taken with each model.

Senescence and geriatric PopPK model

Table 2 shows the scaling equations integrated in the Senescence model. Individual subject's demographics used as input for the extrapolations in the Senescence model are presented in Table S1. Table 3 summarizes the PK parameters of the Senescence and geriatric PopPK model. Additional information on the evaluation of the predictive capacity of the Senescence model is presented in Figure S1. Both models led to very similar PK parameters (all the predicted individual PK parameters predicted with the Senescence model were within the 2-fold range) and model predictions in the population of elderly subjects supporting the validity of the equations and assumptions used to train the Senescence model. A more detailed description of the development and qualification of the geriatric PopPK model is provided in the section 2 of supplementary material.

PBPK model

The final PBPK model parameters and verification, and simulation settings are summarized in section 3 of supplementary material. Two different transporters were included in the final model (Figure 2a), an efflux transporter in the apical membrane which represents the P-gp and an influx transporter in the basolateral site needed to explain the passage from the blood to the enterocyte after i.v. administration. Figure 2b shows the final i.v. PBPK model predictions (black solid line) with subjects' observations superimposed (grey dots). Moreover, different predictions performed during the model development process are also depicted in the same panel demonstrating that both an influx and efflux transporter are needed to fit bilastine PK profile. This result was also supported by the urine excretion data (Figure 2c) where the observed urine data were only well-predicted when both transporters were included in the model. Urine data were overpredicted otherwise. A similar representation is shown in Figure 2d for the p.o. administration where the black solid line represents the final model predictions with subjects' observations superimposed (grey dots). In this specific case, in addition to inclusion of the P-gp, the C3 and C4 parameters of the absorption scale factor (ASF) were manually optimized to

