PII-063

Modeling and Simulation to Support Apixaban Dose Recommendation for Thromboembolism Prevention in Pediatric Subjects with Congenital or Acquired Heart Disease Requiring Anticoagulation – SAXOPHONE Study

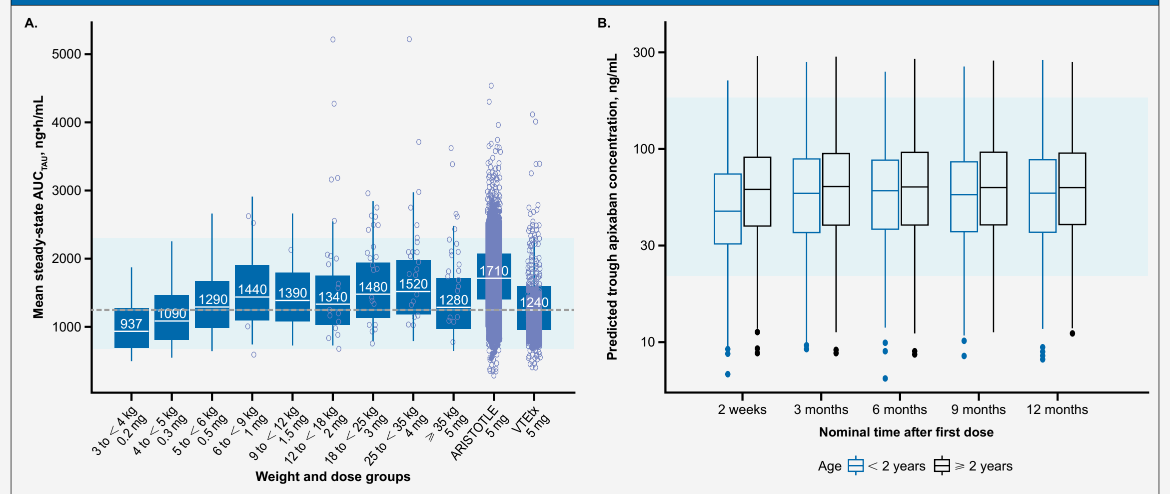
Toni Ajavon-Hartmann,[1] Praneeth Jarugula,[1] Hyunmoon Back,[1] Obinna Obianom,[2] Elizabeth Ludwig,[2] Christina Crevar,[1] David Marchisin,[3] Zhaoqing Wang,[1] Weidong Chen,[1] Bing He,[3] Vidya Perera,[3] Bindu Murthy,[1] Samira Merali[3]

[1]Bristol Myers Squibb, Lawrenceville, NJ, USA; [2]Cognigen, Simulations Plus, Buffalo, NY, USA; [3]Bristol Myers Squibb, Princeton Pike, NJ, USA

Key statement

Simulated apixaban steady-state exposures and trough concentrations with weight-based dose adjustment in pediatric patients were consistent with those in the adult population, suggesting that dose adjustment is accurate

Figure 4. Comparison of (A) Simulated Exposures Between Virtual Pediatric Patients Aged 28 Days to < 18 Years by Weight Tiers and the Adult VTEtx Population and Non-valvular Atrial Fibrillation Study Population (ARISTOTLE)* and (B) Apixaban-Predicted Trough Concentrations from Simulations of the Weight-Based Dose-Adjustment Paradigm in Virtual CAHD Patients Aged < 2 Years and > 2 Years to Assess if the Paradigm was Adequate in Matching Adult Exposures†



A.
Mean steady-state AUC$_{TAU}$, ng•h/mL
937
1090
1290
1440
1390
1340
1480
1520
1280
1710
1240
3 to < 4 kg 0.2 mg
4 to < 5 kg 0.3 mg
5 to < 6 kg 0.5 mg
6 to < 9 kg 1 mg
9 to < 12 kg 1.5 mg
12 to < 18 kg 2 mg
18 to < 25 kg 3 mg
25 to < 35 kg 4 mg
≥ 35 kg 5 mg
ARISTOTLE 5 mg
VTEtx 5 mg
Weight and dose groups
B.
Predicted trough apixaban concentration, ng/mL
2 weeks
3 months
6 months
9 months
12 months
Nominal time after first dose
Age < 2 years ≥ 2 years

Boxes represent the 25th and 75th percentiles. Lines represent the median. Whiskers extend to the 5th and 95th percentiles. Circles represent individual patients.
*Dashed line and shaded region represent the median, 5th percentile, and 95th percentile of exposure in the adult population, respectively.
†Shaded region represents the 5th and 95th percentiles of the target concentrations. Semi-log scale.
AUC$_{TAU}$ = area under the concentration time curve over the dosing interval; CAHD = congenital or acquired heart disease; VTEtx = venous thromboembolism treatment.

