

## ARTICLE

# Population Pharmacokinetics of Apixaban in Subjects With Nonvalvular Atrial Fibrillation

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This analysis describes the population pharmacokinetics (PPK) of apixaban in nonvalvular atrial fibrillation (NVAF) subjects, and quantifies the impact of intrinsic and extrinsic factors on exposure. The PPK model was developed using data from phase I–III studies. Apixaban exposure was characterized by a two-compartment PPK model with first-order absorption and elimination. Predictive covariates on apparent clearance included age, sex, Asian race, renal function, and concomitant strong/moderate cytochrome P450 (CYP)3A4/P-glycoprotein (P-gp) inhibitors. Individual covariate effects generally resulted in < 25% change in apixaban exposure vs. the reference NVAF subject (non-Asian, male, aged 65 years, weighing 70 kg without concomitant CYP3A4/P-gp inhibitors), except for severe renal impairment, which resulted in 55% higher exposure than the reference subject. The dose-reduction algorithm resulted in a ~27% lower median exposure, with a large overlap between the 2.5-mg and 5-mg groups. The impact of Asian race on apixaban exposure was < 15% and not considered clinically significant.

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## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Previous clinical pharmacology studies indicate that individual intrinsic and extrinsic factors have limited effect on apixaban exposure. However, the impact of a combination of factors on exposure was not known.

### WHAT QUESTION DID THIS STUDY ADDRESS?

This study developed a comprehensive PPK model of apixaban in subjects with NVAF in order to quantify the impact of intrinsic and extrinsic factors.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Apixaban exposure was adequately characterized by a two-compartment PPK model with first-order absorption and first-order elimination. With the exception of severe renal impairment, changes in apixaban exposure due to individual demographic factors were < 25% relative to the reference subject.

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

These analyses evaluating the impact of factors, such as Asian race, body weight, renal function, and age, support the use of the fixed-dose regimen and dose-modification scheme used in the global phase III clinical trials.

Apixaban is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa and is approved in a number of countries for multiple indications, including thromboprophylaxis after knee or hip replacement surgery, treatment of deep vein thrombosis (DVT) and PE, prevention of recurrent DVT and PE, and reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).<sup>1–7</sup>

Apixaban exhibits a pharmacokinetic (PK) profile with the following characteristics: oral bioavailability of ~50%, dose-proportional increase in exposure throughout the therapeutic

dose range (2.5–10 mg), and no time dependency. Apixaban has a total clearance of 3.3 L/hour, a steady-state volume of distribution of ~21 liters, and a half-life of ~12 hours following oral administration.<sup>8,9</sup> Multiple pathways are involved in the plasma elimination of apixaban, including metabolism primarily by cytochrome P450 3A4 (CYP3A4), and biliary, renal, and direct intestinal excretion.<sup>8,10–12</sup> Renal clearance following intravenous administration, accounts for ~27% of total systemic clearance in healthy subjects.<sup>9,13</sup> Apixaban is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein.<sup>14,15</sup>

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Two NVAF phase III trials evaluating apixaban have demonstrated a significantly improved benefit–risk profile compared to the standard of care.<sup>3,4</sup> The selected apixaban dose of 5 mg b.i.d. was based primarily on the results and analysis of the phase II dose-ranging study in venous thromboembolism prevention.<sup>16,17</sup> Additionally, the phase III studies<sup>3,4</sup> implemented a dose-modification strategy (which was not evaluated in phase II) based on advanced age, low body weight, and reduced renal function to minimize the potential for higher exposures in a population that may be at an inherently higher bleeding risk than the typical subject.<sup>18,19</sup> Although results of the clinical pharmacology studies indicated that these factors individually have limited effect on apixaban exposure, a combination of more than one intrinsic factor may increase apixaban exposure to a greater extent than a given factor alone.<sup>20–22</sup> In addition, advanced age and poor renal function have been associated with an inherent increased risk of bleeding. Thus, in the phase III trials, a reduced apixaban dose of 2.5 mg b.i.d. was used in subjects meeting two or more of the following criteria: an age of ≥ 80 years, a body weight of ≤ 60 kg, or a serum creatinine level of ≥ 1.5 mg/dL (133 μmol/L), whereas all other subjects received the standard 5-mg b.i.d. dose.

The aim of this analysis was to describe the population pharmacokinetics (PPK) of apixaban in subjects with NVAF, to quantify the impact of intrinsic and extrinsic factors on apixaban PK, and to predict apixaban exposure for the approved dosing regimens in patients with NVAF. To support global development, an *ad hoc* analysis was performed to estimate the impact of Japanese, Korean, and other Asian backgrounds on apixaban PK relative to non-Asian patients with NVAF.

## METHODS

### Study populations and data

The PPK analysis included intensive and sparse apixaban concentration–time data collected from 12 clinical studies: 8 phase I studies, a phase II study in Japanese subjects with acute coronary syndrome (ACS; Japan ACS phase II),

a global phase II study in subjects with ACS (APPRAISE-1), a phase II study in Japanese subjects with NVAF (Japan NVAF phase II), and a subset of subjects from one global phase III NVAF clinical trial, ARISTOTLE (**Table 1**).<sup>4,20–29</sup> This analysis utilized a two-stage approach so the majority of PK model development could be performed with data from the phase I and phase II studies (stage 1). Once data from the phase III study became available, the stage 1 models were re-estimated (updated stage 1) and then redefined with additional covariate testing (stage 2). Two ACS phase II studies, including one in Japanese subjects, were included in the stage 1 analysis to provide apixaban concentration data in a non-NVAF population with similar demographic characteristics, enabling a better evaluation of the effects of race and patients with NVAF status on apixaban PK.

This investigation primarily focused on the estimation of effects of covariates, including, but not restricted to, sex, age, renal function, race, body weight, time of administration (diurnal variation), and concomitant medications on the PK of the compound. These factors were selected based on the known clinical pharmacology profile of apixaban at the time, results of previous PPK analyses, and factors considered to be pertinent to the NVAF patient population.

All study protocols, their amendments, and informed-consent documentation for studies included in the analyses were reviewed and approved by institutional review boards, and all studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and local regulations.