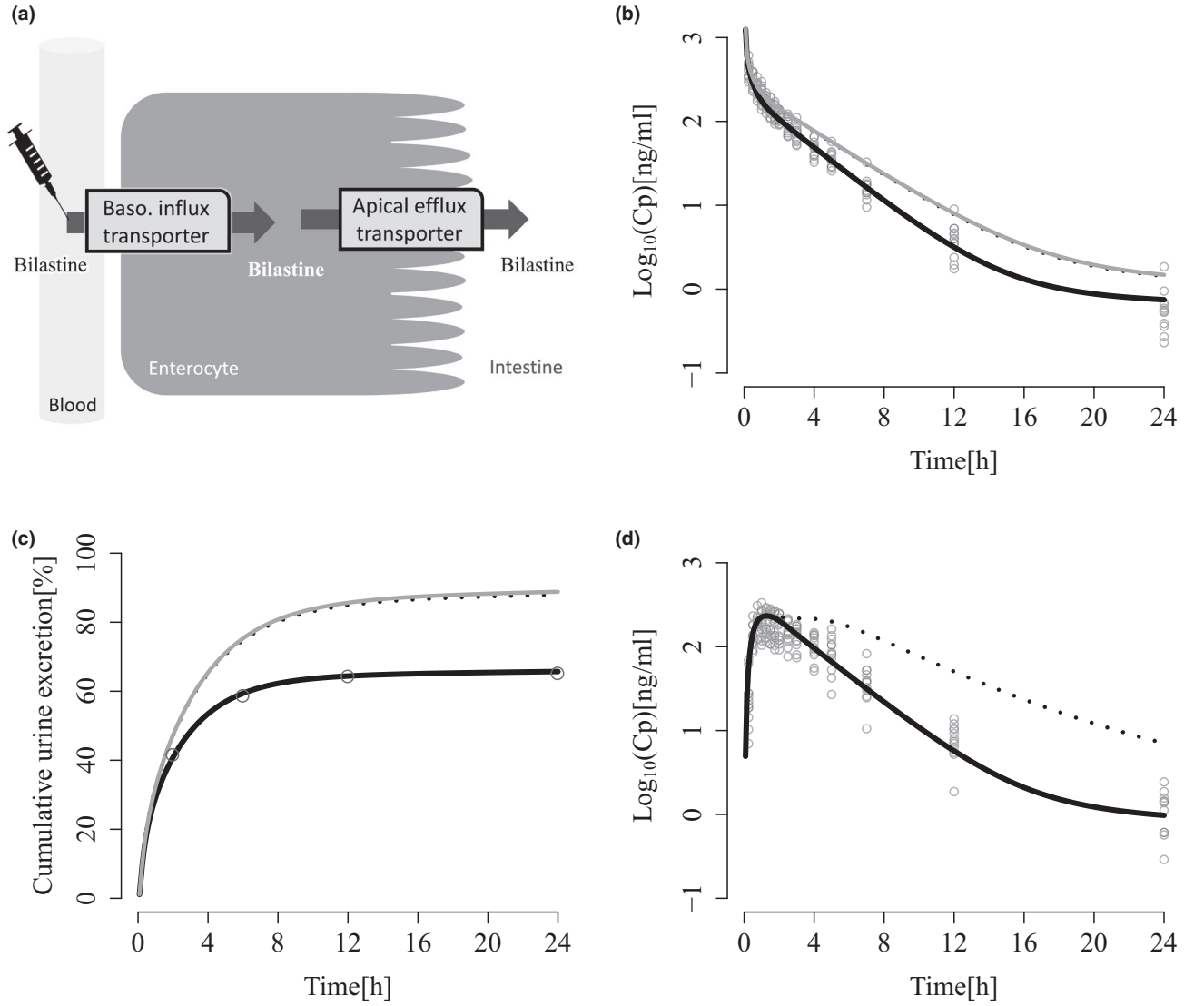

FIGURE 2 Bilastine PBPK model in young adults. (a) Schematic diagram of proposed intestinal transporters involved in bilastine disposition. (b) Predicted versus observed plasma concentrations after 10 mg single i.v. dose (solid black line: final model; dotted line: model without basolateral influx transporter; grey solid line: model without both basolateral influx and apical efflux transporters; open circles: observations). (c) Predicted versus observed cumulative urine excretion after 10 mg single i.v. dose (solid line: final model; dotted line: model without basolateral influx transporter; grey solid line: model without both basolateral influx and apical efflux transporters; open circle: mean observations. (d) Predicted versus observed plasma concentration after single 20 mg p.o. dose (solid line: final model; dotted line: model without Cs adjustment; open circles- observations).

account for lower colonic absorption and avoid overpredictions of bilastine's absorption (black dashed line).

Evaluation of suitability of bilastine 20 mg q.d. oral dose in geriatrics

Figure 3 shows the overlay of predicted median (dashed line) and 95% CIs (light grey shaded area) from young adults with the predicted median (solid black line) and 95% CI (dark grey area) from the geriatric PopPK model (Figure 3a), the Senescence model (Figure 3b), and PBPK mean age of 70 years (Figure 3c), and mean age 80 years (Figure 3d). Moreover, Table 4 summarizes the PK metrics simulated with all the different models, including the extrapolation to older subjects (mean of 80 years). The predictions performed with all the three models felt within the simulations performed with the PopPK model in young adults[10] supporting the adequacy of the 20 mg q.d. oral dose in the geriatric population.

DISCUSSION

Establishing dosing recommendation in underrepresented groups in clinical trials is challenging not only due to lack of data but also due to insufficient understanding on the effect