Introduction

- Apixaban is an oral, direct, selective factor Xa (FXa) inhibitor[1] and may be a treatment option for venous thromboembolism prevention in children (28 days to < 18 years) with congenital or acquired heart disease (CAHD)
- Pharmacokinetics (PK) and pharmacodynamics (PD) of apixaban have been studied in healthy adults and adult patients[2,3]
  - The oral bioavailability of apixaban is ~50% and increases proportionally with dose (2.5–10 mg) in adults[4]
  - Apixaban has a total clearance of ~3.3 L/h, and an ~12-hour half-life[4]
- Apixaban has been studied using age-appropriate oral formulations using a model developed from 2 Phase 1 and 1 Phase 3 pediatric studies (NCT01195727, NCT01707394, and NCT02369653)
- Dose selection for the pediatric population was targeted to achieve similar plasma exposure as seen in adult patients receiving venous thromboembolism treatment (VTEtx) and in the ARISTOTLE trial population

Objectives

- The objectives of this analysis were to:
  - Characterize the PK of apixaban in pediatric patients with CAHD and evaluate the effect of covariates on apixaban PK
  - Assess whether the current fixed-dose by weight-tiered regimen for apixaban in pediatric patients aged 28 days to < 18 years achieved target exposures
  - Characterize the PK/PD relationship between anti-FXa activity (AXA) and apixaban concentration in pediatric patients with CAHD
  - Perform an exploratory PK/PD analysis of inhibition of apparent FXa levels by apixaban, stratified by age group
  - Assess the timing of apixaban dose changes in response to growth and changes in age and weight in pediatric patients

Methods

POPULATION PK MODEL

- Data from a Phase 2 pediatric study (SAXOPHONE; NCT02981472, N = 124) were used to update a previously developed population PK (PPK) model via a nonlinear mixed-effects population estimation algorithm in NONMEM (Icon, Dublin, Ireland) (**Figure 1**)
  - Randomization was stratified by age with 3 groups (28 days to < 2 years, 2 years to < 12 years, and 12 years to < 18 years)

Figure 1. Schematic Overview of PPK Model Development for Apixaban

Base Model

- A previously developed 2-compartment model with first-order absorption, dose-dependent bioavailability, and other covariates as listed below was used as the initial base model. The model was re-estimated after including the data from Study CV185362. The model included the effects of the following covariates on PK parameters:
  - Ka: Age group (9 months to 18 years), pediatric patients with ALL or LL at risk of VTE treated with asparaginase
  - F1: Dose and neonatal sprinkle capsule formulation
  - CL/F: Body weight, Johnson MF with FBirth
  - Vc/F: Body weight, pediatric patients with ALL or LL at risk of VTE treated with asparaginase
  - Q/F: Age

↓

Full Covariate Model

- The effects of subject type (pediatric patients at risk of VTE or ATE, pediatric patients with ALL or LL at risk of VTE treated with asparaginase, and pediatric patients with CAHD at risk of VTE) were evaluated on Ka, CL/F, and Vc/F
- All other covariates included in the base model remained in the full model

↓

Final Model

- A backward elimination process of the covariate effects of subject type was used to retain only significant covariates from the full model to develop the final model. All other covariates in base and full models remained in the final model
- The following covariates remained in the final model:
  - Ka: Age group (9 months to < 18 years), pediatric patients with ALL or LL at risk of VTE treated with asparaginase
  - F1: Dose and sprinkle capsule formulation
  - CL/F: Body weight, Johnson MF with FBirth, pediatric patients with CAHD at risk of VTE
  - Vc/F: Body weight
  - Q/F: Age

ALL = acute lymphoblastic leukemia; ATE = atrial thromboembolism; CAHD = congenital or acquired heart disease; CL/F = apparent clearance; F1 = relative bioavailability; FBirth = fraction of adult activity at birth; Ka = first-order absorption rate constant; LL = lymphoblastic leukemia; MF = maturation function; PK = pharmacokinetic; PPK = population pharmacokinetic; Q/F = apparent intercompartmental clearance; Vc/F = apparent central volume of distribution; VTE = venous thromboembolism.

