External evaluation of population pharmacokinetic models of imatinib in adults diagnosed with chronic myeloid leukaemia

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Aims: Imatinib is considered the standard first-line treatment in newly diagnosed patients with chronic-phase myeloid leukaemia (CML). Several imatinib population pharmacokinetic (popPK) models have been developed. However, their predictive performance has not been well established when extrapolated to different populations. Therefore, this study aimed to perform an external evaluation of available imatinib popPK models developed mainly in adult patients, and to evaluate the improvement in individual model-based predictions through Bayesian forecasting computed by each model at different treatment occasions.

Methods: A literature review was conducted through PubMed and Scopus to identify popPK models. Therapeutic drug monitoring data collected in adult CML patients treated with imatinib was used for external evaluation, including prediction- and simulated-based diagnostics together with Bayesian forecasting analysis.

Results: Fourteen imatinib popPK studies were included for model-performance evaluation. A total of 99 imatinib samples were collected from 48 adult CML patients undergoing imatinib treatment with a minimum of one plasma concentration measured at steady-state between January 2016 and December 2020. The model proposed by Petain et al showed the best performance concerning prediction-based diagnostics in the studied population. Bayesian forecasting demonstrated a significant improvement in predictive performance at the second visit. Inter-occasion variability contributed to reducing bias and improving individual model-based predictions.

Conclusions: Imatinib popPK studies developed in Caucasian subjects including α1-acid glycoprotein showed the best model performance in terms of overall bias and precision. Moreover, two imatinib samples from different visits appear sufficient to reach an adequate model-based individual prediction performance through Bayesian forecasting.

KEYWORDS
cancer, NONMEM, pharmacometrics, population analysis, therapeutic drug monitoring
1 | INTRODUCTION

Chronic myeloid leukaemia (CML) natural history and outcome was revolutionized more than two decades ago by the introduction of tyrosine kinase inhibitors (TKI), the first of which was imatinib. Since imatinib establishment as the standard of care for first-line treatment of newly diagnosed chronic-phase CML patients, their current life-expectancy is virtually what would be expected for their age and gender in the nonleukemic general population.1–5

Imatinib standard dosage has been established as 400 mg orally once a day, which is generally well tolerated. However, a high between-subject variability (BSV) of imatinib pharmacokinetics (PK) has been observed.4,6 Several factors have been proposed as influencing imatinib BSV, mainly demographic factors (ie, sex, age, body weight) and clinical characteristics (ie, disease diagnosis), enzymatic activity (mainly cytochrome P450 CYP3A4), drug interactions or activity of efflux transporters, in addition to therapeutic adherence.7,8 Thus, the one-dose fits all approach of imatinib 400 mg once a day may not represent the optimal dose of this drug for achieving an optimal molecular response, which is the current therapeutic target.9–13

A direct relationship between imatinib trough plasma concentrations (Cmin) greater than 1000 ng/mL and an optimal cytogenetic and molecular response has been proposed by several authors.14–17 However, the use of imatinib target concentration associated with treatment response remains a matter of debate.18 The exposure of leukemic cells to imatinib infra-therapeutic concentrations (Cmin < 1000 ng/mL) has been highlighted as the main cause for the development of treatment resistance.19 Higher imatinib Cmin has also been associated with the development of toxicity, such as eyelid oedema or neutropenia.6,20,21 To optimize therapy in patients diagnosed with CML, therapeutic drug monitoring (TDM) of imatinib plasma concentrations is increasingly recommended in daily clinical practice, especially in patients who do not respond adequately to treatment or who suffer from concentration-dependent adverse events.9,22–24

Population PK (popPK) modelling is widely used within clinical pharmacology for characterizing sources of PK variability of the target patient population and their impact on drug disposition.25 PopPK models, coupled with Bayesian estimation, have the potential to enhance and streamline the TDM process.26 Several imatinib popPK models have been developed in patients diagnosed with CML, which, together with Bayesian forecasting methodology, are able to reduce the uncertainty surrounding individual PK exposures based on a priori and individualized information.7,32 The identification of the covariates is usually useful for explaining part of the variability of the Cmin across the studied population. However, the bias and precision of model predictions improved substantially by including imatinib concentrations using Bayesian forecasting.12,27,28

External evaluation of popPK models involves the use of an independent dataset to assess the accuracy and bias of the overall model performance in subjects with characteristics similar to those with whom the models were developed.29 It is also a useful methodology to evaluate and select the most accurate and precise model in a different target population. Therefore, external evaluation is an adequate approach for available popPK model selection for model-informed precision dosing (MIPD).