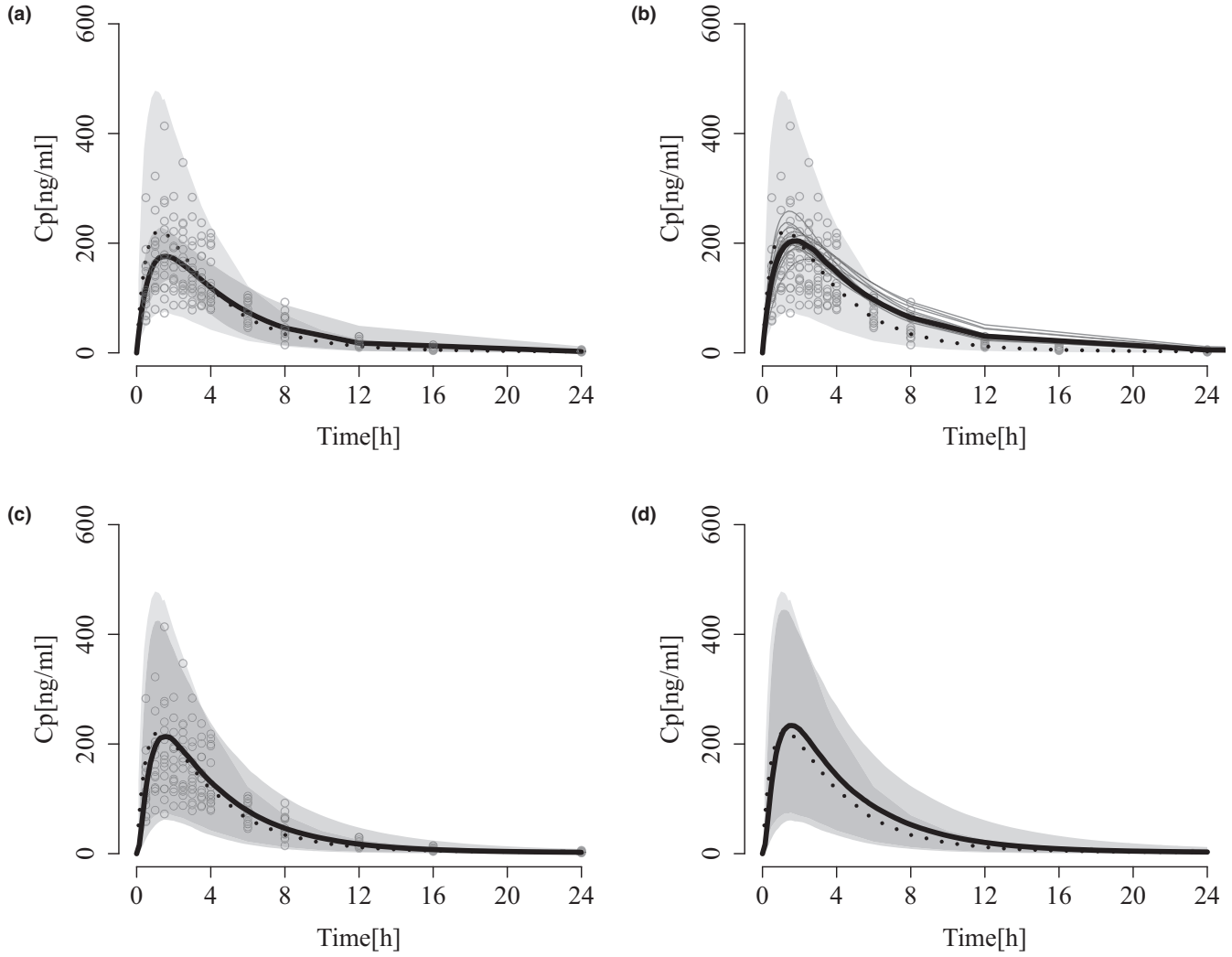

FIGURE 3 Evaluation of the appropriateness of the 20 mg dose in geriatrics with the different models: (a) geriatric PopPK, (b) Senescence, (c) PBPK at mean age of 70 years, and (d) PBPK at mean age of 80 years (dotted line: median PopPK young adults; light grey shaded area: 95% PopPK young adults; solid black lines and dark grey shaded area: median and 95% CI from models (a) Geriatric PopPK, (b) Senescence, and (c, d) PBPK in 70 and 80 year old subjects; light gray lines in (b): individual predictions Senescence model; grey dots: observations). CI, confidence interval; PBPK, physiologically-based pharmacokinetic; PopPK, population pharmacokinetic

TABLE 4 Model prediction of median and 95% CI C_{max} and median AUC

	C_{max} (ng/ml)	AUC (ng·h/ml)
Young adults PopPK ($N = 5000$)	223.29 [74.88–478.12]	1103.88 [370.03–2311.15]
Geriatric PopPK ($N = 1500$)	176.02 [133.04–227.98]	1129.40 [588.65–1891.86]
Senescence at 70 ($N = 16$)	204.06 [170.91–258.51]*	1478.14 [1222.83–2010.15]*
PBPK at 70 ($N = 1500$)	213.39 [62.10–425.26]	1176.82 [280.17–2464.71]
PBPK at 80 ($N = 1500$)	233.63 [60.62–445.22]	1307.59 [278.66–2813.93]

Note: Young adults AUC from the observation: mean = 1160 ng h/ml; range: 481–2528 ng·h/ml.

Young adults C_{max} from the observation: mean = 260 ng·h/ml; range: 63–924 ng/ml.

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; PBPK, physiologically-based pharmacokinetic; PopPK, population pharmacokinetic.

