ORIGINAL ARTICLE

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Population pharmacokinetic-pharmacodynamic modelling of platelet time-courses following administration of abrocitinib

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Aims: Abrocitinib is a selective Janus kinase 1 inhibitor for the treatment of moderate-to-severe atopic dermatitis. Herein we describe the time-course of drug-induced platelet reduction following abrocitinib administration, identify covariates affecting platelet counts, and determine the probability of patients experiencing thrombocytopaenia while receiving abrocitinib.

Methods: This analysis included data from two Phase 2 and three Phase 3 studies in psoriasis and atopic dermatitis patient populations administered abrocitinib 10–400 mg QD orally for up to 12 weeks, with platelet counts determined up to week 16. A semi-mechanistic model was developed to assess the impact of baseline platelet counts (170, 220 and $270 \times 1000/\mu L$), age and race on the platelet nadir and week 12 counts with once-daily abrocitinib 200 mg or 100 mg.

Results: Decreases in platelet counts were transient with the nadir occurring on average 24 days (95% prediction interval, 23–24) after continuous administration of abrocitinib 200 mg QD. Following administration of once-daily abrocitinib 200 mg, the probabilities of thrombocytopaenia ($<150 \times 1000/\mu L$) at the nadir were 8.6% and 95.5% for the typical patient with baseline platelet count of $270 \times 1000/\mu L$ or $170 \times 1000/\mu L$, respectively. Adolescents had a lower probability of thrombocytopaenia compared with adults; platelet count distribution was similar in Asian and Western patients at the nadir and at week 12.

Conclusion: This analysis supports the safety of once-daily abrocitinib 200 mg and 100 mg dosing regimens, with low probability of thrombocytopaenia during treatment, except for higher risk of low-grade thrombocytopaenia that diminished after 4 weeks in patients with low baseline platelet counts.

KEYWORDS
dermatology, pharmacodynamics, pharmacokinetics, platelets

1 | INTRODUCTION

Abrocitinib is an oral selective **Janus kinase 1** (JAK1) inhibitor[1] for the treatment of moderate-to-severe atopic dermatitis (AD).[2–4] Transient

platelet reductions have been observed with abrocitinib treatment in clinical studies of patients with psoriasis[5] and AD,[2–4] and were shown to be dose-dependent. The mechanism that leads to a reduction in platelet count is unclear but could be a pharmacological effect of the drug that is potentially mediated by the inhibition of JAK1 and downstream inhibition of thrombopoietin production.[6]

Platelet modelling can be used to provide meaningful insights about platelet count fluctuations during abrocitinib treatment. A semi-mechanistic kinetic-pharmacodynamic (K-PD) model consisting of the proliferation of progenitor cells, maturation to platelets, and transit to blood circulation compartments has previously been developed to simulate platelet counts with a range of abrocitinib doses using data from a Phase 2b study in adult patients with moderate-to-severe AD.[7] Following publication of the K-PD model, a population pharmacokinetic (PK) model of abrocitinib in healthy volunteers, and patients with psoriasis or AD, was developed.[8] Intrinsic patient factors of significant clinical interest that accounted for variability in abrocitinib concentrations were total body weight, age (adolescent *vs* adult), and race (Asian *vs* Western). On average, weight-matched adolescent patients demonstrated 33% lower steady-state area under the concentration–time curve for the dosing interval (AUC$_\tau$), compared with adult patients. Furthermore, after accounting for both weight and race effects on abrocitinib exposure, the typical Asian patient with AD (weighing 66 kg) experienced 1.48-fold higher AUC$_\tau$ relative to the typical Western patient with AD (weighing 80 kg).

Combined population PK-PD models can be used to quantitatively describe the impact of continuous abrocitinib administration on platelet time-courses, specifically the severity of the nadir and the subsequent recovery of the platelet count. Additionally, the impact of covariates, both those affecting abrocitinib exposure (such as total body weight, age, race), as well as those that are independent of drug exposure (such as baseline platelet counts), on the observed variability in platelet time-courses can be evaluated. The effect of tachyphylaxis (diminishing response to continuous administration of abrocitinib) can also be tested in the model.

The objectives of this analysis are to establish the relationship between abrocitinib exposure and the time-course of drug-induced platelet reduction and to determine the probability of patients experiencing thrombocytopaenia while receiving abrocitinib.

2 | METHODS

2.1 | Study population

Two Phase 2 and three Phase 3 studies in populations of patients with psoriasis and AD were included in this analysis (Table A1). Doses of abrocitinib ranging from 10 to 400 mg QD and including 200 mg BID were administered orally over 4–12 weeks; platelet counts were measured at regular intervals up to week 16. Full details of dosing and platelet sampling schedule are provided in Table A1. In total, there were 12 189 platelet counts from 2333 individuals.

What is already known about this subject

- Transient platelet reductions have been observed with abrocitinib treatment in clinical studies of patients with psoriasis and atopic dermatitis.
- A semi-mechanistic model of drug-induced myelosuppression has been used to describe the time-course of hematopoietic endpoints including platelets.

What this study adds

- The probability of patients experiencing thrombocytopaenia while receiving once-daily abrocitinib 200 mg or 100 mg is low.
- Baseline platelet count and abrocitinib dose were the largest predictors of an individual experiencing thrombocytopaenia.

2.2 | Software

Nonlinear mixed effects model development used NONMEM® Version VII Level 4.3 (ICON Development Solutions, Ellicott City, MD, USA).[9] Population parameter estimation used the first-order conditional estimation method with interaction (FOCE-I) algorithm and individual parameters obtained from empirical Bayes estimates (EBE). The ADVAN13 subroutine with TOL = 9 was used. Perl-speaks-NONMEM (version 4.8.0) was used for bootstrap procedures.[10,11] Statistical and graphical output were generated using R programming and statistical language (R version 3.6.1).[12]

2.3 | Structural model development

The semi-mechanistic model was based on the chemotherapy-induced myelosuppression model by Friberg et al.[13] The model consisted of a platelet proliferation pool compartment (*PROL*) (Equation 1) representing platelet progenitor cells, three transit compartments (*TRANS1*) (Equation 2), (*TRANS2*) (Equation 3), (*TRANS3*) (Equation 4) to represent the maturation of megakaryoblasts and megakaryocytes into platelets, and a compartment representing circulating observed platelets (*CIRC*) (Equation 5).

$$\frac{dPROL}{dt} = k_{PROL} \cdot PROL \cdot \left(1 - \frac{E_{max} \cdot CONC}{EC_{50} + CONC}\right) \cdot \left(\frac{CIRC_0}{CIRC}\right)^\gamma - k_{TR} \cdot PROL \quad (1)$$

$$\frac{dTRANS1}{dt} = k_{TR} \cdot PROL - k_{TR} \cdot TRANS1 \quad (2)$$

$$\frac{dTRANS2}{dt} = k_{TR} \cdot TRANS1 - k_{TR} \cdot TRANS2 \quad (3)$$

$$\frac{dTRANS3}{dt} = k_{TR} \cdot TRANS2 - k_{TR} \cdot TRANS3 \tag{4}$$

$$\frac{dCIRC}{dt} = k_{TR} \cdot TRANS3 - k_{CIRC} \cdot CIRC \tag{5}$$

Where the rate of generation of progenitor cells in $PROL$ was dependent on the number of cells in the compartment and the first-order proliferation rate constant, k_{PROL} (hr^{-1}), k_{TR} is the first-order rate constant of movement (hr^{-1}), k_{CIRC} is the first-order rate constant for elimination of platelets from the circulation (hr^{-1}), and the feedback mechanism $\left(\frac{CIRC_0}{CIRC}\right)^{\gamma}$ described the rebound or overshoot of platelets with respect to baseline (where $CIRC$ is the circulating platelet count, $CIRC_0$ is the baseline platelet count, and γ is the feedback parameter). Abrocitinib plasma concentrations were assumed to reduce the proliferation rate by an E_{max} relationship, where E_{max} is the maximum inhibitory effect on platelet proliferation, EC_{50} is the half-maximal concentration, and $CONC$ is the individual predicted abrocitinib concentration. A previously developed population PK model in healthy volunteer, and patients with psoriasis and AD[8] was used to predict abrocitinib concentrations based on EBE of PK parameters for analysis individuals.