This study aimed to perform an external evaluation of available imatinib popPK models developed mainly in adult patients, and to evaluate the improvement in individual model-based predictions through Bayesian forecasting computed by each model on different treatment occasions.

2 | METHODS

2.1 | Review and selection of popPK models of imatinib

A literature search was conducted in PubMed and SCOPUS of the available imatinib popPK models developed mainly in adult patients published between January 1980 and May 2021. The search was performed using the terms “imatinib” AND “population pharmacokinetic” in the abstract field. The identified studies were reviewed, and their references examined to identify further potential articles for inclusion. The search did not cover case reports or studies not containing original research or data. Reviews or external evaluation of models, and articles with insufficient information about adequate model implementation in NONMEM were excluded. Models including free and
total imatinib plasma concentrations were not considered. Data from studies presented in multiple publications were identified to avoid duplications and were reported as a single study. The following modelling information was extracted from the articles selected: population background, number of subjects and samples, imatinib daily dose at baseline, model structure (ie, number of compartments, absorption model, etc), typical population PK parameters, BSV, residual-unknown variability (RUV), and covariates relationship and their magnitude effect on PK parameters. Time-varying PK of imatinib was also reflected within the PK information.

2.3 | External evaluation data

2.3.1 | Patients

TDM was systematically practiced in all patients undergoing imatinib treatment. TDM samples were collected in adult outpatients diagnosed with chronic phase CML who were treated with imatinib, irrespective of dosing modifications, with at least one quantifiable imatinib sample, were used for external evaluation. TDM was performed in all patients at 1, 3 and 12 months after the initiation of imatinib treatment. In addition, a TDM follow-up was performed annually as a standard procedure. Patients in the accelerated and blastic phase of the disease and patients with poor quality of life were excluded from the analysis. The study protocol was approved by the hospital’s Clinical Research Ethics Committee after evaluation of compliance with ethical standards and good clinical practice (CEIC Ref 2016/06/93). Written informed consent was obtained from all the subjects.

2.3.2 | Data collection

Imatinib was orally administered mainly as 400 mg once a day. Blood samples were collected at steady state (at least 1 month after the last imatinib dosage was established) just before imatinib administration \( (C_{min}) \) as a routine TDM procedure. Alternatively, blood samples 12 hours after the last imatinib dose intake were collected when \( C_{min} \) was not feasible. Blood samples were collected in ethylene diamine tetraacetic acid (EDTA)-containing tubes, centrifuged for 10 minutes and stored at \(-20^\circ C\) until plasma drug quantification.\(^{19,30}\)

The following clinical and demographic patient information was recorded: age, sex, weight, height, serum creatinine, estimated glomerular filtration rate (calculated following the CKD-EPI equation\(^{31}\)), albumin, α1 acid glycoprotein, blood cells count and treatment information (imatinib daily dose, disease stage and time since diagnosis of CML, duration of treatment at first TDM visit, time of imatinib administration and time of blood sampling). Last observation was carried forward or backward for missing covariate values with the available patient information. Mean population value of the dataset was imputed in those variables when no previous individual information was available.\(^{32}\)

2.3.3 | Bioanalytical method

The imatinib plasma concentrations collected were quantified by an ultra-performance liquid chromatography system associated with an ultraviolet detector (UV/UPLC). The analytical method was successfully validated in terms of linearity, accuracy and precision within the range of 250-3000 ng/mL following the European Medicines Agency (EMA) and Food and the Drug Administration (FDA) recommendations for the validation of analytical methods in biological fluids.\(^{33,34}\) Overall precision and accuracy were lower than 6% in all the samples evaluated.\(^{35}\)

2.4 | External evaluation of the predictive capability of popPK models

The predictive performance of the selected candidate models was evaluated in the external dataset using the software NONMEM version 7.4.3. (ICON Development Solutions, Ellicott, Maryland, USA). Statistical analyses and graphical representations of the results were performed with R version 4.0.2. Prediction-based diagnostics, simulation-based diagnostics and Bayesian forecasting analysis were carried out in NONMEM and the results were processed in R to evaluate the predictive capability of the identified models.