### Pharmacokinetic assay

Apixaban concentrations were determined using a validated liquid chromatography assay coupled with atmospheric pressure ionization mass spectrometry method (Intertek Pharmaceutical Service, El Dorado Hills, CA), with a lower limit of quantification of 1 ng/mL.<sup>30</sup>

### Stage 1 population pharmacokinetic analysis

#### Stage 1 base model

The structural component of the base model was taken from a previously developed<sup>31</sup> linear two-compartment PPK model, parameterized in terms of apparent oral clearance (CL/F; L/hour), apparent intercompartmental clearance (Q/F; L/hour), apparent volume of distribution (central (V<sub>c</sub>/F), and peripheral (V<sub>p</sub>/F); L), and first-order absorption rate constant (k<sub>a</sub>; hour<sup>-1</sup>). Total apixaban clearance was split into renal and nonrenal elimination components. The effect of renal function (calculated creatinine clearance (cCrCL): calculated with the Cockcroft-Gault equation<sup>32</sup>) on CL/F was incorporated into the base model using a power function. To model the effect of cCrCL on the apparent renal clearance (CL<sub>R</sub>/F) and avoid the limitations of the Cockcroft-Gault formula<sup>32</sup> for extremes of body weight, a breakpoint of 150 mL/minute was included as follows (Eq. 1):

$$\frac{CL_i}{F} = \left\{ \frac{CL_{NR}}{F} + \frac{CL_R}{F} \cdot \left[ \frac{cCrCL_i}{cCrCL_{ref}} \right]^{\theta_1} \cdot (1 - FLAG) + \frac{CL_R}{F} \cdot \left[ \frac{150}{cCrCL_{ref}} \right]^{\theta_2} \cdot FLAG \right\} e^{\eta_i} \quad (1)$$

where CL<sub>i</sub>/F is apixaban apparent plasma clearance for individual i, CL<sub>NR</sub>/F is the nonrenal component of CL<sub>i</sub>/F, CL<sub>R</sub>/F is the renal component of CL<sub>i</sub>/F, cCrCL<sub>i</sub> is the calculated creatinine clearance for individual i, cCrCL<sub>ref</sub> is the reference value of 80 mL/minute, θ<sub>1</sub> and θ<sub>2</sub> are the power coefficients for the relationship between cCrCL<sub>i</sub> and CL<sub>i</sub>/F, FLAG is an indicator variable that is 1 when cCrCL<sub>i</sub> is > 150 mL/minute and zero otherwise, and η<sub>i</sub> is the random effect for individual i.

Based on the inclusion of data from dose-ranging studies, and observation of less than proportional exposure with doses > 10 mg due to decreased dissolution at higher doses,<sup>8</sup> a reduction in relative bioavailability (F<sub>rel</sub>) was incorporated into the model. The F<sub>rel</sub> was fixed to 1 for the lowest dose group (2.5 mg) and estimated as a parameter for doses > 2.5 mg using Eq. 2:

**Table 1** Summary of data sources

Study type	Target population	Apixaban dose and regimen	Nominal PK sampling schedule
Phase I studies <sup>a</sup>			
Multiple doses <sup>22</sup>	Healthy adult male subjects (N = 36)	2.5–25 mg b.i.d. for 7 days 10–25 mg q.d. for 7 days	Days 1, 4, and 7: predose (0 hour); postdose (hour), b.i.d. and q.d.: 1, 2, 3, 4, 6, 9, 12, and 24; b.i.d. only: 13, 14, 15, 16, 18, and 21 day 3, b.i.d. and q.d.: predose (72 hours) postdose day 7, b.i.d. and q.d.: 48 (day 9) and 72 hours (day 10)
Race <sup>23</sup>	Healthy white and Japanese subjects (N = 24)	2.5, 10, 25, and 50-mg single dose	Predose (0 hour) postdose (hour): 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 72
Renal impairment <sup>19</sup>	Healthy and renally impaired subjects (N = 32)	10-mg single dose	Predose (0 hour) postdose (hour): 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96
Age and sex <sup>20</sup>	Healthy young (≤ 45 years) and elderly (≥ 65 years) male and female subjects (N = 79)	20-mg single dose	Predose (0 hour) postdose (hour): 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96
Race <sup>24</sup>	Healthy Japanese subjects (N = 18)	2.5, 5, and 10 mg b.i.d. for 7 days	Days 1 and 7: predose (0 hour); postdose (hour): 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, and 17; days 2, 3, 5, 6, 8, and 9: predose (0 hour) or corresponding time <sup>a</sup> day 4: predose (0 hour), 12 hours
Race <sup>25</sup>	Healthy Chinese subjects (N = 12)	10-mg single dose, then 10 mg b.i.d. for 6 days	Day 1: predose (0 hour); postdose (hour): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72 days 7 and 8: predose (0 hour) day 9: predose (0 hour); postdose (hour): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72 <sup>a</sup>
Body weight <sup>21</sup>	Healthy subjects of high (≥ 120 kg), normal (65–85 kg), and low (≤ 50 kg) body weight (N = 55)	10-mg single dose	Day 1: predose (0 hour); postdose (hour): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72
Multiple doses	Healthy subjects (N = 14)	2.5 mg b.i.d. for 4 days	Day 1: predose (0 hour) day 4: predose (0 hour); postdose (hour): 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, 24, 36, 48, and 60
Phase II study <sup>a</sup>			
APPRAISE 1 <sup>26</sup>	ACS treatment subjects (N = 951)	2.5 and 10 mg b.i.d. 10 and 20 mg q.d. for 26 weeks	Weeks 3 and 26: random sample
JAPAN ACS phase II <sup>27</sup>	Japanese subjects with ACS (N = 93)	2.5 and 5 mg b.i.d. for 24 weeks	Weeks 1, 4, and 12: predose (0 hour); postdose: 1–3 hours and 3–5 hours
Japan NVAF phase II <sup>28</sup>	Japanese subjects with NVAF (N = 139)	2.5 and 5 mg b.i.d. for 12 weeks	Weeks 1 and 8: predose (0 hour); postdose: 1–3 hours and 3–5 hours
Phase 3 study			
ARISTOTLE <sup>4</sup>	Adult subjects with NVAF (N = 2932)	5 mg b.i.d. (2.5 mg b.i.d. in select subjects) for 6 months	Month 2, single random sample

ACS, acute coronary syndrome; NVAF, nonvalvular atrial fibrillation; PK, pharmacokinetic.

<sup>a</sup>Dose-reduction algorithm was not evaluated in phase II studies including Japan NVAF phase II.

$$F_{rel} = 1 - \frac{I_{MAX} \times (Dose - 2.5)^\gamma}{ED_{50}^\gamma + (Dose - 2.5)^\gamma} \quad (2)$$

where  $F_{rel}$  is the relative bioavailability of a given dose > 2.5 mg,  $I_{MAX}$  is the maximum reduction in relative bioavailability,  $ED_{50}$  is the dose at which half of the maximal reduction in  $F_{rel}$  is achieved, and  $\gamma$  is the shape parameter that controls the relationship between dose and  $F_{rel}$ .

Interindividual variance (IIV) terms were described by an exponential error model, with the random variability distributed with a mean of zero and a variance of  $\omega^2$ . The residual

variability was described by a log-normal error model (implemented as an additive error model using a log transform-both-sides approach). All modeling and simulations were conducted using First Order Conditional Estimation with Interaction with NONMEM (version 7.1).<sup>33</sup> Postprocessing of NONMEM output and creation of derived datasets and figures was completed using SAS (version 9) or S-plus (version 8.2) software.