*Due to sparse *N* size, minimum value and maximum value are presented.

of their physiological and clinical characteristics on drug PK and/or PD. Conventional PopPK analysis can be conducted if clinical trial data exist. However, there is usually a limitation in the number of participants from special populations in the development of drugs restraining the performance of covariate analysis and reducing the confidence

of dosing recommendations for these populations. To overcome these limitations, physiologically based approaches have been proposed.[17,22,23] Allometric scaling of PK parameters by using predictive biomarkers such as body weight or body surface area (BSA) in children would be one of the well-recognized strategies frequently used for establishing dosing recommendations in pediatrics. However, when a case to be studied is even more complicated, such as geriatrics, establishing dosing recommendations still remains to be solved.[24] Why the need is yet unmet is mainly because of the substantial heterogeneity of the geriatric group derived from various aging rate/extent and high number of comorbidities and comedications.[25] This impedes using common scaling factors of dose adjustment, such as age, weight, or BMI.[24,26] Eventually, this issue requires conducting highly personalized approaches for guiding dosing in older adults based on a thorough understanding of physiological/pathological characteristics in a specific subject. Conducting head-to-head clinical trials examining every possible scenario is neither time nor cost efficient. Hence, testing different dosing scenarios in virtual subjects using modeling and simulation provides a great alternative to support precise dosing recommendations. The present study proposed two mechanistic-based approaches to support dose recommendations in healthy geriatrics using bilastine as a case example. The application is being expanded to patients with comorbidities and comedications.

The strength of the Senescence model includes that it utilizes the existing PopPK model structure in young adults, thereby saving time and efforts. In addition, the model was used to confirmed that key age-dependent variables impacting bilastine disposition already identified in pediatrics, such as glomerular filtration rate (GFR) that were essential to obtain accurate predictions of plasma concentrations in elderly subjects. Interestingly, a previous research showed that the volume of distribution relates with the physiological total body water (TBW) in rats and dogs.[18] This relationship was assumed to be maintained in humans and successfully used to predict the volume in young adults and then also in children.[14,17,18] However, this consideration did not work for elderly subjects where both TBW and body fat were needed for accurate predictions of this parameter. This aging effect was expected considering bilastine lipophilic nature and the 10–15% decrease in TBW and 20–40% increase in the total body fat in older adults with respect to younger subjects.[27] The renal clearance in the Senescence model was scaled by means of a function that incorporates age-related changes in the GFR and in unbound fraction (fu). A ratio CLtotal/CLrenal greater than 1 supported the hypothesis of secretion mechanism in young adults. This ratio was used to empirically correct for additional mechanisms affecting bilastine CL in the Senescence model. Considering that bilastine is mostly eliminated renally by glomerular filtration without significant metabolism or biliary excretion as well as the evidence of clinical involvement of transporters in the PKs, this additional mechanism is expected to be the P-gp, contributing to the fecal secretion of the drug (as was further investigated and confirmed with the PBPK model). The estimated total apparent clearance (CL/F) from the Senescence (12.78 L/h) and geriatric PopPK (18.04 L/h) model were slightly smaller than that of the young adult PopPK model from Jauregizar et al. 2009 (18.10 L/h). The aligned CL/F values (key PK parameter for the exposure of repeated doses) from these three models strongly suggest that there may be no need for dose adjustment in geriatric subjects. The Senescence model could be further applied to predict the PK in older adults by using published demographics from this population, and could be an alternative when the development of a full PBPK model is not doable due to, for example, insufficient data.

The second approach utilized in this project was the PBPK model. Generally, this type of model needs more time and resources to be developed. Nevertheless, once developed, they provide the framework to investigate hypothesis on the mechanisms involved in drugs PK. As an example, the PBPK model developed in the present study aided to investigate the influence of transporters on drug PK and support the dose selection in healthy geriatrics. Additionally, due to the comprehensive and integrative consideration of the physiology in the model, it may also facilitate, with some modifications and adjustments, the prediction of bilastine PK in geriatrics with comorbidities and/or comedications. Based on strong evidence of the interaction between P-gp and bilastine, an apical efflux transporter representing the P-gp was initially introduced.[9,15] However, the sole inclusion of the apical efflux transporter was not able to fit on the i.v. data. Particularly, the cumulative urine excretion data indicated that 66% of the 10 mg i.v. dose was excreted via urine in humans but the model overpredicted the cumulative urine excretion when the basolateral transporter was not considered, or when transporters were considered in isolation.[2] Bilastine permeation into the enterocyte without introducing a basolateral influx intestinal transporter was highly restricted. The consequence was almost no exposure of the drug to the P-gp after i.v. administration. These results suggested that along with the P-gp other basolateral influx transporter in the enterocyte may be involved in bilastine secretion in humans, probably the OCT1, although only moderate evidence was found in vitro with the higher dose tested.[15] Additional research is needed to further support this finding and to investigate the effect of aging on drug transporters in the gut wall. However, the results of the study do not suggest a significant impact of age-related changes at this level.