MODEL-BASED STOCHASTIC SIMULATIONS

- Stochastic simulations were performed to assess whether exposures from apixaban doses in ~1000 virtual patients with CAHD per weight tier (9 groups) aged 28 days to < 18 years matched adult exposures
  - Age and sex were randomly assigned, and body weight was generated by random sampling from the Centers for Disease Control and Prevention growth chart[5]
- The final PPK model was used to simulate steady-state area under the concentration time curve over the dosing interval (AUC_{TAU}) for a given fixed-dose by weight tier regimen
  - Timing of dose adjustment in response to weight gain was assessed in graphical analysis and by using stochastic simulations
- The simulated steady-state AUC_{TAU} in pediatric patients grouped by weight tiers was compared with the target median steady-state of 1240 ng•h/mL observed in adult patients receiving apixaban 5 mg twice daily (BID) for VTEtx and of 1710 ng•h/mL observed in the ARISTOTLE study population receiving apixaban 5 mg BID

PK/PD ANALYSIS

- A linear mixed-effects analysis was performed to estimate the slope of the relationship between observed apixaban concentration and observed AXA activity level
  - AXA activity = slope × apixaban concentration
- A linear mixed-effects model was also assessed to identify interindividual variability (IIV) in the slope parameter
- Model evaluation was conducted using prediction-corrected visual predictive check (pcVPC) methodology and bootstrap procedures
- A graphical analysis of inhibition of chromogenic factor X versus apixaban concentration was performed by weight group

Results

PPK ANALYSIS

- The final apixaban PPK model was a 2-compartment model with first-order absorption, dose-dependent relative bioavailability (F1), and first-order elimination (**Table 1**)
  - IIV was estimated in first-order absorption rate constant (Ka), apparent total clearance (CL/F), apparent central volume of distribution (Vc/F), apparent intercompartmental clearance (Q/F), and apparent peripheral volume of distribution using an exponential variance model
  - Residual variability was estimated using an additive variance model on log concentrations
  - Apixaban CL/F was modestly lower (~21%) in pediatric patients with CAHD compared with adults
  - Apixaban Vc/F was also modestly lower (16.5%) in pediatric patients with CAHD compared with adults
  - All parameters in the final model were estimated with good precision (% relative standard error [RSE] ≤ 21%) for fixed- and random-effect parameters

Table 1. Parameter Estimates and Standard Errors for the Final Apixaban PPK Model for the Study

Parameter Label	Parameter	Estimate* (%RSE)†	IIV Estimate* (%RSE)†
Ka: First-order absorption rate constant (1/h)	θ_1	0.525 (7.29)	0.632 (11.3)
CL/F: Apparent total clearance (L)	θ_2	4.7 (2.91)	0.386 (5.67)
Vc/F: Apparent central volume of distribution (L)	θ_3	32.5 (3.59)	0.268 (18.9)
Q/F: Apparent intercompartmental clearance (L/h)	θ_4	1.43 (9.76)	0.994 (13.6)
Vp/F: Apparent peripheral volume of distribution (L)	θ_5	20.8 (9.87)	0.669 (2.33)
F1: Shape factor for reduction in F1 at dose > 2.5 mg (−)	θ_6	0.89 (10.5)	
F1: LOGIT max reduction in F1 at dose > 2.5 mg (−)	θ_7	−0.457 (7.54)	
Vc/F: Exponent of (WT/67.4) for Vc/F (−)	θ_8	0.882 (2.9)	
CL/F: Exponent of (WT/67.4) for CL/F (−)	θ_9	0.68 (3.61)	
Q/F: Exponent of (AGE/25) for Q/F (−)	θ_{10}	0.751 (8.39)	
Ka: Effect of age 9 months to 18 years on Ka (−)	θ_{11}	1.23 (19.1)	
CL/F: Non-renal ontogeny function – shape parameter (−)	θ_{12}	0.83 FIXED	
CL/F: Non-renal ontogeny function - AGE50 (years)	θ_{13}	0.244 FIXED	
F1: Relative F1 for a sprinkle capsule formulation (−)	θ_{14}	1.1 FIXED	
CL/F: Non-renal ontogeny function FBirth (−)	θ_{15}	0.05 FIXED	
Ka: Effect of pediatric patient with ALL at risk of VTE on Ka (−)	θ_{16}	−0.988 (11.6)	
CL/F: Effect of pediatric patient with ALL at risk of VTE on Ka (−)	θ_{17}	−0.185 (20.2)	
Covariance between IIV of Vc/F and CL	$\omega_{3.2}$	0.289 (10.2)	
Covariance between IIV of Vc/F and Vp/F	$\omega_{5.4}$	1.03 (10.7)	
Additive RV on Log conc (−)	$\sigma_{1.1}$	0.328 (0.968)	