### Stage 1 full and final models

The following covariates were incorporated into the base model simultaneously to form the stage 1 full PPK model.

Apparent renal clearance ( $CL_R/F$ ): race (white, black, Asian, other), subject status (healthy, ACS, NVAF), and dosing time (morning (12:01AM to 11:00AM), afternoon (11:01AM to 5:00PM), and evening (5:01PM to 12:00AM)).

The apparent nonrenal clearance ( $CL_{NR}/F$ ): age, sex, baseline body weight, race, subject status, and dosing time.

Apparent volume of central compartment ( $V_C/F$ ): baseline body weight and subject status.

Absorption rate ( $k_a$ ): dosing time.

Continuous covariates were normalized to a typical reference value and were included in the model using a power function. Categorical covariate effects were parameterized as a fractional change. The covariate parameterizations are described by Eq. 3:

$$TVP_i = \theta_n \cdot \prod_1^m \left( \frac{cov_{mi}}{ref_m} \right)^{\theta_{(m+n)}} \cdot \prod_1^p \theta_{(\rho+m+n)}^{cov_{\rho i}} \quad (3)$$

where TVP is the typical value of a model parameter,  $cov_{mi}$  is the individual continuous covariate,  $ref_m$  is the reference continuous covariate value,  $cov_{\rho i}$  is the individual categorical (0–1) covariate,  $\theta_n$  is an estimated parameter describing the typical PK parameter value for an individual with covariates equal to the reference covariate values ( $cov_{mi} = ref_m$ ,  $cov_{\rho i} = 0$ ), and  $\theta_{(m+n)}$  and  $\theta_{(\rho+m+n)}$  are estimated parameters describing the magnitude of the covariate–parameter relationships.

Wald’s Approximation Method (WAM) was used to identify a subset of reduced PK models relative to the stage 1 full model.<sup>34</sup> The WAM procedure ranks all  $2^k$  possible submodels derived from the presence or absence of the  $k$  covariate parameters in the full model. The WAM algorithm approximates the log-likelihood surface by a quadratic equation in the covariate effects based on the estimates and asymptotic variance–covariance matrix of the estimates from the stage 1 full model fit. Maximization of Schwarz’s Bayesian Criterion (SBC), calculated using the approximation, was used to rank all  $2^k$  possible models. The top 15 ranked models were fit using NONMEM to calculate the actual SBC.

The stage 1 final parsimonious model (**Supplemental File S1**) was selected to be the model with the maximum value of NONMEM-based SBC among the top 15 ranked models determined by the WAM procedure.

### Stage 2 population pharmacokinetic analysis

Stage 1 base, full, and final model parameter estimates were updated to include the apixaban concentrations from the NVAF phase III study and refitted to ensure that the stage 1 final model remained parsimonious (referred to as the updated stage 1 final model; **Table 3**). The updated stage 1 final model was then adapted to include concomitant medications known to produce changes in apixaban PK. The influence of strong and moderate CYP3A4/P-gp inhibitors as well as strong CYP3A4/P-gp inducers were evaluated as time-varying covariates on total CL/F after initially being tested on both  $CL_R/F$  and  $CL_{NR}/F$  (**Table 3**). Model reduction was then performed using a WAM procedure as described for the stage 1 analysis to determine the stage 2 final model (**Table 3 and Supplemental File S2**).

### Model assessment

The adequacy of the model to describe the data was assessed through evaluation of objective function values (OFVs), standard diagnostic and graphical assessments, as well as precision of parameter estimates. Additionally, a posterior predictive check (PPC) method was performed to determine if the model was capable of simulating data that was consistent with the observed apixaban concentrations.<sup>35</sup> The time course of the mean and 90% prediction intervals were plotted stratified by study and dose, and the corresponding observed PPC statistics were overlaid.

### Prediction of steady-state exposure and evaluation of apixaban exposure obtained with dose-adjustment algorithm

The stage 2 final PPK model was used to predict the steady-state concentration–time profiles in subjects with NVAF who received 5 mg b.i.d. and in those who met the criteria to receive the reduced dose of 2.5 mg b.i.d. (subjects with at least two of the three following factors: age  $\geq$  80 years, body weight  $\leq$  60 kg, or serum creatinine  $\geq$  1.5 mg/dL). In order to generate predictions of apixaban, the multivariate normal distribution was used as an approximate asymptotic posterior distribution to generate 500 sets of population parameter values from which 500 simulated datasets were generated. For each of 500 simulated parameter datasets, 1,000 patients were simulated each for the dose-modification group receiving 2.5 mg b.i.d. apixaban and the reference group receiving 5 mg b.i.d. apixaban. Simulated total daily apixaban exposures were generated for each group based on covariates that were generated using a nonparametric bootstrap (sampling with replacement) of the observed PK covariates within each group to preserve the correlation structure among the covariates.

### Ad hoc analysis of stratification of Asian race into Japanese, Korean, and other Asians

The stage 2 final PPK model that included Asian race as a covariate on the total CL/F of apixaban was subsequently refined to include separate covariate effects for Japanese, Korean, and other Asian races. As the Japan NVAF phase II trial randomized 2.5-mg and 5-mg apixaban dose levels, and did not evaluate the dose-reduction algorithm, apixaban concentrations were generated for the overall Japanese population by dose and compared with observed concentrations according to whether or not the phase III NVAF dose-reduction algorithm criteria would have been met.

## RESULTS

The stage 2 final PPK analysis dataset consisted of 11,968 apixaban concentrations from 4,385 subjects. The stage 1 analysis included 9,036 apixaban concentrations from 270 phase I study subjects and 1,183 phase II subjects with NVAF or ACS. Stage 2 included an additional 2,932 apixaban concentrations from 2,932 NVAF subjects from the phase III ARISTOTLE study. **Table 2** provides summary statistics of the baseline demographic covariates and concomitant medication usage, stratified by indication. The overall