The maturation chain described the movement of platelets through the transit compartments and allowed for the time delay between administration of abrocitinib and the observed effect on circulating platelet count. It was assumed that the only loss of platelets was into the next transit compartment until the last compartment, $CIRC$, from which they are then eliminated. To improve interpretability, mean transit time (MTT) was estimated (Equation 6):

$$MTT = \frac{(n+1)}{k_{TR}} \tag{6}$$

where n is the number of transit compartments (in this model $n = 3$). The system was assumed to be at steady-state prior to the administration of abrocitinib; it was also assumed that the rate of change in platelet proliferation was 0 (Equations 1–5) $k_{PROL} = k_{TR}$, $k_{TR} = k_{CIRC}$, and the initial conditions for all compartments were set to the baseline platelet count.

Additional structural components were evaluated such as baseline platelet count (on maximum drug effect, E_{max}) and the implementation of tachyphylaxis (diminishing response to continued administration of abrocitinib not accounted for by inbuilt feedback mechanisms) as described by an exponential function proportional to E_{max} (Equation 7):

$$TCPX = \begin{cases} DELTATCPX \cdot \left(1 - e^{\left(-1 \cdot \frac{ln2}{k_{TCPX}} \cdot t\right)}\right) & \text{if } AMT > 0 \\ 0 & \text{if } AMT = 0 \end{cases} \tag{7}$$

where $TCPX$ is the effect of tachyphylaxis on E_{max} with respect to time after first dose of active treatment, t, $DELTATCPX$ is the extent of diminished response (i.e., 0 suggests the drug effect does not change

over time, and 1 suggests that drug effect is completely diminished over time), and k_{TCPX} is the rate of change in $TCPX$ with respect to time expressed as a half-life in days. AMT is the actual amount of dose received. For individuals receiving placebo, or when drug is withdrawn (i.e., AMT = 0), $TCPX$ is set to 0.

Structural components were evaluated by changes in the Akaike Information Criterion, uncertainty in model parameters (< 30% relative standard error [RSE] for θ and < 50% RSE for ω^2), and η-shrinkage in EBE (< 30%).

2.4 | Random effects model development

Inter-individual variance (IIV) was assumed to be log-normally distributed for parameters (Equation 8):

$$P_i = \theta_P \cdot e^{\eta_i} \tag{8}$$

where P_i is the individual value for parameter P in the ith subject, θ_P is the population typical value for parameter P, and η is a normally distributed independent random variable describing the variability in P among patients with a mean of 0 and variance ω^2. The suitability of random effects was evaluated for $CIRC_0$, MTT, E_{max} and γ, considering full and diagonal parameterizations of the covariance matrix.

A residual error model with a combination of additive and proportional effects was used to describe random unexplained variability in platelet counts.

2.5 | Covariate model development

Covariates tested on key PD parameters in the model were sex, age (continuous or adolescent [12–17 years] vs adult), race, patient type (AD vs psoriasis), and baseline haematological parameters (i.e., white blood cells [WBC], neutrophils, haematocrit). Covariates were further screened for pairwise correlation by graphical analysis as one covariate could be highly correlated with another and act as a surrogate marker for the true predictor variable. If a strong correlation existed, the more statistically and clinically relevant covariate continued to further covariate analyses. Plots of EBEs of the PD parameter from the structural model versus candidate covariates were generated to identify how variability from the population mean was related to different categories or values of a covariate.

The effect of a categorical covariate on a parameter was represented as a discrete relationship. For example, the effect of sex on a parameter, P, was described as (Equation 9):

$$P = \theta_P \cdot COVSEX \text{ for } COVSEX = \begin{cases} 1 & \text{if } SEX = 1 \\ 1 + \theta_{SEX} & \text{if } SEX = 2 \end{cases} \tag{9}$$

where SEX has a value of 1 for male patients and 2 for female patients, and θ_{SEX} is a parameter for the effect of female sex on P.

The effect of a continuous covariate on a parameter was represented as a power model referenced to the median of the observed data. For example, the effect of age on *P* was described as (Equation 10):

$$P = \theta_P \cdot \left(\frac{AGE_i}{AGE_{ref}} \right)^{\theta_{AGE}} \tag{10}$$

where AGE_i is the age (years) of the ith subject, AGE_{ref} is the median age in the observed population, and θ_{AGE} is the parameter for the effect of age on *P*.

2.6 | Covariate selection

Candidate covariates from screening procedures were independently added to the structural model to evaluate their individual significance in improving the fit of the model to the observed data. All covariates shown to be important from the univariate analyses were carried forward to the multivariate analyses.

In univariate analyses, the effect of incorporating an additional covariate parameter compared with the structural model was assessed by the likelihood ratio test (LRT). The covariate model

TABLE 1 Patient demographics and clinical characteristics

Covariate	Psoriasis, N = 59	Atopic dermatitis, N = 2274	All patients, N = 2333
Dosing regimen, n (%)			
Placebo	14 (23.7)	210 (9.2)	224 (9.6)
Abrocitinib 10 mg QD	0	49 (2.2)	49 (2.1)
Abrocitinib 30 mg QD	0	50 (2.2)	50 (2.1)
Abrocitinib 100 mg QD	0	369 (16.2)	369 (15.8)
Abrocitinib 200 mg QD	15 (25.4)	1596 (70.2)	1611 (69.1)
Abrocitinib 200 mg BID	14 (23.7)	0	14 (0.6)
Abrocitinib 400 mg QD	16 (27.1)	0	16 (0.7)
Age, median (range), years	47 (20–65)	30 (12–84)	30 (12–84)
Age group, n (%)			
Adolescent (<18 years)	0	340 (15.0)	340 (14.6)
Adult (≥18 years)	59 (100.0)	1934 (85.0)	1993 (85.4)
Sex, n (%)			
Male	40 (67.8)	1256 (55.2)	1296 (55.6)
Female	19 (32.2)	1018 (44.8)	1037 (44.4)
Race, n (%)			
White	42 (71.2)	1632 (71.8)	1674 (71.8)
Asian	5 (8.5)	410 (18.0)	415 (17.8)
Black	10 (16.9)	167 (7.3)	177 (7.6)
Other race	2 (3.4)	51 (2.2)	53 (2.3)
Unknown	0	14 (0.6)	14 (0.6)
Ethnicity, n (%)			
Hispanic/Latino	4 (6.8)	290 (12.8)	294 (12.6)
Not Hispanic/Latino	55 (93.2)	1968 (86.5)	2023 (86.7)
Unknown	0	16 (0.7)	16 (0.7)
Japanese status, n (%)			
Japanese	0	44 (1.9)	44 (1.9)
Not Japanese	59 (100.0)	2230 (98.1)	2289 (98.1)
Body weight, median (range), kg	88 (48–133)	73 (34–204)	73 (34–204)
Haematocrit, median (range), %	44 (36–50)	43 (30–55)	43 (30–55)
Neutrophils, median (range), %	65 (38–80)	62 (25–93)	62 (25–93)
White blood cells, median (range), ×1000/μL	7 (3–12)	7 (3–18)	7 (3–18)
Platelets, median (range), ×1000/μL	238 (142–357)	275 (118–651)	274 (118–651)

BID, twice daily; QD, once daily.

was considered significantly better than the structural model if *P*-value < .01. Candidate covariates also needed to satisfy additional criteria: 95% confidence interval (CI) of the covariate parameter estimate did not include zero, addition of the covariate resulted in a reduction in IIV on the target population parameter, and improvement of model diagnostic plots compared with the structural model by correcting any systematic trends in EBE versus covariates.

Covariates identified in univariate analyses were added sequentially to the structural model in order of statistical significance to form the full model. The sequential addition of a covariate to the model was in order of lowest to highest *P*-value and still needed to fulfil the requirements described for univariate analyses. Selection of the final model was conducted by backwards elimination from the full model using a significance threshold of *P*-value < .001.

2.7 | Final model evaluation

Non-parametric bootstrap analysis of the final model was performed to calculate the median and 95% CI of parameter estimates from 1000 samples. The predictive performance of the final model was evaluated by a visual predictive check (VPC) based on 1000 simulations of the analysis dataset and by goodness-of-fit diagnostic plots.