2.4.1 | Prediction-based diagnostics

Bias and precision of the imatinib popPK models selected were evaluated using the prediction error (PE), mean prediction error (MPE), median absolute prediction error (MAPE) and root mean squared prediction error (RMSE). The population predicted concentrations \( (C_{pred}) \) were estimated by fixing the parameters in the structural, including covariate relationships, and stochastic
models to the final estimates. Cpred were compared with the corresponding concentrations observed (Cobs) by estimating the PE (Equation 1).

$$\text{PE} (\%) = \frac{\text{Cpred} - \text{Cobs}}{\text{Cobs}} \times 100$$

(1)

MPE was used for evaluation of overall bias of predictions (Equation 2). Moreover, model-based prediction bias was visually evaluated by plotting the distribution of PE obtained by each popPK model evaluated. Overall model performance was confirmed through goodness-of-fit plots by representing Cobs versus Cpred.

$$\text{MPE} (\%) = \frac{1}{N} \times \sum_{i=1}^{N} \text{PE}_i$$

(2)

The precision of imatinib predictions was evaluated by calculating MAPE and RMSE (Equations 3 and 4, respectively) and the percentage of PE within 20% (F20) and 30% (F30). In general, the closer to zero the MAPE and RMSE, the higher the precision of the predictions. If a model reached the criteria of MPE ≤ 30%, F20 ≥ 35% and F30 ≥ 50%, its predictive performance was considered to be satisfactory and clinically acceptable.36-41

$$\text{MAPE} (\%) = \text{median of } |\text{PE}|$$

(3)

$$\text{RMSE} (\%) = \sqrt{\frac{1}{N} \sum_{i=1}^{N} \text{PE}_i^2}$$

(4)

where N is the number of concentrations taken into account, Cpred is the population predicted concentration and Cobs is the individual concentrations observed.

2.4.2 | Simulation-based diagnostics

The predictability of each candidate popPK model was assessed via simulation-based diagnostics by comparing the appropriate statistics from the simulated and external evaluation dataset computing a visual predictive check (VPC).42 Stochastic simulations were carried out in NONMEM for 1000 subproblems or replicates of the original external validation dataset. Steady-state condition and additional sampling times (each 0.5 h) were considered in the simulation dataset to characterize the full concentration-time profile of imatinib. To identify systematic bias between the observed and simulated data, the median and several prediction intervals (90%, 80% and 50% PI) of the simulated imatinib Cipred at each time were calculated and compared with the Cobs; both the Cipred and the Cobs were normalized by the standard imatinib dosage of 400 mg once a day. Statistical calculations of the simulated data (ie, 5th, 10th, 25th, 75th, 90th and 95th percentiles of each model at each time point) and graphical representation were performed in R.

2.4.3 | Bayesian forecasting

Bayesian forecasting analysis considering the maximum a posteriori distribution of the PK parameters defined in the popPK models selected was conducted with NONMEM for overall model improvement in terms of bias and precision. A subgroup of the outpatients in whom observed imatinib concentrations across three different samples were available (Bayesian dataset) was used to evaluate the impact of additional TDM data on model performance. An occasion or TDM visit was defined as a dose interval for which an observed imatinib concentration was available. A single imatinib concentration was quantified per TDM visit or occasion.

The Bayesian estimation was performed sequentially on each occasion without excluding imatinib concentrations measured on previous occasions. Subsequently, only the data from the last visit was considered for evaluating the predictability of the model as prior individual PK information increased.43 Thus, Cipred based on the previous results and compared with its corresponding Cobs by the individual prediction error (IPE%) was calculated using the following equation:

$$\text{IPE} (\%) = \frac{\text{Cipred} - \text{Cobs}}{\text{Cobs}} \times 100$$

(5)

Additionally, PK parameters were initially calculated based on no prior individual imatinib concentration on the first occasion (Cpred).