**Table 2** Summary of baseline demographic covariates for PPK analysis

Covariate	Phase I subjects	NVAF	ACS	Total
Age (years)				
<i>n</i>	270	3,071	1,044	4,385
Mean (SD)	38.89 (18.2)	69.33 (9.2)	60.84 (11.4)	65.44 (13.0)
Median (min–max)	33 (18–85)	70 (26–94)	61 (28–89)	68 (18–94)
Baseline body weight (kg)				
<i>n</i>	270	3,071	1,044	4,385
Mean (SD)	75.97 (21.9)	84.74 (20.4)	81.52 (15.7)	83.44 (19.6)
Median (min–max)	71.2 (37.7–175.1)	83.0 (32–198.2)	80.0 (44–175.5)	81.4 (32–198.2)
Creatinine clearance (mL/minute)				
<i>n</i>	270	3,071	1,044	4,385
Mean (SD)	114.32 (47.2)	79.87 (31.5)	93.35 (33.5)	85.2 (34.5)
Median (min–max)	112.8 (15–317.5)	74.35 (18.8–279.8)	89.27 (11.9–319.7)	79.3 (11.9–319.7)
Sex, <i>n</i> (%)				
Male	181 (67.04)	2,079 (67.70)	820 (78.54)	3,080 (70.24)
Female	89 (32.96)	992 (32.30)	224 (21.46)	1,305 (29.76)
Race, <i>n</i> (%)				
White	181 (67.04)	2,531 (82.42)	937 (89.75)	3,649 (83.22)
Asian	49 (18.15)	509 (16.57)	94 (9.00)	652 (14.87)
Japanese	30 (11.11)	278 (9.05)	93 (8.91)	401 (9.14)
Korean	0 (0)	69 (2.25)	0 (0)	69 (1.57)
Other Asian	19 (7.04)	162 (5.28)	1 (0.10)	182 (4.15)
Black/African American	30 (11.11)	25 (0.81)	6 (0.57)	61 (1.39)
Other	10 (3.70)	6 (0.20)	7 (0.67)	23 (0.52)
Strong CYP3A4/P-gp inhibitors, <sup>a</sup> <i>n</i> (%)				
No	270 (100)	3,068 (99.9)	1,044 (100)	4,382 (99.93)
Yes	0 (0)	3 (0.1)	0 (0)	3 (0.07)
Moderate CYP3A4/P-gp inhibitors, <sup>a</sup> <i>n</i> (%)				
No	270 (100)	2,399 (78.12)	998 (95.59)	3,667 (83.63)
Yes	0 (0)	672 (21.88)	46 (4.41)	718 (16.37)
Strong CYP3A4/P-gp inducers, <sup>a</sup> <i>n</i> (%)				
No	270 (100)	3,017 (98.24)	1,030 (98.66)	4,317 (98.45)
Yes	0 (0)	54 (1.76)	14 (1.34)	68 (1.55)

ACS, acute coronary syndrome; CYP, cytochrome P450; NVAF, nonvalvular atrial fibrillation; P-gp, P-glycoprotein; PPK, population pharmacokinetic.  
<sup>a</sup>Concomitant medication usage was designated as “Yes” if a subject was on a pertinent concomitant medication when at least one pharmacokinetic sample was collected.

analysis population had a mean age of 65 years, an average body weight of 83.4 kg, and a mean cCrCL of 85.2 mL/minute. NVAF subjects comprised 70% of the subjects in the PPK analysis dataset. Asians accounted for ~15% of the analysis dataset (9.1% Japanese, 1.6% Korean, and 4.2% other Asians). Approximately 5% of the NVAF population enrolled in the phase III trial met the criteria for the 2.5-mg dose. For graphical displays and comparison across populations, a typical reference NVAF subject was defined as a man, non-Asian subject aged 65 years, with a body weight of 70 kg and a cCrCL of 80 mL/minute.

**PPK model development**

**Stage 1 population pharmacokinetic analysis**

Parameter estimates and precision for the stage 1 base, full, and final models are shown in **Table S1**. Initial attempts to fit a full model to the apixaban concentration–time data did not result in successful convergence. A series of modifications were made, including separate residual

variability for healthy subjects vs. patients and estimation of off-diagonal elements of the variance–covariance matrix of IIV. Parameterization resulted in an estimate of ~1 for the correlation between IIV-CL/F and IIV- $V_c$ /F, indicating a perfect correlation for these random effects. It was hypothesized that the high correlation could be reduced by reparameterizing the base model so that subject-specific random effects were estimated on the microconstants ( $k_{10}$ ,  $k_{21}$ , and  $k_{12}$ ). This model converged successfully, but the covariance step failed with a singular R-matrix. Thus, the model was further simplified by assuming that changes in  $CL_{R1}/F$  were proportional to changes in cCrCL, forming the final stage 1 base PPK model. Additionally, the covariate effects for race, subject status, and dosing time were evaluated on total CL/F instead of each component separately in the stage 1 full PPK model.

Nine covariate effects were incorporated into this model, including dosing time on  $k_a$ ; baseline body weight, NVAF subject status, and ACS subject status on  $V_c/F$ ; age and sex



on  $CL_{NR}/F$ ; and Asian race, NVAF subject status, and ACS subject status on  $CL/F$ . This model accounted for 96.4% of the reduction in OFV relative to the full model. Based on these results, the highest ranked model was parsimonious and selected as the stage 1 final model (Table S1). Overall, the stage 1 final model provides an adequate fit to the apixaban plasma concentration vs. time data in healthy subjects and subjects with NVAF or ACS.

### Stage 2 population pharmacokinetic analysis

Although successful convergence was achieved when phase III data were added and the stage 1 models re-fitted, some model instability was noted. The models estimated with the updated dataset were more susceptible to numerical problems and demonstrated higher correlations ( $\rho > 0.95$ ) for the parameters describing the relationship between  $F_{rel}$  and dose (i.e.,  $\gamma$ ,  $\text{logit } I_{MAX}$ , and  $ED_{50}$ ). Therefore, the parameterization for  $F_{rel}$  was simplified using a power model to stabilize the updated stage 1 model:

$$F_{rel} = 1 - I_{50} \left[ \frac{(Dose - 2.5)}{47.5} \right]^\gamma \quad (4)$$
$$I_{50} = \frac{e^{\theta_9}}{1 + e^{\theta_9}}$$

where  $F_{rel}$  is the relative bioavailability of a given dose  $> 2.5$  mg,  $I_{50}$  is the decrease in relative bioavailability for a 50-mg apixaban dose, and  $\gamma$  is the shape parameter that controls the relationship between dose and  $F_{rel}$ .

A total of 10 intrinsic and extrinsic covariate effects were included in the stage 2 final model (Table 3 and Table S2). The WAM procedure was not implemented in stage 2 model development because only two covariate parameters (strong or moderate CYP3A4/P-gp inhibitors and strong CYP3A4/P-gp inducers) were added to the model. The concomitant medication categories for strong and moderate CYP3A4/P-gp inhibitors were collapsed because only three subjects contributed a PK sample while on a concomitant strong inhibitor (Table 2). The effects of concomitant medications on apixaban  $CL/F$  were estimated to be relatively small in magnitude; the effect of strong or moderate CYP3A4/P-gp inhibitors resulted in only a 14.6% decrease in  $CL/F$ . The effect of strong inducers on apixaban  $CL/F$ , included in the full stage 2 model, was very small and poorly estimated, which suggested that the data do not contain much information to describe this relationship. Thus, the effect was not included in the final stage 2 model.

Administration of apixaban in the evening resulted in a 43% decrease in  $k_a$  relative to administration in the morning or afternoon. Baseline body weight and subject status were found to influence  $V_c/F$ , with the effect estimated as a 23.3% reduction for a 50-kg subject and a 22% increase for a 90-kg subject relative to the typical 70-kg NVAF subject. In addition, female subjects had a 21.6% reduction in  $CL_{NR}/F$  relative to male subjects. Finally, Asian race, NVAF, ACS, or strong or moderate CYP3A4/P-gp inhibitors resulted in reduced  $CL/F$  of 11.9%, 13.9%, 21.5%, and 14.6%, respectively, compared with non-Asian subjects, healthy subjects, or subjects who did not receive concurrent administration of a CYP3A4/P-gp inhibitor (Figure 1).