2.8 | Assessment of baseline platelet count on overall platelet time-course

The impact of baseline platelet counts (170–350 × 1000/µL) on the nadir and week 12 outcomes were evaluated using the final model. Platelet time-courses for 1000 typical individuals (White, 30-year-old male patient with AD weighing 70 kg) administered 100 mg and

TABLE 2 Parameter estimates for the final model

Parameter	Value	95% CI	Bootstrap median	Bootstrap 95% CI	SHR (%)
Objective function value	103325.1	–	–	–	–
Condition number	12.5	–	–	–	–
Population parameter					
Baseline platelet count ($CIRC_0$; × 1000/µL)	270	(267–273)	270	(267–274)	–
Feedback exponent (GAM; γ)	0.232	(0.214–0.250)	0.231	(0.186–0.276)	–
Mean transit time (MTT; days)	7.21	(6.95–7.47)	7.21	(6.74–7.65)	–
Maximum drug effect on platelet proliferation (E_{max})	0.109	(0.102–0.116)	0.109	(0.0889–0.134)	–
Concentration at 50% of maximum drug effect (EC_{50}; ng/mL)	55.3	(42.8–67.8)	55.6	(30.4–112)	–
Half-life of tachyphylaxis (k_{TCPX}; days)	151	(130–172)	149	(113–202)	–
Effect of $CIRC_0$ on E_{max}	−1.11	(−1.21 to −1.01)	−1.11	(−1.36 to −0.869)	–
Proportional residual error ($RUV\ PRO$; SD)	0.120	(0.117–0.123)	0.119	(0.109–0.129)	–
Additive residual error ($RUV\ ADD$; SD)	16.4	(15.3–17.5)	16.2	(12.4–20.1)	–
Effect of baseline WBC on $CIRC_0$ (referenced to 6.9 × 1000/µL)	0.199	(0.173–0.225)	0.200	(0.171–0.227)	–
Effect of female sex on $CIRC_0$	0.0584	(0.0395–0.0773)	0.0580	(0.0387–0.0794)	–
Effect of age on $CIRC_0$ (referenced to 30 years)	−0.0695	(−0.0854 to −0.0536)	−0.0695	(−0.0846 to −0.0538)	–
Effect of baseline haematocrit on $CIRC_0$ (referenced to 43%)	−0.203	(−0.301 to −0.105)	−0.201	(−0.307 to −0.101)	–
Effect of psoriasis patients on $CIRC_0$	−0.118	(−0.159 to −0.0768)	−0.118	(−0.161 to −0.0712)	–
Inter-individual variability					
$\omega CIRC_0$ (% CV)	17.5	(16.3–18.7)	17.5	(16.7–18.2)	4.66
Random unexplained variability					
ε_{res}	1.00	Fixed	1.00	Fixed	8.55

CI, confidence interval; SHR, shrinkage; WBC, white blood cells.

Condition number = square root of ratio of largest to smallest eigenvalues of correlation matrix, coefficient of variation CV = $\sqrt{\omega^2} \times 100$, asymptotic 95% CI are presented based on %RSE of final parameter estimates.

78.0% of bootstraps minimized successfully. The remaining 22.0% failed owing to rounding errors.

Random unexplained variability was parameterized using θ for the estimates of the standard deviation of proportional and residual error components, where NONMEM RUVSD = sqrt (RUVPRO*RUVPRO*IPRE*IPRE+RUVADD*RUVADD) and Y = IPRE+RUVSD*EPS(1).

200 mg QD of abrocitinib for 12 weeks were simulated. Variability in platelet profiles among the simulated individuals was incorporated by IIV in PK and PD parameters and random unexplained variability on platelet outcomes. Based on the simulated distribution of the nadir and week 12 platelet count for three target baseline scenarios (170, 220 and 270 × 1000/μL), the probability of observing any grade of thrombocytopaenia and a count <100 × 1000/μL was determined. Grades of thrombocytopaenia were defined per the Common Terminology Criteria for Adverse Events v5.0[14]: Grade 1, 75–150 × 1000/μL; Grade 2, 50–75 × 1000/μL; Grade 3, 25–50 × 1000/μL; Grade 4, <25 × 1000/μL.

2.9 | Evaluation of dosing interruptions on platelet time-course

Within a 16-week trial period (12 weeks active dosing, 4 weeks washout), the impact of missing seven consecutive doses of abrocitinib 200 mg on the overall platelet time-course was simulated using the final model. The profile for a population-typical individual administered 200 mg for 12 weeks was simulated and the time of the missed-

dosing period varied from week 2 to week 8 of active dosing over four scenarios. When dosing restarts, the occurrence and degree of the second nadir (if applicable) was graphically evaluated.

2.10 | Evaluation of age and race on platelet time-course

The impact of differences in abrocitinib exposure was evaluated on platelet time-courses using the final combined PK-PD model. EBE for PK and PD parameters for each individual randomized to abrocitinib 100 mg or 200 mg in the analysis population were used to predict platelet counts for 12 weeks. The predicted nadir and 12-week platelet count were summarized by age group (adolescents, adults <65 years, and adults ≥65 years) and race (Japanese, non-Japanese Asian, Western [White, Black, unknown] and other). The final model was also used to simulate platelet time-courses for 200 new individuals in each age category (randomly drawn η for $CIRC_0$ based on distributions described by the final model and characteristics (i.e., weight, sex, age, patient status, baseline WBCs, baseline haematocrit, sampled from the analysis population).
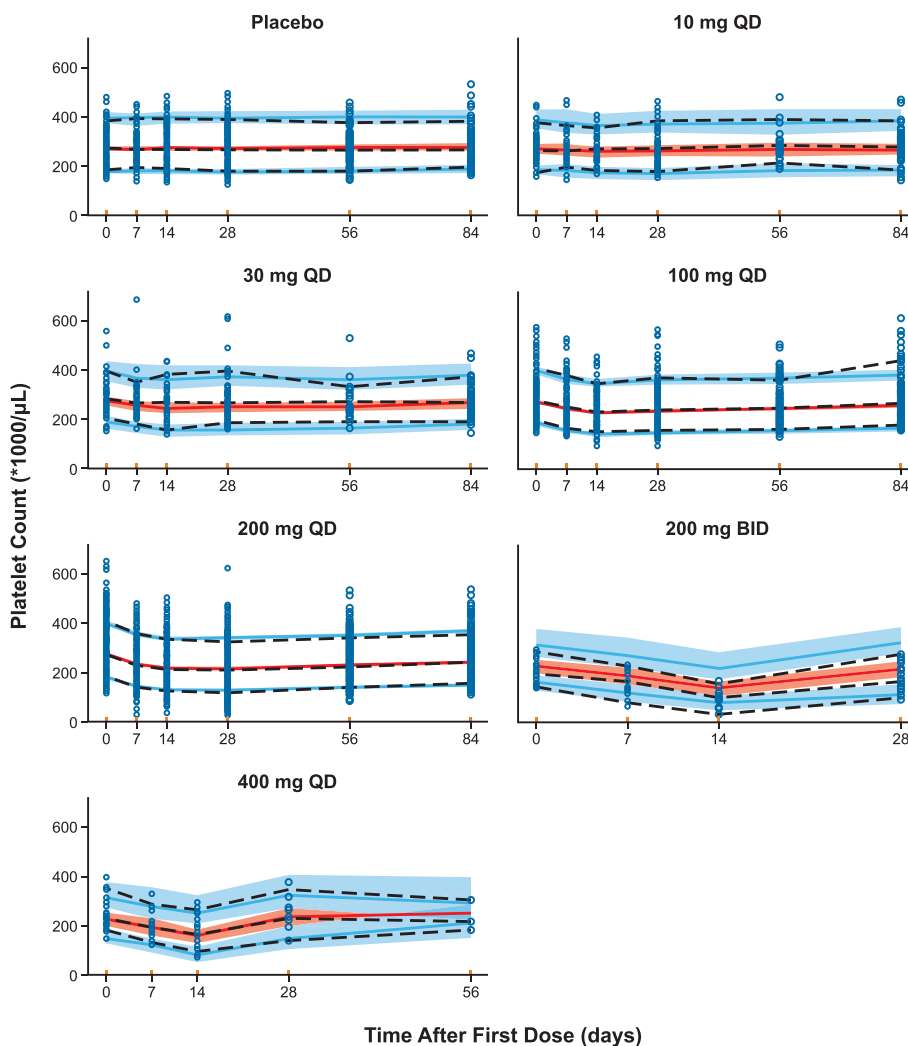

FIGURE 1 Visual predictive check stratified by treatment group. The observed data are represented by blue circles and the dashed black lines (median, 5th and 95th percentiles). Simulated platelet counts based on the analysis population ($n = 1000$ simulations) are represented by the red line and red shaded ribbon (median and 95% prediction intervals of the median, respectively), and the blue lines and blue shaded ribbons (median and 95% prediction intervals of the 5th and 95th percentiles, respectively). Yellow indicators in the x-axis represent the time bins for summarizing the data (0, 7, 14, 28, 56 and 84 days). BID, twice daily; QD, once daily