3 | RESULTS

3.1 | Review of population pharmacokinetic models of imatinib

After the literature search, 14 imatinib popPK models were identified for external evaluation. An overview of the selection strategy used in the literature search is shown in Supporting Information Figure S1. Several valuable popPK models were not selected for this analysis for the following reasons: incomplete structural model, covariate relationship or stochastic model reported,11,44-46 joint model of free and total imatinib plasma concentrations,11,47 Candidate models were developed mainly in CML patients (n = 8)18,48-54 or subjects diagnosed with gastrointestinal stromal tumours (GIST) (n = 4).55-58 The popPK models selected were developed in Caucasian (n = 11) or Asian populations (n = 3)49,52,53 and mainly fitted to a one-compartment PK model (n = 12). Inter-occasion variability (IOV) was included in several models on duration time of first-order absorption process,55 clearance,50,57 volume of distribution50,56 or bioavailability.59 Drug elimination was described as a process varying over time, being reduced by approximately 30% after the first month from the start of treatment with population clearances ranging from 7.3 to 13.8 L/h. Imatinib absorption was described mostly as a zero- or first-order process eventually including an additional delay on the start of absorption (ie, lag time, transit compartments). The imatinib volume of
distribution reported was highly variable, ranging from 128 to 430 L across the studies selected. Treatment duration, weight, age or total serum proteins were the most frequent source of PK variability identified in the imatinib popPK models evaluated. Detailed information of the imatinib candidate popPK models selected for external evaluation is summarized in Table 1.

3.2 Patients and data

A total of 99 imatinib plasma concentrations from 48 adult Caucasian patients diagnosed with CML were collected from June 2016 to June 2020. All imatinib concentrations were adequately quantified. A summary of the baseline demographic and clinical characteristics of the external validation dataset is shown in Table 2.

Imatinib was orally administered as monotherapy at a median dosage of 400 mg once daily, ranging from 300 to 600 mg, administered for at least 2 months. The mean of all the imatinib concentrations was 1451 ng/mL (423-3156 ng/mL) with a median sampling time of 20.2 hours (9-27 hours) since the previous drug administration. A total of 48, 34 and 17 samples were collected at the first, second and third imatinib TDM visits, respectively. The mean age was 59 years ranging from 23 to 79 years and 53% of the studied population were males. A small proportion of missing data of the variables included in the popPK models evaluated were recorded in the external dataset. One quarter of the α1-acid glycoprotein was not available in the external dataset, thus a mean of 96.2 g/dL was imputed in 14 records, and previous individual information was used in 11 records. One value of white blood cell counts was not available and a mean of 6.9 × 10³/μL was imputed.

| Article                  | No. of patients/observations | Dose (mg/day) | Diagnosis | CL/F (L/h) | V/F (L) | Ka (h⁻¹) | TK₀ (h) | Covariates included |
|-------------------------|------------------------------|---------------|-----------|------------|---------|----------|---------|---------------------|
| Judson 2005⁶⁰          | 43/517                       | 400-1000      | STS/GIST  | 10.6⁶     | 182     | NA       | 1.51    | TBW, NEU, HG, TD    |
| Schmidli 2005⁴⁸         | 371/1390                     | 400           | CML       | 13.8⁴     | 252²    | NA       | 1.5     | TBW, HG, WBC, TD    |
| Delbaldo 2006⁵⁵         | 35/166                       | 300-600       | GIST      | 7.97⁵     | 168     | NA       | 2.53    | HB, ALB, TD, AGP    |
| Petain 2008⁵⁶           | 67/505¹                      | 300-600       | GIST      | 7.29⁴     | 202     | 1.03     | NA      | TBW, AGE, AGP, ALB  |
| Demetri 2009⁵⁷          | 73/73                       | 400-800       | GIST      | 8.18⁶     | 168⁸    | NA       | 1.69    | ALB, WBC, TD        |
| Menon-Andersen 2009⁵⁹   | 41/84²                       | 260-570⁷      | CML/GIST  | 10.8      | 284     | NA       | 1.67    | TBW                |
| Yamakawa 2011⁴⁹         | 34/466                       | 100-600       | CML       | 8.7       | 430     | 2.06     | NA      | PM (SLCO1B, ABCB1)  |
| Eechoute 2012³⁵⁸        | 50/1743                      | 400-800       | GIST      | 9.12      | 128     | 0.67     | NA      | Liver metastases    |
| Di Paolo 2014¹⁸¹        | 60/117                       | 200-600       | CML       | 13.1      | 359     | 1.29     | NA      | AGP, PM             |
| Golabchifar 2014⁵⁰      | 61/533                       | 300-800       | CML       | 10.8      | 278     | NA       | 1.43    | TBW, AGE            |
| Gotta 2014⁴⁴           | 2478/4095                    | 100-1200      | CML       | 17.3⁹     | 430     | NA       | 3.1     | AGE, GENDER         |
| Renard 2015⁵¹           | 101⁴/572                     | 200-400       | CML       | 10.8      | 267     | NA       | 1.52    | HG, Bosentan treatment |
| Park 2016⁵²            | 112³/1773                    | 100, 400      | CML       | 13.6      | 153     | 0.998    | NA      | AGE                |
| Wang 2019⁵³            | 170/229                     | 400           | CML       | 9.25      | 222     | 0.329    | NA      | TBW                |