### Model assessment

The final stage 2 model parameters were well estimated (Table 2) and no trends for model misspecification were observed in the diagnostic plots (data on file; Bristol-Myers Squibb). A PPC was conducted to determine if the stage 2 final model was capable of simulating data that were consistent with the observed PK measurements in NVAF subjects (Figure S1); PPCs for the NVAF population for healthy and ACS subjects are shown in Figures S2 and S3, respectively. Overall, the model captures the general shape of the apixaban concentration-time profile in both healthy subjects and patients, despite some instances where the observed data are not contained within the 90% prediction interval. Although there seemed to be a modest under-prediction of the 5-mg b.i.d. data, no systematic trends for model misspecification were observed in the NVAF subject data.

### Predicted apixaban exposure in NVAF subjects

The distribution of the predicted total daily exposure (area under the curve at steady-state ( $AUC_{ss}$ )) stratified by dose for subjects enrolled in the ARISTOTLE study<sup>4</sup> is shown in Figure 2. The median exposure predicted by the PPK model is lower for the dose-modification group than the reference group assigned to the 5-mg b.i.d. dose (Figure 2). Table 4 provides a summary of the predicted daily steady-state apixaban exposure in NVAF subjects upon treatment with the 5-mg or 2.5-mg b.i.d. dose. These results show that NVAF subjects who require dose adjustment to 2.5 mg b.i.d. would be expected to have ~27% lower AUC compared with subjects receiving 5 mg b.i.d. Table S3 shows the predicted exposures for NVAF subjects who met dose-modification criteria.

### Ad hoc analysis of stratification of Asian race into Japanese, Korean, and other Asian subgroups

Stratification of the effects of Asian race on  $CL/F$  resulted in -15.1%, +3.3%, and -4.3% change in population mean total  $CL/F$  for Japanese, Korean, and other Asian races, respectively, relative to non-Asian typical patients with NVAF (men, 65 years, 70 kg, and  $cCrCL$  of 80 mL/minute), corresponding to +17.7%, -3.2%, and +4.5% changes in daily  $AUC_{ss}$ , respectively (Table 3 and Table S2).

The plots of the observed and predicted apixaban plasma concentrations in Japanese subjects with NVAF at steady state are shown in Figure 3. The predicted apixaban plasma concentrations for 2.5 and 5 mg b.i.d. showed a general dose-proportionality. Observed concentrations after administration of apixaban 2.5 mg b.i.d. in Japanese subjects not meeting the phase III dose-reduction criteria were generally lower than the apixaban 2.5-mg b.i.d. observed data in subjects who met the phase III dose-reduction criteria. Additionally, observed concentrations after administration of apixaban 5 mg b.i.d. in Japanese subjects meeting the phase III dose-reduction criteria seemed to be distributed around the 5-mg b.i.d. predicted line in typical Japanese subjects and were within the variability of apixaban 5-mg b.i.d. observed data in Japanese subjects who did not meet the dose-reduction criteria.

**Table 3** Updated stage 1 final, stage 2 final, and stage 2 final *ad hoc* model parameter estimates

Fixed effects parameters	Estimate ± SE updated stage 1 final model	Estimate ± SE stage 2 final model	Estimate ± SE stage 2 final <i>ad hoc</i> <sup>c</sup> model
OFV	-5,878.214	-5,888.403	-5,900.112
$k_a$ ( $\theta_1$ ) (1/hour)	0.471 ± 0.0204	0.473 ± 0.0208	0.471 ± 0.0218
Evening dosing ( $AM/PM = 2$ ) ( $\theta_{10}$ )	-0.434 ± 0.0234	-0.433 ± 0.0236	-0.436 ± 0.0237
Afternoon dosing ( $AM/PM = 3$ ) ( $\theta_{27}$ )	NE	NE	NE
$CL_R/F$ ( $\theta_2$ ) (L/hour)	1.57 ± 0.118	1.57 ± 0.117	1.60 ± 0.126
cCrCL ( $\theta_7$ )	1 FIXED	1 FIXED	1 FIXED
$CL_{NR}/F$ ( $\theta_6$ ) (L/hour)	2.02 ± 0.11	2.02 ± 0.108	2.02 ± 0.113
D_WTB ( $\theta_{26}$ )	NE	NE	NE
Age ( $\theta_{14}$ )	-0.429 ± 0.0681	-0.429 ± 0.0678	-0.414 ± 0.0727
Female ( $\theta_{15}$ )	-0.215 ± 0.0263	-0.216 ± 0.0263	-0.227 ± 0.0269
CL/F	3.59 <sup>a</sup>	3.59 <sup>a</sup>	3.62 <sup>a</sup>
Black ( $\theta_{28}$ )	NE	NE	NE
Asian ( $\theta_{16}$ )	-0.12 ± 0.0184	-0.119 ± 0.0183	
Japanese ( $\theta_{24}$ )	NE	NE	-0.151 ± 0.0202
Korean ( $\theta_{25}$ )	NE	NE	0.0325 ± 0.0753
Other Asians ( $\theta_{16}$ )	NE	NE	-0.0427 ± 0.0403
NVAF ( $\theta_{17}$ )	-0.149 ± 0.0298	-0.139 ± 0.0305	-0.145 ± 0.0326
ACS ( $\theta_{18}$ )	-0.217 ± 0.0284	-0.215 ± 0.0286	-0.212 ± 0.0304
Strong/moderate inhibitors ( $\theta_{19}$ )	NE	-0.146 ± 0.0421	-0.140 ± 0.0419
Strong/moderate inducers ( $\theta_{20}$ )	NE	NE	NE
$V_c/F$ ( $\theta_3$ ) (L)	29.8 ± 0.981	30.0 ± 0.971	30.0 ± 1.04
D_WTB ( $\theta_{11}$ )	0.806 ± 0.0649	0.790 ± 0.0645	0.792 ± 0.0648
NVAF subjects ( $\theta_{12}$ )	-0.0217 ± 0.0501	-0.0405 ± 0.0491	-0.0530 ± 0.0508
ACS subjects ( $\theta_{13}$ )	-0.177 ± 0.0449	-0.180 ± 0.0446	-0.184 ± 0.0463
Q/F ( $\theta_4$ ) (L/hour)	1.89 ± 0.151	1.91 ± 0.163	1.92 ± 0.202
$V_p/F$ ( $\theta_5$ ) (L)	26.7 ± 1.89	27.0 ± 2.03	27.3 ± 2.78
Shape parameter for $F_{rel}$ ( $\gamma$ ) ( $\theta_8$ )	0.853 ± 0.0693	0.857 ± 0.0684	0.875 ± 0.0779
Logit for reduction in $F_{rel}$ at 50 mg ( $I_{50}$ ) ( $\theta_9$ )	-0.321 ± 0.0512	-0.322 ± 0.0512	-0.327 ± 0.0519
<b>IIV components</b>	<b>Estimate ± SE (%CV<sup>b</sup>)</b>	<b>Estimate ± SE (%CV<sup>b</sup>)</b>	<b>Estimate ± SE (%CV<sup>b</sup>)</b>
$\omega^2-k_a$	0.271 ± 0.0319 (52.1)	0.263 ± 0.0311 (51.3)	0.264 ± 0.0312 (51.4)
$\omega^2-k$	0.101 ± 0.00989 (31.8)	0.0954 ± 0.00964 (30.9)	0.0961 ± 0.00987 (31.0)
$\omega^2-V_c/F$	0.0287 ± 0.0055 (16.9)	0.0294 ± 0.00553 (17.1)	0.0290 ± 0.00550 (17.0)
$\omega^2-k_{21}$	0.243 ± 0.0412 (49.3)	0.240 ± 0.0404 (49.0)	0.241 ± 0.0409 (49.1)
$\omega^2-k_{12}$	1.49 ± 0.163 (122)	1.55 ± 0.169 (124)	1.55 ± 0.186 (124.5)
<b>Residual variance components</b>	<b>Estimate ± SE (%CV<sup>c</sup>)</b>	<b>Estimate ± SE (%CV<sup>c</sup>)</b>	<b>Estimate ± SE (%CV<sup>c</sup>)</b>
$\sigma$ HV and Studies Japan NVAF phase II <sup>28</sup> , Japan ACS phase II <sup>27</sup> ( $\theta_{21}$ )	0.31 ± 0.00282 (31)	0.31 ± 0.00282 (31)	0.31 ± 0.00284 (31)
$\sigma$ Study APPRAISE 1 <sup>26</sup> ( $\theta_{22}$ )	0.666 ± 0.0182 (66.6)	0.668 ± 0.0183 (66.8)	0.667 ± 0.0187 (66.7)
$\sigma$ Study ARISTOTLE <sup>4</sup> ( $\theta_{23}$ )	0.451 ± 0.0169 (45.1)	0.460 ± 0.0163 (46.0)	0.457 ± 0.0165 (45.7)