2.11 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[15]

3 | RESULTS

3.1 | Patient population

Most patients were adults (85.4%), were White (71.8%) and had AD (97.5%) (Table 1).
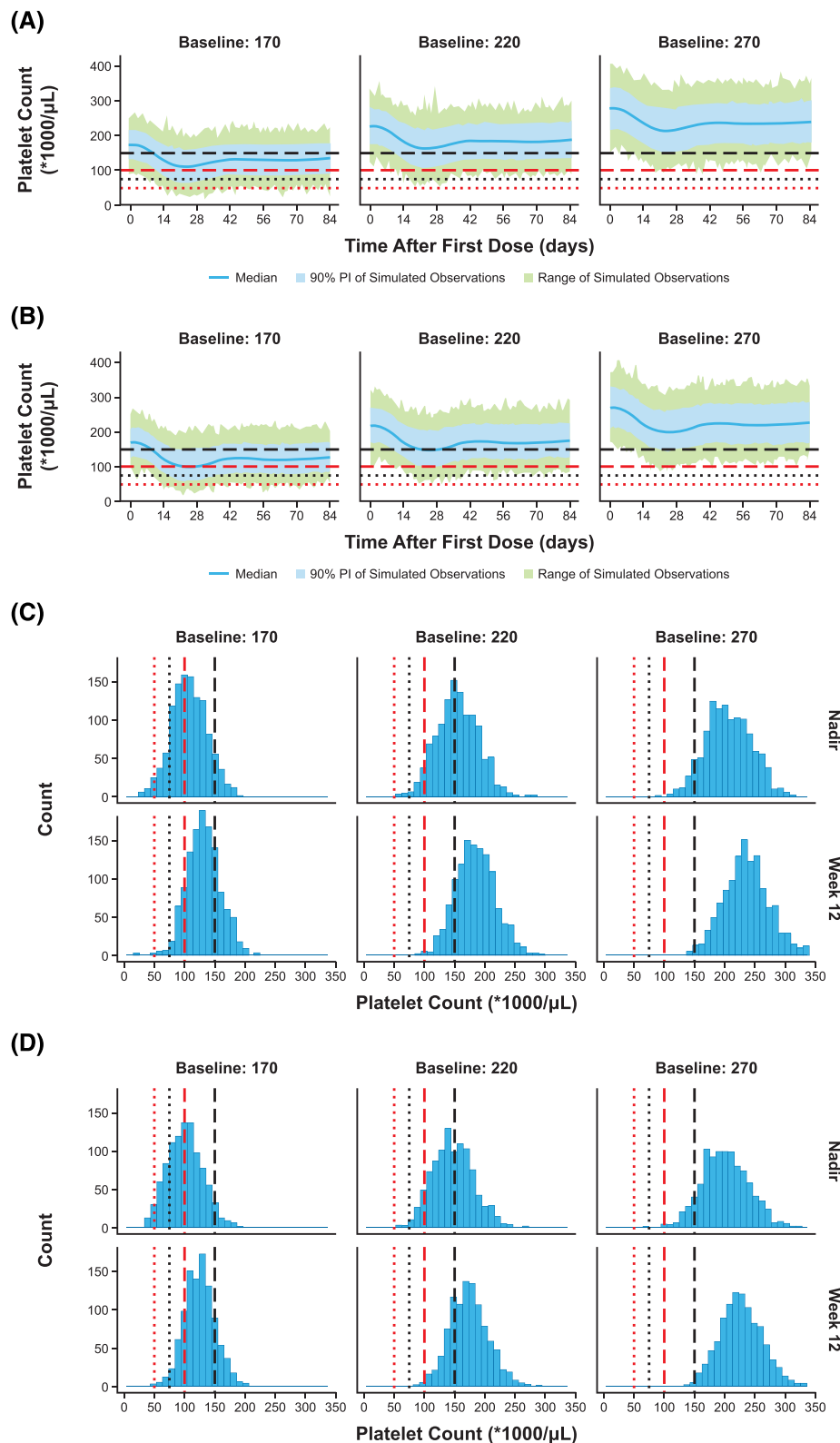
FIGURE 2 Platelet time-course for 1000 simulated typical individuals with baseline platelet counts 170, 200 or 270 × 1000/μL administered 100 mg (**A**) or 200 mg (**B**) for 12 weeks. Distribution of the nadir and platelet count at week 12 in typical individuals with baseline platelet counts 170, 200 or 270 × 1000/μL administered 100 mg (**C**) or 200 mg (**D**) for 12 weeks. Typical individual is White, 30-year-old male patient with atopic dermatitis weighing 70 kg. Horizontal lines (**A, B**) and vertical lines (**C, D**) represent thrombocytopaenia thresholds Grade 1 (<150 × 1000/μL; black dashed), Grade 2 (<75 × 1000/μL; black dotted) and Grade 3 (<50 × 1000/μL; red dotted), and platelet count of 100 × 1000/μL (red dashed). PI, prediction interval

3.2 | Final model

The final model adequately described the time-course of platelets and characterized the magnitude of effect of abrocitinib concentrations on platelet proliferation. One random effect quantifying IIV in baseline platelet count ($CIRC_0$) could be supported as the addition of random effects on other parameters such as E_{max} and MTT, resulting in high η-shrinkage (37.2% and 97.6%, respectively). The implementation of tachyphylaxis significantly improved the fit of the model. The *DELTATCPX* parameter was 0.991, suggesting that over time the effect of abrocitinib on platelet proliferation would approach 0. In the final model, *DELTATCPX* was fixed to 1 to aid parameter estimation and model convergence. The effect of $CIRC_0$ on E_{max} was incorporated as a structural effect and was represented by a power model referenced to the population typical estimate for baseline platelet count with a parameter quantifying the effect of $CIRC_0$ on E_{max}.

The following covariates were carried forward for multivariate analysis as their inclusion improved the fit of the model at a *P*-value of .01 according to the LRT, reduced net IIV, and were not a subset of, or highly correlated with, more statistically and clinically significant covariates: (1) baseline WBC count on $CIRC_0$, (2) effect of female sex on $CIRC_0$, (3) effect of age (as a continuous variable) on $CIRC_0$, (4) effect of baseline haematocrit on $CIRC_0$ and (5) effect of psoriasis patients on $CIRC_0$. Following the backward elimination procedures, no covariates were removed and the full model was deemed to be the final model.

A bootstrap analysis confirmed the robustness of the parameter estimates for the final model (Table 2). Final model diagnostic plots and a VPC stratified by treatment group indicated that the model was consistent with observed data (Figure A1, Figure 1).

The impact of abrocitinib concentrations on the platelet time-course was incorporated on the rate of platelet proliferation via an E_{max} relationship. The final model's estimate for EC_{50} was 55.3 ng/mL, and the range of predicted concentrations for the average AD subject administered abrocitinib 200 mg at steady-state was 13.0–1181 ng/

mL. Therefore, the typical time above EC_{50} was 15.3 hours in a 24-hour dosing interval at steady-state. The time delay between dosing and a decrease in circulating platelets was 7.21 days as dictated by the final model's estimate for *MTT*, corresponding to a time of nadir of 24 days.

3.3 | Simulated platelet time-course and probability of thrombocytopaenia

Based on the platelet time-course for 1000 simulated individuals, the platelet count nadir occurred 24 days (95% prediction interval [PI], 23–24) after administration of abrocitinib 200 mg (Figure 2). Based on the distributions of simulated nadirs and week 12 platelet counts for typical individuals with baseline platelet counts of 170, 220 and 270 × 1000/μL administered abrocitinib 100 mg and 200 mg, the probability of Grade 3 (25–50 × 1000/μL) or Grade 4 (<25 × 1000/μL) thrombocytopaenia was low (Figure 2). Figure 3 shows the decreasing risk of all grades of thrombocytopaenia at the nadir and at week 12 over the continuum of baseline platelet counts (in increments of five baseline counts) from 170–350 × 1000/μL. At the nadir, the probability of any grade of (<150 × 1000/μL) thrombocytopaenia for typical individuals with baseline platelet counts of 170, 220 and 270 × 1000/μL administered 100 mg abrocitinib was 92.1%, 43.5% and 7.0%, respectively; and 95.5%, 53.9% and 8.6%, respectively, for those administered abrocitinib 200 mg (Figure 3 and Table 3). At week 12, the probability of Grade 2 or higher thrombocytopaenia was 0% for individuals with baseline platelet counts of 220 or 270 × 1000/μL and was <2% for those with a count of 170 × 1000/μL (Figure 3 and Table 3).