Note: All pharmacokinetic models describe a first order linear elimination. All pharmacokinetic models were developed in Caucasian population with the exception of three models which were developed in Asian population.⁴⁹,⁵²,⁵³ The imatinib administration route was orally on all models except in Demetri model was intramuscular. All pharmacokinetic parameters are referred to the steady state phase, when applicable.

Abbreviations: ALB, albumin; AGP, alpha-acid glycoprotein; CL/F, apparent clearance; CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumours; HB, haemoglobin; Ka, absorption first-order rate constant; LNF, lymphocytes; NA, not applicable; NEU, neutrophils; PM, genetic polymorphism; STS, soft tissue sarcoma; TBW, total body weight; TD, treatment duration; TK₀, duration of zero-order absorption; V/F, apparent volume of distribution; WBC, white blood cells.

¹Dose in mg/m².
²CL for male patients.
³CL in extension phase; describes a higher CL/F on day 1 than on day 29.
⁴Higher CL/F and V/F on day 1 than on day 29.
⁵It also describes a lower CL/F in steady state.
⁶Includes 305 samples of children in his population.
⁷Includes 424 samples of N-dimethyl-imatinib, the active metabolite of imatinib. Exclusively adolescent population and children.
⁸Describes a CL/F on day 1 higher than on day 29 and a V/F on day 1 lower than on day 29.
⁹Includes patients in an accelerated phase of the disease.
¹⁰Two-compartment kinetics (Q/F = 8.64 L/h; V₂/F = 65.5 L [63.35-63.81]).
¹¹Two-compartment kinetics (Q/F = 24.9 L/h; V₂/F = 197 L [145-265]).
¹²Wild-type hOCT1 genotype (CC) and AGP lower than 94 g/dL was considered.
¹³Patients with pulmonary arterial hypertension under treatment.
¹⁴Population in healthy subjects.
3.3 | External evaluation

3.3.1 | Prediction-based diagnostics

The results of the model performance based on prediction-based diagnostics using the 14 popPK models selected are shown in Table 3. The goodness-of-fit plots, which represent the overall performance of the models evaluated, are shown in Supporting Information Figure S2. In general, none of the models significantly overestimate the imatinib concentrations highlighting the model proposed by Petain et al.\textsuperscript{56} as the best match between imatinib model-based prediction and observed concentrations.

The bias of the imatinib popPK models evaluated is shown in Figure 1. Most of the models showed a slightly acceptable negative
bias except the model proposed by Park et al., which showed pronounced biased results (systematic underprediction). The smaller bias was presented for the models proposed by Eechoute et al., Debaldo et al., and Wang et al., with a MPE close to zero.

The results of overall bias and precision for the models evaluated are shown in Table 3. Most of the popPK models showed adequate precision for the metrics taken into account, particularly those developed by Petain et al. (MAPE = 20.1%, F30 = 64.6%), Wang et al. (MAPE = 23.1%, F30 = 59.6%) and Delbaldo et al. (MAPE = 23.4%, F30 = 64.6%), with better model performance in terms of prediction-based evaluation. On the other hand, popPK models proposed by Park et al., Gotta et al., and Judson et al. did not reach any of the precision criteria defined.