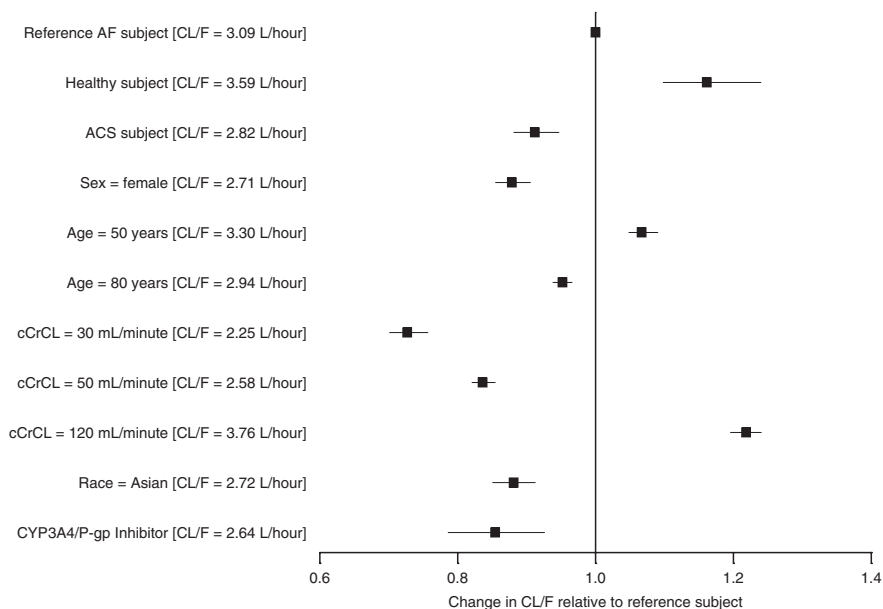
%CV, percentage of coefficient of variation; ACS, acute coronary syndrome; AM/PM, dose time; cCrCL, calculated creatinine clearance; CL/F, apparent total clearance;  $CL_{NR}/F$ , apparent nonrenal clearance;  $CL_R/F$ , apparent renal clearance;  $F_{rel}$ , relative bioavailability; HV, healthy volunteer; decrease in relative bioavailability for 50-mg dose; IIV, interindividual variability; k, k<sub>12</sub>, and k<sub>21</sub>, first-order rate constants;  $k_a$ , absorption rate constant; NE, not evaluable; NVAF, nonvalvular atrial fibrillation; OFV, objective function value; Q/F, apparent intercompartmental clearance;  $V_c/F$ , apparent volume of distribution of the central compartment;  $V_p/F$ , apparent volume of distribution of the peripheral compartment; WTB, baseline body weight.

<sup>a</sup>CL/F values were calculated as the simple sum of the population parameters estimates for  $CL_R/F$  and  $CL_{NR}/F$  and do not represent model-estimated parameters. <sup>b</sup>Approximate %CV reported as 100· $\omega$ . <sup>c</sup>Approximate %CV reported as 100· $\sigma$ . <sup>d</sup>Parameter estimates associated with the *ad hoc* analysis of the stratification of the Asian race into Japanese, Korean, and other Asian.

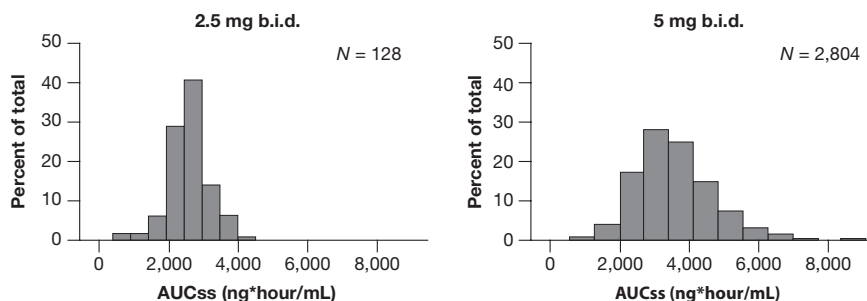
## DISCUSSION

Apixaban exposure in NVAF subjects was adequately described with a two-compartment model with first-order

absorption and elimination. The finding of a lower  $k_a$  in the evening does not seem to be of clinical relevance given the b.i.d. dosing of apixaban and robust safety and efficacy findings from the phase III NVAF clinical trials.<sup>3,4</sup>



**Figure 1** Illustration of covariate effects on total apparent clearance (CL/F). Solid squares represent the ratio of the typical predicted CL/F relative to the reference subject. The black line represents the 90% confidence interval of the ratio. The reference subject is a 65-year-old, non-Asian, male subject with nonvalvular atrial fibrillation (NVAF) that has a calculated creatinine clearance (cCrCL) with the Cockcroft-Gault equation of 80 mL/minute and did not receive a concomitant strong or moderate cytochrome P450 (CYP)3A4/P-glycoprotein (P-gp) inhibitor. ACS, acute coronary syndrome; AF, atrial fibrillation.