The initial PBPK p.o. model predicted a substantial amount of bilastine absorbed in the large intestine. Consequently, the predicted plasma profile looked similar to that of a sustained release formulation and was far from the observations. Ungell et al., in 1998, reported that a lipophilic drug, which has relatively high *logD* shows a tendency to have higher colonic permeability than their jejunal permeability. This becomes the basis for developing the ASF model in GastroPlus 9.6.[21,28] The default values of the ASF model parameters were estimated by regression from multiple set of compound data, thus do not guarantee to work for every case. Especially, like in the case of bilastine where intestinal transporters are involved, the prediction of ASF with respect to *logD* alone is no longer valid, and the default fitted constants for ASF need to be drug-specifically adjusted.[21] Even after introducing transporters in the model, the PBPK p.o. model still predicted high absorption in large intestine (caecum: 44.5%, ascending colon: 21.0% of total dose). To solve this issue, we optimized the values for the fitted constants of the colon part, C3 and C4, being the final values 0.05 and 0, respectively. The model could then properly fit the observations with a reasonable regional gastrointestinal (GI) absorption (caecum: −1.4%, ascending colon: −1.5% of total dose). The need of optimizing C3 and C4 to values close or equal to 0 while keeping default values for C1 and C2 supports the hypothesis that P-gp's efflux capacity and/or its distribution within the GI track may not be constant, whereas the impact of the P-gp on the large intestine may be higher than in other GI regions.[29,30]

The predictions of the Senescence, PBPK, and geriatric PopPK models showed that drug exposures were similar to that from the young adults. Median predictions with all the three geriatric models were within the 95% CI of young adults, and the median values were not much deviated from young adult median. As the Senescence model and geriatric PopPK model were based on BILA/459-05 demographics and its PK data, respectively, variabilities of the two model were very narrow (small number of subjects and homogenous demographic distribution). Additionally, although the PBPK model predicted AUC and C_{max} values tend to increase with aging and its 95% prediction interval of the age of 80 years were slightly wider, the prediction interval was very similar to the 95% CI of young adults, supporting that the current dose recommendation of 20 mg q.d. p.o. is also suitable not only for young geriatrics (i.e., elderly subjects in trial BILA/459-05; mean age of 68.69 years) but also for the older subjects. The safety of the 20 mg dose in geriatric has been further evaluated in a safety trial involving 150 elderly subjects as part of bilastine risk management that demonstrated the favorable safety profile with a low incidence of treatment-emergent adverse events.[31]

In conclusion, this study demonstrated the utility of mechanistic modeling in proposing dose recommendations in geriatric subjects. Specifically, we evaluated the posology of bilastine in geriatrics using two different mechanistic-based models, the Senescence (PopPK-based semi-mechanistic model) and the PBPK model. Considering the lack of guidance documents for model-informed dosing recommendation in geriatrics, and the insufficient understanding of aging processes, convergence of the conclusion from the different approaches reinforces and supports each model's output. This research showed that a dual PopPK-PBPK approach can be applied to support clinical decision making for underrepresented groups in traditional clinical trials.

CONFLICT OF INTEREST

C.C. and A.G.-B. are employees of FAES FARMA, S.A. All other authors declared no competing interests for this work.

AUTHORS' CONTRIBUTION

C.K., V.L.R., M.R., J.C.L., N.L., C.C., A.G., E.S., S.S., and V.V. wrote the manuscript. M.R. and V.V. designed the research. C.K., V.L.R., J.C.L., M.R., and V.V. performed the research. C.K., V.L.R., J.C.L., and V.V. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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