3.3.2 | Simulation-based diagnostics

Overall model performance based on simulations are shown in Figure 2. The VPC-like plots showed the differences in the median imatinib concentration-time profile and its variability across the popPK models considered together with the Cobs for the external validation dataset. Model-based simulations, considering the 90% PI, covered the imatinib Cobs in most of the popPK models evaluated. However, significant differences in the median concentration-time profile across the studies considered have been shown.

3.3.3 | Bayesian forecasting

Imatinib Cobs were obtained at three different TDM visits in 17 patients who were chosen (Bayesian dataset) to evaluate the predictability of the model as prior information increased. Distributions of IPE derived from the Bayesian forecasting analysis for each model at each imatinib occasion considered are shown in Figure 3. Reductions of 64% and 42% on overall bias and precision, respectively, were observed when the MAPB approach was applied with all the external datasets in comparison with the a priori model-based prediction (Cpred), when no individual PK information was used. In general, model performance bias improved (median of IPE closer to zero) as additional information was taken into account together with the increase in the variability of this metric. The popPK models evaluated provided adequately unbiased individual predictions (IPE close to zero) considering the first two imatinib TDM visits or samples, except the one developed by Park et al.. Models with relatively biased predictions for the first occasion experienced the greatest benefits in precision and bias improvement by the addition of individual PK information. Overall, dispersion of IPE was significantly lower in those models including IOV when additional individual PK information is considered.

4 | DISCUSSION

TDM of imatinib has been highlighted as one of the best tools for CML treatment optimization as it both increases the molecular response rate and decreases the appearance of side effects. To optimize imatinib dosage with guarantees, it is necessary to apply reliable popPK models, even if their extrapolated predictability is unclear at present. Therefore, it is necessary to evaluate the transferability of popPK published models into the clinical practice trough using, for example, external validation procedures.

The external evaluation performed in this work was carried out at three different levels: (a) prediction-based diagnostics, which are frequently used and of interest mainly for their simplicity in illustrating how well the observations and predictions are in agreement; (b) simulation-based diagnostics, which compare the model-based simulations of a single dataset with real measured drug concentration and can be a useful diagnostic, revealing model misspecification patterns not easily diagnosed by other methods; and (c) Bayesian forecasting analysis, which is based on prior observations in each individual together with a popPK model and is regularly used to facilitate dosage adjustments in clinical practice.

Most of the candidate popPK models selected presented adequate model performance of the external dataset evaluated (MPE < ±30%, F20 > 35% and F30 > 50%). The models proposed by Petain et al. and Delbaldo et al. showed the best overall model performance in terms of bias and precision across the 14 studies evaluated. These results are supported by the similarities of the demographic characteristics of the study populations, imatinib dose ranges and bioassay methods. Furthermore, both models take into account the α1-acid glycoprotein as a source of imatinib PK variability, which
might be of potential relevance. Several trials suggested that elevated α1-acid glycoprotein may result in lower drug concentration in blast cells due to a decrease in the free fraction of imatinib.63,64 Our results showed an overall model performance improvement for those models including α1-acid glycoprotein, which most likely is related to the high protein binding shown for imatinib and the saturable nature of this process.7,65 Indeed, an increase in imatinib clearance of 50% has been shown for α1-acid glycoprotein values lower than 50 g/dL.66 Thus, the usefulness of α1-acid glycoprotein as a potential index of treatment efficacy for CML patients has already been proposed.67 In contrast, models developed in the Asian population, except for the one developed by Wang et al, showed inadequate predictive capability, likely due to differences across the studied populations (ie, Asian, healthy subjects), in the dosage administered (single imatinib dose of...
100 or 400 mg) and in the structural model misspecification (two compartments, in the case of Park et al). These results also support the significant PK differences observed across different ethnic groups.24 A large BSV has been reported for imatinib, which might be directly related to treatment response variability. In addition to the previously mentioned α1-acid glycoprotein and ethnicity, total body weight,7,48,53 white blood count and hemoglobin alterations,7,48,65 might have a significant impact on imatinib exposure and most likely on treatment response. Age, gender and genetic polymorphisms (ie drug transport genes, CYP polymorphisms) have also been suggested to influence imatinib exposure.7,18,53,65

Most of the models adequately described imatinib PK behaviour and its variability compared to the external dataset (Figure 2). The VPC-like plots show the differences in the absorption process across the popPK models considered, in agreement with the highly variable absorption reported in the literature.12 Only the model proposed by Park et al52 showed inadequate VPC evaluation, underestimating the observed concentrations, especially at the end of the dosage interval, which may be attributable to the target population of the original popPK model (Asian healthy subjects).