**Figure 2** Distribution of predicted daily area under the curve at steady state (AUC<sub>ss</sub>) for the ARISTOTLE Study Stratified by Dose Group. The 2.5-mg dose group is the modified dose group and includes subjects meeting at least 2 of the 3 dose-reduction criteria.

**Table 4** Predicted apixaban steady-state exposure in patients with NVAF

Steady-state parameter (units) <sup>a</sup>	5 mg b.i.d.			2.5 mg b.i.d. <sup>b</sup>		
	Median (90% CI)	5th percentile	95th percentile	Median (90% CI)	5th percentile	95th percentile
Daily AUC (ng*hour/mL)	3,280 (3,170–3,390)	1,600	6,590	2,410 (2,320–2,510)	1,250	4,560
C <sub>max</sub> (ng/mL)	171 (167–177)	91	321	123 (119–128)	68.5	221
C <sub>min</sub> (ng/mL)	103 (98.7–107)	40.9	230	79.2 (75.2–83.2)	34.4	162
T <sub>max</sub> (hour)	2.89 (2.81–2.99)	1.63	4.13	2.86 (2.75–2.96)	1.55	4.14

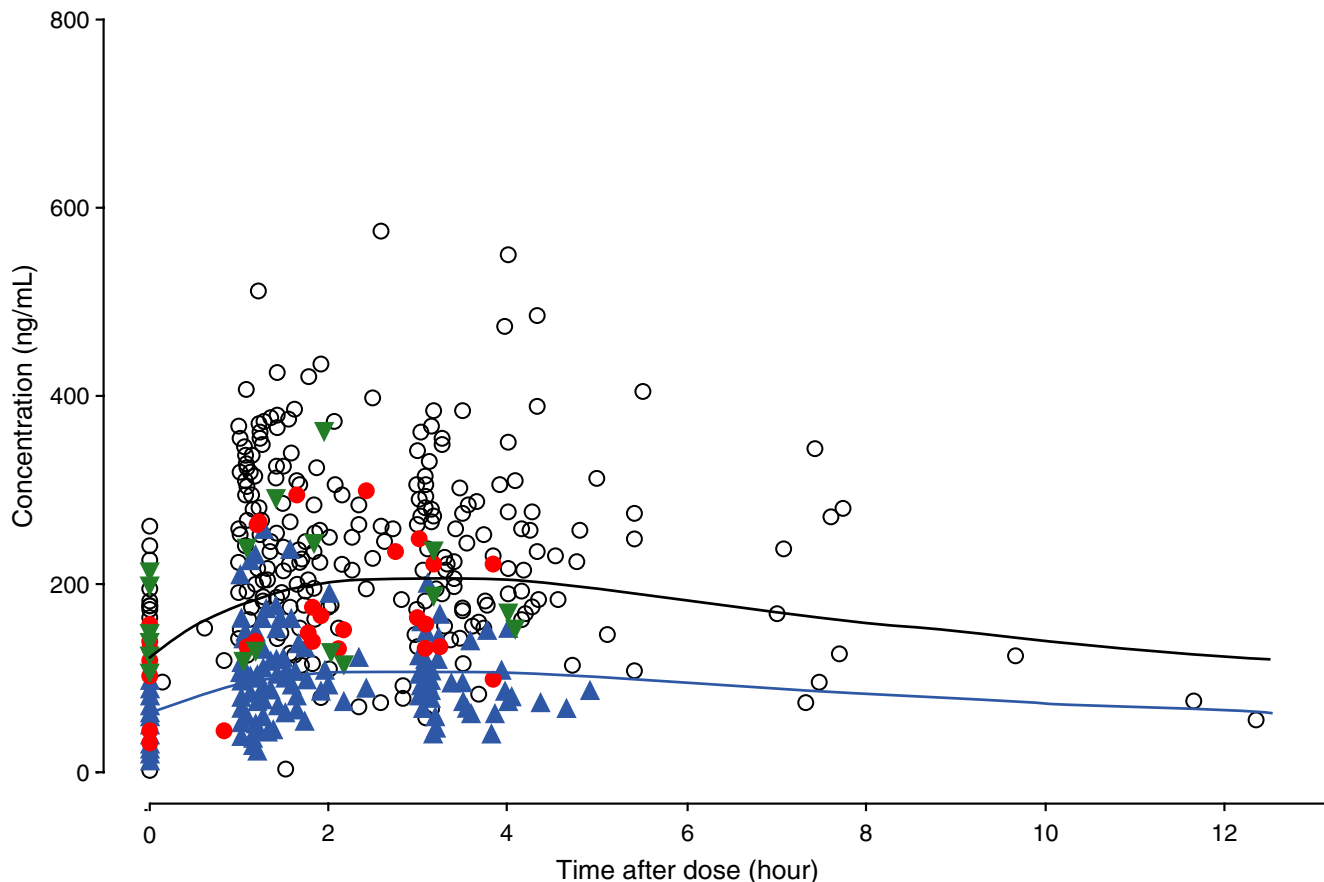
AUC, area under the concentration time curve; CI, confidence interval; C<sub>max</sub>, peak plasma concentration; C<sub>min</sub>, trough plasma concentration; NVAF, nonvalvular atrial fibrillation; T<sub>max</sub>, time of maximum plasma concentration.

<sup>a</sup>Represents daily steady-state parameters. <sup>b</sup>The 2.5-mg b.i.d. dose administered in subjects who meet the prespecified criteria in the ARISTOTLE<sup>4</sup> and AVERROES<sup>3</sup> studies for adjustment of the apixaban dose from 5 mg b.i.d. to 2.5 mg b.i.d.