3.4 | Dosing interruption evaluation

There is a lag in response from the start of the missed dosing period to when an increase in platelet count is observed as the mean transit

FIGURE 3 Probability of thrombocytopaenia grades at the nadir and week 12 across different baseline platelet count scenarios administered abrocitinib 100 mg or 200 mg QD, once daily. Lines represent probabilities of developing thrombocytopaenia Grade 1 (75–150 × 1000/μL; blue), Grade 2 (50–75 × 1000/μL; red), Grade 3 (25–50 × 1000/μL; green) and Grade 4 (<25 × 1000/μL; purple) generated from 1000 simulated individuals per baseline and dosing scenario
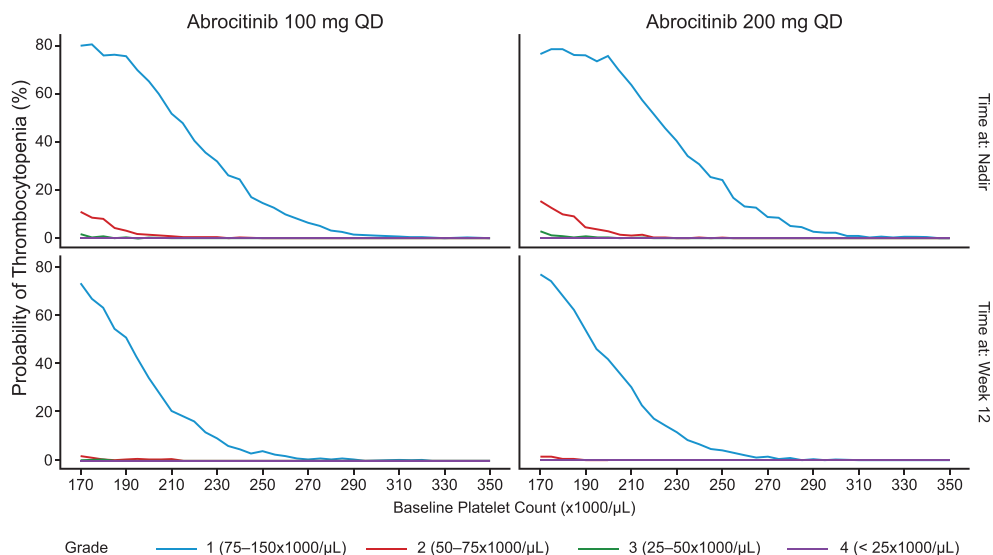
TABLE 3 Probability of thrombocytopaenia grades and magnitude of change for platelet counts at the nadir and week 12 for three different baseline platelet count scenarios administered abrocitinib 100 mg or 200 mg

| Baseline platelet count	Abrocitinib 100 mg			Abrocitinib 200 mg		
	170 × 1000/μL	220 × 1000/μL	270 × 1000/μL	170 × 1000/μL	220 × 1000/μL	270 × 1000/μL
Nadir						
Median (95% PI) absolute change from baseline in platelet count, 1000/μL	−63.9 (−109.4 to −12.0)	−65.4 (−117.5 to −8.9)	−66.0 (−124.3 to −2.1)	−70.1 (−114.0 to −21.9)	−73.4 (−122.0 to −13.8)	−71.5 (−129.9 to −7.2)
Median (95% PI) percent change from baseline in platelet count, %	−37.6 (−64.3 to −7.1)	−29.7 (−53.4 to −4.1)	−24.4 (−46.0 to −0.8)	−41.2 (−67.0 to −12.9)	−33.4 (−55.5 to −6.3)	−26.5 (−48.1 to −2.7)
Probability of Grade 1 thrombocytopaenia, %	80.5	42.8	7	76.2	53.4	8.5
Probability of Grade 2 thrombocytopaenia, %	9.7	0.7	0	16.3	0.5	0.1
Probability of Grade 3 thrombocytopaenia, %	1.9	0	0	2.8	0	0
Probability of Grade 4 thrombocytopaenia, %	0	0	0	0.2	0	0
Probability of platelet count <100 × 1000/μL, %	40.9	4	0.2	50.1	6.3	0.4
Week 12						
Median (95% PI) absolute change from baseline in platelet count, 1000/μL	−38.8 (−78.3–6.4)	−38.2 (−87.5–16.5)	−37.0 (−94.9–25.3)	−44.5 (−82.5 to −2.0)	−46.6 (−92.0–5.9)	−42.6 (−94.8–15.0)
Median (95% PI) percent change from baseline in platelet count, %	−22.9 (−46.1–3.8)	−17.3 (−39.8–7.5)	−13.7 (−35.2–9.4)	−26.2 (−48.5 to −1.2)	−21.2 (−41.8–2.7)	−15.8 (−35.1–5.6)
Probability of Grade 1 thrombocytopaenia, %	75.6	14.1	0.8	81.7	20.7	0.2
Probability of Grade 2 thrombocytopaenia, %	0.8	0	0	1.6	0	0
Probability of Grade 3 thrombocytopaenia, %	0	0	0	0.2	0	0
Probability of Grade 4 thrombocytopaenia, %	0.1	0	0	0	0	0
Probability of platelet count <100 × 1000/μL, %	10.7	0.4	0	15.5	0.1	0
Duration of thrombocytopaenia (95% PI), days[a]						
Grade 1 thrombocytopaenia	74.3 (23.9–76.0)	0 (0–33.9)	0 (0–0)	74.7 (64.5–76.1)	9.2 (0–60.7)	0 (0–0)
Grade 2 thrombocytopaenia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–7.6)	0 (0–0)	0 (0–0)
Grade 3 thrombocytopaenia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Grade 4 thrombocytopaenia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Platelet count <100 × 1000/μL	0 (0–24.1)	0 (0–0)	0 (0–0)	5.1 (0–48.7)	0 (0–0)	0 (0–0)

PI, prediction interval.

Thrombocytopaenia definition(s): Grade 1 is 75–150 × 1000/μL, Grade 2 is 50–75 × 1000/μL, Grade 3 is 25–50 × 1000/μL and Grade 4 is <25 × 1000/μL.

$n = 1000$ typical individuals (White, 30-year-old, male, patient with atopic dermatitis weighing 70 kg).

[a]Based on individual predicted platelet time-course, not simulated observed.

time for platelets from the proliferation pool to the circulation is approximately 7 days. A lag of the same duration is observed from when dosing is resumed to a decrease in platelet count (Figure 4). On

average, the nadir occurs approximately 24 days after the first dose for 100% compliance to the 200 mg QD regimen. If a week of doses are missed prior to day 17, the nadir is delayed. For the scenario

FIGURE 4 Impact of missed consecutive doses on platelet time-course for patients administered abrocitinib 200 mg. Black lines represent the population-typical (White, 30-year-old male patient with atopic dermatitis weighing 70 kg) platelet 16-week time-course administered 200 mg QD for 12 weeks followed by 4-week washout period. Each panel represents a scenario where seven consecutive doses are missed within a given week of the trial period. Blue shaded regions represent the time-period where doses were not administered, and green shaded regions are the washout period for the trial. Red lines represent the scenario where no doses are missed. Times after the missed-dosing period resume 200 mg QD dosing of abrocitinib
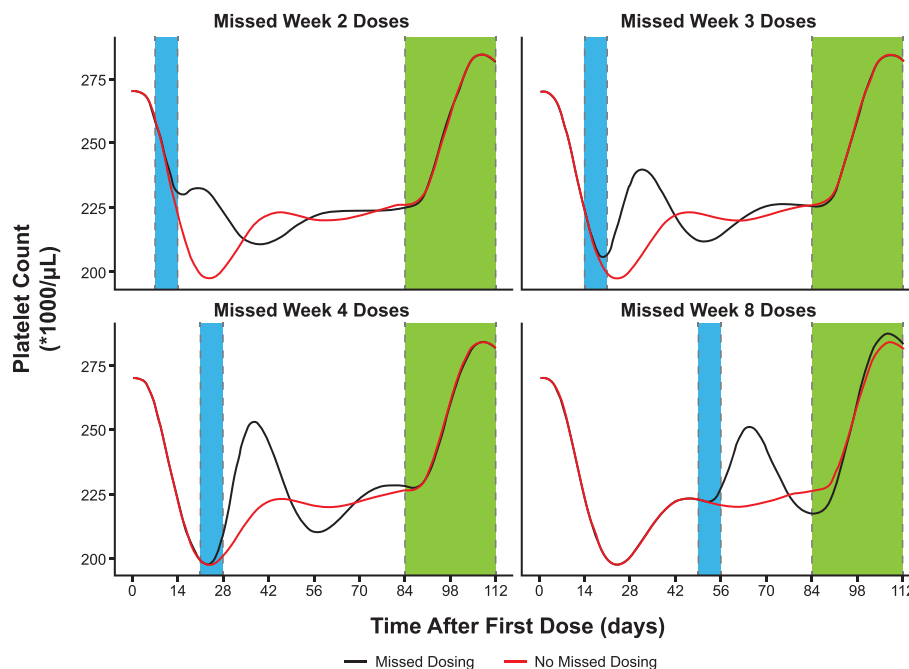
where doses are missed in week 3, the nadir occurs earlier on day 20. Owing to the implementation of tachyphylaxis in the model, the effect of drug on platelet proliferation at restart of dosing is diminished compared with its effect at the time of the first dose for scenarios where doses are missed in week 4 onward. Hence, the second decrease in platelets is not expected to be as severe as the first, despite lower platelet counts at dosing restart compared with baseline (Figure 4).