Model performance significantly improved, as expected, by a Bayesian forecasting approach in all the studies considered shows that popPK models combined with individual imatinib plasma concentrations and Bayesian algorithms is a very powerful tool for imatinib dosage adjustments (Figure 3).38,39,41 The models evaluated in this study provided a mean IPE close to zero (unbiased) as early as the second imatinib TDM visit. In addition, the models presented in this research also suggest that additional imatinib TDM samples (more than two) are required in those cases when the first occasion did not provide adequate individual model performance. Despite the difficulty in applying the definition of occasion across different studies (trial design, TDM sampling schedule, treatments protocols, missing covariate values, etc), IPE were significantly improved in those models including IOV when additional individual PK information is taken into account.68 Ignoring IOV, either by omitting known IOV or by failing to separate BSV and IOV, led to overly optimistic shrinkage and precision predictions, and lower precision in the individual PK parameters estimated.69,70 However, implementing IOV from previous popPK models can be challenging as the definition of occasion is not always adequately provided and/or not always applicable to the external dataset.

The external evaluation carried out in our study presents several limitations, such as a reduced number of patients (n = 48) and imatinib plasma samples (n = 99), which can limit the robustness of the results derived, differences across structural and stochastic popPK models developed, the exclusion criteria of the popPK models (ie, models including free and total imatinib plasma concentrations), the potential missing values of covariates included in the popPK models considered, which might not have an important impact in this specific work as only missing WBC were higher than 10% in the external dataset, or the adherence to imatinib treatment and differences in treatment duration follow-up (models not considering time-varying clearance).71 In addition, the impact of ethnicity on model performance could not be evaluated as all the subjects included in this analysis were Caucasian.

The present study shows the bias and precision of the popPK models of imatinib developed mainly in adult populations to date applied to an external adult Caucasian population diagnosed with chronic-phase CML. It also includes a deep imatinib PK characterization across different populations highlighting the source of PK variability with potential impact on imatinib dosage optimization. The models proposed by Petain et al and Debaldo et al arise over the alternative models as the best performance capabilities (bias and precision) and would be recommended for imatinib MIPD in the target population studied in this work and very similar ones. In addition, overall bias and precision were improved by 64% and 42%, respectively, when MAPB was performed. Two imatinib TDM visits appear to be sufficient for optimal individual predictions through Bayesian forecasting for popPK models which provide adequate IPE at the first occasion. Alternative strategies such as adaptive MAP by an iteratively estimation,68 Bayesian data assimilation72 or the use of the PRIOR subroutine in NONMEM73,74 have been proposed as powerful approaches for model-based dose optimization but were not explored in this study.

5 | CONCLUSIONS

Imatinib popPK models previously developed mainly in adult populations have been externally evaluated, highlighting those carried out in Caucasian subjects including α1-acid glycoprotein as the best model performance in terms of bias and precision. This illustrates that caution is required when using a popPK model in an external population for the use of MIPD in clinical practice. Moreover, Bayesian forecasting substantially improved the model predictability by decreasing by 64% and 42% the overall bias and precision, respectively, especially pronounced in those models including IOV in the stochastic model. Two imatinib TDM visits appear sufficient to reach an adequate model-based individual prediction performance trough Bayesian forecasting.

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CONTRIBUTORS

M.J.O. and J.S.P.B. designed the study. A.Z.C. performed the imatinib quantification in plasma. J.S.P.B. and A.C.A. performed the pharmacokinetic and statistical analysis, interpreted the data and wrote the
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DATA AVAILABILITY STATEMENT
Research data are not shared.

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