Overall, the effects of renal function, race, patient type, and strong/moderate CYP3A4/P-gp inhibitors were found to be significant predictors of apixaban clearance. The model allowed for empirical separation of the total

plasma CL/F into renal and nonrenal components with predicted increases in AUC<sub>ss</sub> of 9%, 28%, and 55% for patients with NVAF with mild (cCrCL = 65 mL/minute), moderate (40 mL/minute), and severe (15 mL/minute)





- Predicted apixaban concentration–time profile for apixaban 2.5 mg twice daily (b.i.d.) in patients with median body weight, age, and calculated creatinine clearance (cCrCL) in Japanese patients who did not meet the dose-reduction criteria
- Predicted apixaban concentration–time profile for apixaban 5 mg BID in patients with median body weight, age, and cCrCL in Japanese patients who did not meet the dose-reduction criteria
- Apixaban 2.5 mg BID observed data in Japanese patients who met the dose-reduction criteria ( $N = 12$ )
- Apixaban 5 mg BID observed data in Japanese patients who did not meet the dose-reduction criteria ( $N = 180$ )
- ▲ Apixaban 2.5 mg BID observed data in patients who were allocated to 2.5 mg BID in Japan NVAF Phase 2 study but did not meet the dose-reduction criteria ( $N = 64$ )
- ▼ Apixaban 5 mg BID observed data in patients who were allocated to 5 mg BID in Japan NVAF Phase 2 study but met the dose-reduction criteria ( $N = 4$ )

**Figure 3** Observed and predicted apixaban plasma concentrations in Japanese patients with nonvalvular atrial fibrillation (NVAF) at steady state. Median values for body weight, age, and calculated creatinine clearance used to calculate typical Japanese predictions were 64.1 kg, 70 years, and 65.1 mL/minute, respectively.

renal impairment, respectively, compared with those with normal renal function. The results are generally consistent with the estimates from phase I studies<sup>20,22</sup> in which mild, moderate, and severe renal impairment were associated with an ~16%, 29%, and 44% higher estimated apixaban  $AUC_{INF}$  than those with normal renal function.<sup>20</sup> Several factors identified in previous phase I clinical trials, including age, sex, body weight, and mild-to-moderate renal impairment, were shown to modestly influence apixaban PK and these factors alone do not require any clinical dose adjustment.

Considering the elimination pathways of apixaban and the results of human drug–drug interaction studies, strong/

moderate inhibitors of both CYP3A4 and P-gp were suspected to be an influential covariate. Although they were evaluated in this analysis, the overall results estimated a small change (~17% increase) in exposure. A 99% and 40% increase in AUC was observed when apixaban was co-administered with ketoconazole, a strong CYP3A4/P-gp inhibitor, and diltiazem, a moderate CYP3A4/P-gp inhibitor, respectively.<sup>8,36</sup> The effect of strong CYP3A4/P-gp inducers on clearance was also evaluated in this analysis. Given the sparse sampling strategy and limited data available, the effect was very small and poorly estimated, and, thus, this covariate was removed from the final model. Given the limitation of the PPK data with

respect to these variables, greater emphasis should be placed on the phase I results for the purposes of clinical considerations regarding the potential impact of CYP3A4 and P-gp inhibitors.

The phase III NVAF studies included a dose modification for subjects who met at least two of the following criteria: age  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 1.5$  mg/dL.<sup>3,4</sup> Individually, these factors have been shown to have limited effects on exposure,<sup>20–22</sup> both within the analyses described herein as well as in individual trials. In addition, each of these factors on their own was not expected to result in clinically meaningful change in the benefit–risk profile of apixaban, as confirmed by a subgroup analysis performed in subjects who met only one of the dose-reduction criteria.<sup>37</sup> However, an inherently higher risk of bleeding may be associated with the population of subjects exhibiting at least two of these criteria.<sup>38</sup> Coupled with the knowledge that the combination of at least two of these factors may increase apixaban exposure to a greater extent than a given factor alone, the dosing algorithm for NVAF was designed to address these concerns while maintaining efficacy.<sup>38</sup> The dose-reduction algorithm resulted in a ~27% lower median exposure for the 2.5-mg dose group compared to the 5-mg dose group, with a large overlap between the groups. Most importantly, primary study outcomes (stroke or systemic embolism, International Society of Thrombosis and Haemostasis (ISTH) major bleeding) vs. warfarin were similar in those receiving 2.5 mg b.i.d. or 5 mg b.i.d.<sup>37</sup>

The overall impact of Asian race on apixaban exposure was small. The Asian population represented 15% of the overall population in the analysis dataset, with 9% being Japanese subjects. The CL/F for Asian subjects was 11.9% lower compared to non-Asian subjects. An *ad hoc* analysis of further stratification of Asian race to Japanese, Korean, and other Asians showed that Asian race effects on CL/F of apixaban were 15.1% lower, 3.3% higher, and 4.3% lower in the Japanese, Korean, and other Asian subjects, respectively, relative to non-Asian subjects. The reasons for the differences in the CL/F between Asian and non-Asian subjects are unclear. In spite of no dose-reduction criteria being implemented in the Japan NVAF phase II study, the apixaban PK data in Japanese subjects from the study showed that the global dose-reduction criteria can be used in Japanese NVAF subjects.

A comprehensive PPK model for apixaban in the NVAF population was developed. Apixaban exposure was adequately characterized by a two-compartment PPK model with first-order absorption and first-order elimination. Demographic factors that may affect apixaban PK were identified, however, none resulted in more than a 25% change in apixaban exposure relative to the reference subject, except for severe renal impairment. The effect of Japanese race was small and consistent with the effect of Asian race,<sup>24</sup> and exposure was not meaningfully different from that in the non-Asian population. In summary, these analyses evaluating the impact of factors, such as Asian race, body weight, renal function, and age, support the use of the fixed-dose regimen and dose-modification scheme used in the global phase III clinical trials.

**Supporting Information.** Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website ([www.psp-journal.com](http://www.psp-journal.com)).

**Figure S1.** Posterior predictive check for atrial fibrillation patients following apixaban doses at steady-state.

**Figure S2.** (a) Posterior predictive check for healthy subjects following apixaban dose on day 1. (b) Posterior predictive check for healthy subjects following apixaban doses at steady-state.

**Figure S3.** Posterior predictive check for acute coronary syndrome patients following apixaban dose at steady-state.

**Table S1.** Stage 1 base, full, and final model parameter estimates.

**Table S2.** Covariate parameters of the final model including separate race effects for Japanese, Koreans, and other Asians.

**Table S3.** Predicted apixaban steady-state exposure in patients with NVAF in dose modification subgroups receiving 2.5 mg b.i.d. apixaban.

**Supplemental File S1.** NONMEM code – apixaban stage 1 final model

**Supplemental File S2.** NONMEM code – apixaban stage 2 final model – Asian race

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**Conflict of interest.** A.R., N.T., X.W., T.L., and C.F. are employees of Bristol-Myers Squibb. B.C. and F.L. were employees of Bristol-Myers Squibb at the time of the research. W.B. and R.B. are employees of Pfizer. T.U. is an employee of Bristol Myers Squibb K.K. M.O. is an employee of Pfizer Japan. K.K. and J.N. were paid consultants to Bristol-Myers Squibb.

**Author Contributions.** B.C., K.K., J.N., A.R., N.T., W.B., R.B., X.W., T.L., F.L., T.U., M.O., and C.F. wrote the manuscript. X.W., F.L., and C.F. designed the research. R.B., X.W., and C.F. performed the research. B.C., K.K., J.N., A.R., N.T., W.B., R.B., X.W., T.L., F.L., T.U., M.O., and C.F. analyzed the data.

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