3.5 | Age evaluation

At nadir, the probability of Grade 1 thrombocytopaenia (<150 × 1000/μL) with abrocitinib 100 mg was 4.5% in adolescents, and 9% and 18% in adults <65 and ≥65 years, respectively. At week 12, the probability of Grade 1 thrombocytopaenia was 2% in both adolescents and adults aged <65 years, and was 6.5% in adults aged ≥65 years (Figure 5A).

At nadir, the probability of Grade 1 thrombocytopaenia (<150 × 1000/μL) with abrocitinib 200 mg was 6% in adolescents, and 18% and 22% in adults aged <65 and aged ≥65 years, respectively. At week 12, the probability of Grade 1 thrombocytopaenia was 1% in adolescents, 5% in adults aged <65 years and 7.5% in adults aged ≥65 years (Figure 5B).

For both 100 mg and 200 mg doses and all age populations, the probability of higher grades of thrombocytopaenia was ≤1%.

3.6 | Race evaluation

While the central tendencies of both the nadir and week 12 platelet counts demonstrated that Asian populations exhibit lower platelet counts compared with Western individuals, most Asian patients lie within the overall distribution of their Western counterparts at both 100 and 200 mg doses (Figure 6).

At nadir, the probability of Grade 1 thrombocytopaenia (<150 × 1000/μL) with abrocitinib 100 mg was 14.5% for Japanese, 13% for non-Japanese Asians, 10% for Western and 5% for other races. The probability of Grade 2 or higher thrombocytopaenia was ≤1% for all groups. By week 12, the probability of Grade 1 thrombocytopaenia was 6% for Japanese, 2% for non-Japanese Asians, 1% for Western and 1% for other races. The probability of Grade 2 or higher thrombocytopaenia was ≤0.5% for all groups (Figure 6A).

At nadir, the probability of Grade 1 thrombocytopaenia with abrocitinib 200 mg was 29.5% for Japanese, 16.5% for non-Japanese Asians, 10.5% for Western and 20.5% for other races. The probability of Grade 2 or higher thrombocytopaenia was ≤0.5% for all groups. By week 12, the probability of Grade 1 thrombocytopaenia was 9.5% for Japanese, 2% for non-Japanese Asians, 3% for Western and 6% for other races. The probability of Grade 2 or higher thrombocytopaenia was 0% for all races (Figure 6B).

4 | DISCUSSION

The present analysis characterized the effect of abrocitinib treatment on platelet time-courses based on five clinical trials (two Phase 2 studies and three Phase 3 studies) in populations of patients with psoriasis and AD. The typical patient (baseline platelet count 270 × 1000/μL) had a 0% probability of Grade 2–4 thrombocytopaenia (<75 × 1000/μL) with once-daily abrocitinib 100 mg or 200 mg. For patients with a low baseline platelet count (170 × 1000/μL), the probability of Grade 3 or 4 thrombocytopaenia (<50 × 1000/μL) is <3% with abrocitinib treatment at 100 mg or 200 mg. With higher baseline platelet counts and lower weight-matched abrocitinib exposure, adolescents have a
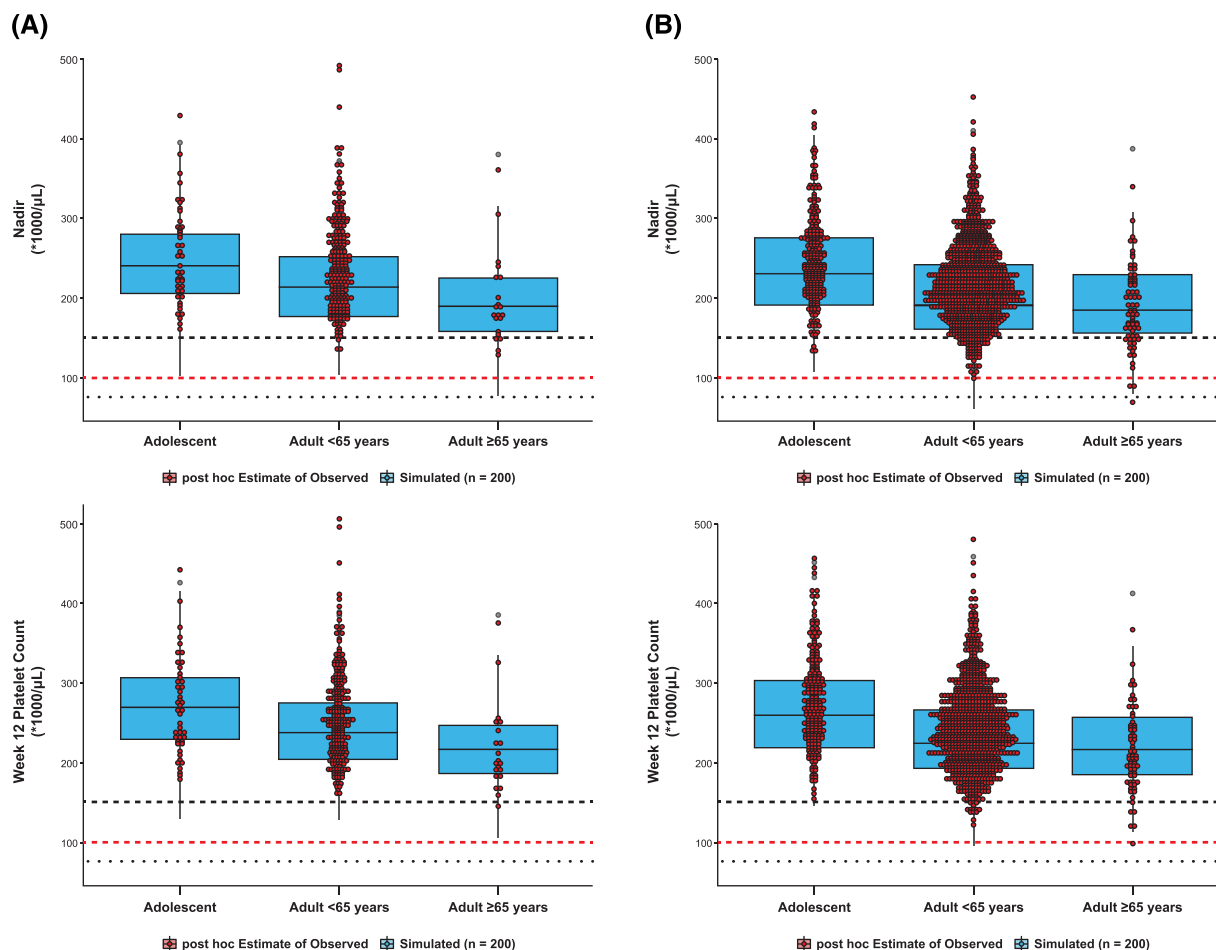
FIGURE 5 Evaluation of age on platelet nadir and week 12 platelet count in patients with atopic dermatitis administered abrocitinib 100 mg (**A**) or 200 mg (**B**). Red circles represent the distribution of the nadir or week 12 platelet count based on the empirical Bayes estimates for all atopic dermatitis patients in the analysis population randomized to 100 mg QD or 200 mg QD, and blue box-and-whisker plots depict newly simulated individuals ($n = 200$) based on the final population PK model. Horizontal lines represent Grade 1 ($<150 \times 1000/\mu L$; black dashed) and Grade 2 ($<75 \times 1000/\mu L$; black dotted) thrombocytopaenia thresholds, and platelet count of $100 \times 1000/\mu L$ (red dashed). The model provides an appropriate depiction of the observed differences between the age categories

lower probability of thrombocytopaenia compared with adults with abrocitinib treatment at 100 mg or 200 mg. Asian populations exhibit lower platelet counts compared with Western individuals at the nadir and week 12 of treatment with abrocitinib 100 mg or 200 mg as a result of higher abrocitinib exposure. However, both nadir and week 12 platelet counts from most Asian patients were within the overall distribution of Western patients.

There is no evidence that abrocitinib affects platelet clearance. Abrocitinib may decrease platelets by several mechanisms that affect thrombopoietin production; first, by inhibition of the hepatic Ashwell Morell receptor–**JAK2** signalling cascade and, second, by inhibition of the hepatic interleukin-6–JAK1 signalling cascade.[6,16,17] In this model, the rate of platelet proliferation is the product of the steady-state proliferation rate, drug effect and the feedback loop, the latter of which promotes a greater rate of platelet proliferation in response to decreasing circulating platelets. Physiologically, a decrease in the number of functional platelets

owing to abrocitinib stimulates the release of thrombopoietin from the liver, which promotes maturation of progenitor cells into platelets. The diminishing impact of drug on platelet proliferation over time could be due to a gradual increase in the feedback mechanisms in response to continuous platelet suppression over time.[17] The impact of tachyphylaxis could not be differentiated owing to the multiplicative nature of the components determining the rate of proliferation and sparse platelet sampling. Therefore, it was assumed that time-dependence in response was due to tachyphylaxis of drug effect on platelet proliferation. The half-life of tachyphylaxis estimated by the final model suggested that 100% of the drug effect on suppression of platelet proliferation would be diminished after approximately 108 weeks. In the context of the average study duration in this analysis, it was predicted that the effect of abrocitinib on platelet proliferation would decrease by 32% after 12 weeks of abrocitinib administration. The evidence of tachyphylaxis will be reviewed again when sufficient
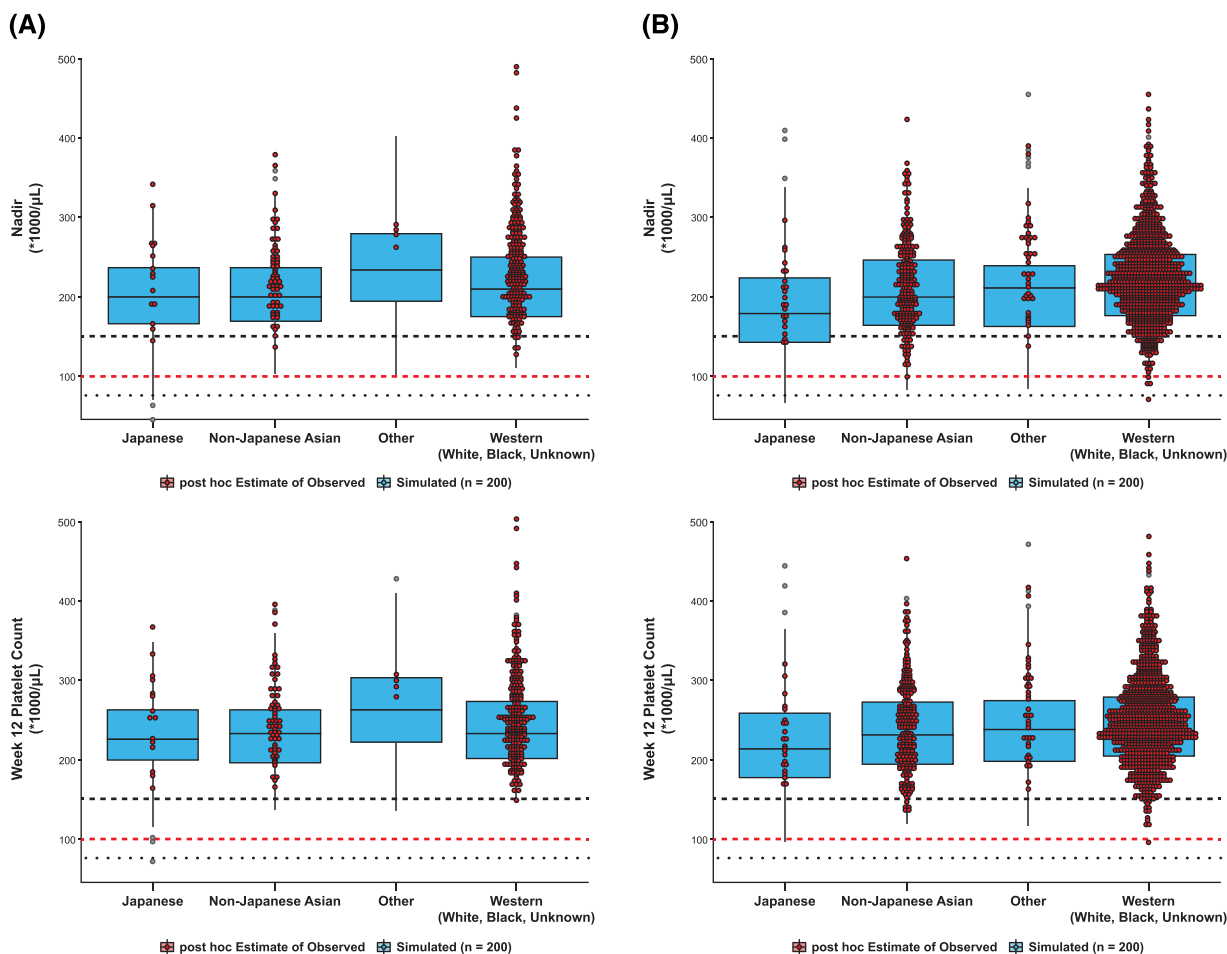
FIGURE 6 Evaluation of race on platelet nadir and week 12 platelet count in atopic dermatitis patients administered abrocitinib 100 mg (**A**) or 200 mg (**B**). Red circles represent the distribution of the nadir or week 12 platelet count based on the empirical Bayes estimates for all atopic dermatitis patients in the analysis population randomized to 100 mg QD or 200 mg QD, and blue box-and-whisker plots depict newly simulated individuals ($n = 200$) based on the final population PK model. Horizontal lines represent Grade 1 (<150 × 1000/μL; black dashed) and Grade 2 (<75 × 1000/μL; black dotted) thrombocytopaenia thresholds, and platelet count of 100 × 1000/μL (red dashed). The model provides an appropriate depiction of the observed differences between the race categories

long-term data (i.e., beyond 12 weeks) become available for abrocitinib in AD.

For all baseline platelet counts, the probability of Grade 3 thrombocytopaenia (<50 × 1000/μL) or greater was low at both 100 mg and 200 mg doses (<3%). However, for an individual with a baseline platelet count of 170 × 1000/μL, the probability of a nadir in Grade 1 thrombocytopaenia or more severe (<150 × 1000/μL) was 92.1% for 100 mg and 95.5% for 200 mg, and the probability of Grade 1 thrombocytopaenia or more severe (<150 × 1000/μL) at week 12 was 76.5% for 100 mg and 83.5% for 200 mg. Although the absolute change in platelet counts was consistent across the different baseline scenarios, the percent change from baseline for the nadir and week 12 platelet counts was greatest when baseline was 170 × 1000/μL for both 100 mg and 200 mg dosing.

Several covariates identified in this analysis explained differences in platelet time-courses by incorporation on baseline platelet count

($CIRC_0$). The effect of baseline WBC was the most significant intrinsic factor incorporated into the final model to explain differences in baseline platelet counts between individuals. Additionally, differences in haematocrit (proportion of red blood cells in blood), explained variability in baseline platelet count between individuals. These predictors are consistent with the common regulatory mechanisms involved for these haematological parameters, and other studies examining predictors of platelet indices.[18]

Other known predictors of platelet counts, such as age and female sex, were also identified as important factors for quantifying differences in baseline platelet counts in this analysis.[18] The final model showed that, on average, female patients demonstrated 6% higher baseline platelet count compared with males after accounting for age. Younger (14 years; 5th percentile) and older (64 years; 95th percentile) ages demonstrated 5% higher and lower baseline platelet count, respectively. Additionally, the population PK model identified

that, on average, adolescent patients demonstrated 33% lower steady-state 24-hour area under the curve compared with weight-matched adults. With higher baseline platelet counts and lower exposure, adolescents have a lower probability of thrombocytopaenia compared with adults.

The population PK model identified that, on average, Asian patients demonstrated a 51% increase in steady-state AUC_τ compared with Western (White, Black and unknown) patients of the same weight. The central tendencies of both the nadir and week 12 platelet counts demonstrated that Asian populations exhibit lower platelet counts compared with Western individuals; however, all Asian patients were within the overall distribution of their Western counterparts.

Study limitations include that there was no long-term follow-up included in this study, and therefore no statements can be made about long-term treatment effects; longer-term data would provide more certainty in the return of count towards baseline levels. The semi-mechanistic structure assumes that a decrease in platelets is due to a decrease in production and, based on the available data, it is not possible to estimate separate rates of proliferation, maturation and destruction of platelets.

In conclusion, the platelet time-course following abrocitinib administration was adequately described by a semi-mechanistic model; decreases in platelet counts were shown to be transient with the nadir occurring at 24 days (95% PI, 23–24 [for 200 mg QD]) after continuous administration of abrocitinib. Patients with low platelet counts were at increased risk of low-grade thrombocytopaenia, but the effect was transient, and a further decline in platelet counts after the nadir at 4 weeks was unlikely. This analysis supports the safety of once-daily abrocitinib 200 mg and 100 mg dosing regimens, with low probability of thrombocytopaenia during treatment. This analysis provides perspective of differences observed in abrocitinib exposure and the impact on platelet time-course and probability of thrombocytopaenia (i.e., Asian race, adolescents).

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COMPETING INTERESTS

All authors are employees and shareholders of Pfizer Inc.

CONTRIBUTORS

J.W. and T.N. conceived and designed the study. J.W., L.F., H.V. and T.N. were responsible for acquisition, analysis and interpretation of the data. All authors critically reviewed the manuscript for intellectual content. All authors had full access to all data in the study and agreed to be accountable for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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APPENDIX A.

TABLE A1 Summary of clinical trials included in the analysis

| Protocol	Phase	Protocol design	Population	N	Dose administration	Platelet count sampling
B7451005	2	A Phase 2 randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of abrocitinib in patients with moderate-to-severe psoriasis[5]	Psoriasis	59	200 mg BID, 400 mg QD, or 200 mg QD of abrocitinib or matching placebo for 4 weeks	Screening, week 0, 1, 2, 3 and 4, and follow-up at week 8
B7451006	2b	A Phase 2b randomized, double-blind, placebo-controlled, parallel, multi-centre, dose-ranging study to evaluate the efficacy and safety profile of abrocitinib in patients with moderate-to-severe atopic dermatitis[2]	Atopic dermatitis	269	10, 30, 100, 200 mg QD of abrocitinib or matching placebo for 12 weeks	Screening, week 0, 1, 2, 4, 6, 8 and 12, and follow-up at week 13, 14 and 16
B7451012 (JADE MONO-1)	3	A Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-centre study to evaluate the efficacy and safety of abrocitinib monotherapy in patients aged 12 years and older, with moderate-to-severe atopic dermatitis[3]	Atopic dermatitis	387	100 or 200 mg QD of abrocitinib or matching placebo for 12 weeks	Screening, week 0, 2, 4, 8 and 12, and follow-up at week 16
B7451013 (JADE MONO-2)	3	A Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-centre study to evaluate the efficacy and safety of abrocitinib monotherapy in patients aged 12 years and older, with moderate-to-severe atopic dermatitis[4]	Atopic dermatitis	391	100 or 200 mg QD of abrocitinib or matching placebo for 12 weeks	Screening, week 0, 2, 4, 8 and 12, and follow-up at week 16
B7451014 (JADE REGIMEN)	3	A Phase 3 randomized withdrawal, double-blind, placebo-controlled, multi-centre study investigating the efficacy and safety of abrocitinib in patients aged 12 years and over, with moderate-to-severe atopic dermatitis with the option of rescue treatment in flaring patients	Atopic dermatitis	1236	200 mg QD of abrocitinib for 12 weeks, then randomized to 100 or 200 mg QD of abrocitinib or matching placebo for 40 weeks	Screening, week 0, 2, 4, 8 and 12

BID, twice daily; QD, once daily.
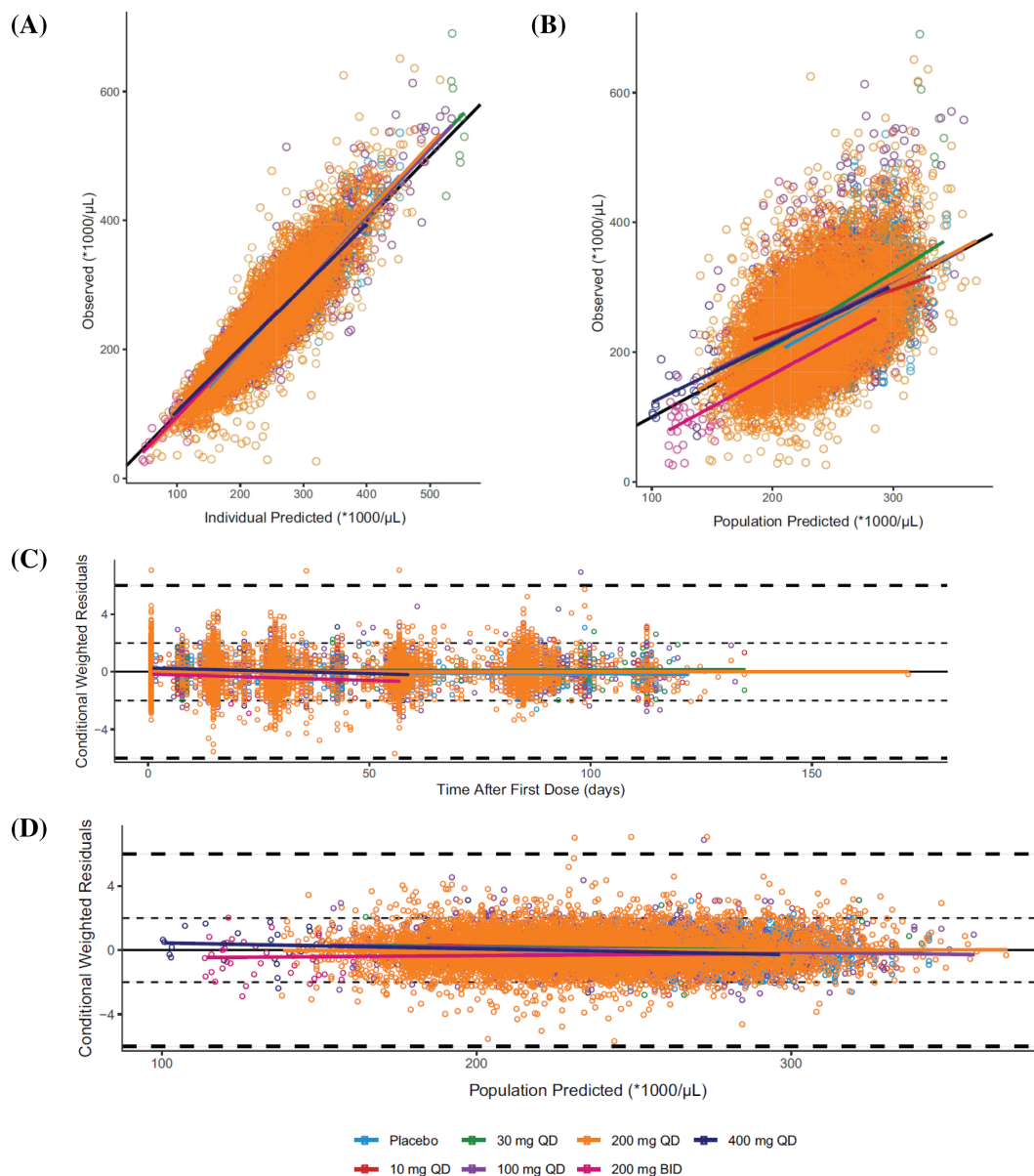
FIGURE A1 Final model diagnostic plots stratified by treatment group. (**A**) Observed *vs* individual predicted platelet counts, (**B**) observed *vs* population predicted platelet counts, (**C**) conditional weighted residuals *vs* time after first dose, (**D**) conditional weighted residuals *vs* population predicted platelet counts. The black line is the line of identity, coloured lines are the linear regression stratified by treatment group, black dashed lines represent conditional weighted residuals ± 2 (fine) and ± 6 (bold) standard deviations from the mean