The labels for effect of pediatric subjects with ALL on Ka or Vc/F refer to pediatric subjects with ALL or lymphoblastic lymphoma at risk of VTE treated with asparaginase in Study CV185155. See parameter-covariate relationships.

*Random effect and residual error parameter estimates are shown as standard deviation for diagonal and off-diagonal elements.
†%RSE is the relative standard error (standard error as a percentage of estimate).
ALL = acute lymphoblastic leukemia; AGE/25 = age of reference subject (25 years); CAHD = congenital or acquired heart disease; FBirth = fraction of adult activity at birth; FFORM = θ_{14} fixed to 1.1 for subjects receiving sprinkle capsule formulation (0.1 mg) and 1 for others; IIV = interindividual variability; PED9M = 0 for subjects aged < 9 months and ≥ 18 years; PPK = population pharmacokinetic; PTYPE = pediatric subject subset; RSE = relative standard error; RV = residual variability; TVF1 = relative bioavailability; VTE = venous thromboembolism; WT/67.4 = weight of reference subject (67.4 kg).

- Parameter-covariate relationships:

$$Ka_i = (\theta_1 \bullet (1 + PED9M \bullet \theta_{11})) \bullet e^{\theta_{16}\,(if\ PTYPE=ALL)} \bullet e^{\eta_{Ka,i}}$$

$$CL/F_i = \theta_2 \bullet \left(\frac{BBWT_i}{67.4}\right)^{\theta_9} \bullet \left(F_{Birth} + \frac{(1 - F_{Birth}) \bullet Age_i^{\theta_{12}}}{Age_i^{\theta_{12}} + \theta_{13}^{\theta_{12}}}\right) \bullet e^{\theta_{17}\,(if\ PTYPE=CAHD)} \bullet e^{\eta_{CL,i}}$$

$$Vc/F_i = \theta_3 \bullet \left(\frac{BBWT_i}{67.4}\right)^{\theta_8} \bullet e^{\eta_{Vc,i}}$$

$$Q/F_i = \theta_4 \bullet \left(\frac{AGE_i}{25}\right)^{\theta_{10}} \bullet e^{\eta_{Q,i}}$$

$$Vp/F_i = \theta_5 \bullet e^{\eta_{VP,i}}$$

$$TVF1_i = 1, When\ Dose_i \leq 2.5\ mg$$

$$TVF1_i = \left\{1 - \left(\frac{exp(\theta_7)}{1 + exp(\theta_7)} \bullet \left(\frac{DOSE_i - 2.5}{47.5}\right)^{\theta_6}\right)\right\} \mid Dose_i > 2.5\ mg$$

$$F1_i = TVF1_i \bullet \theta_{14} \bullet FFORM$$

- Apixaban CL/F increased with age, reaching adult clearance values in adolescents aged ≥ 12 years (data not shown)[6]
- Observed and predicted apixaban concentrations correlated well for the overall data (**Figure 2A**)
- Conditional weighted residuals were randomly distributed around 0 over the duration of the study and over the range of population predictions (**Figure 2B**)
- The pcVPC for pediatric patients with CAHD at risk of VTE indicated medians and 5th and 95th percentiles of the simulated profiles were concordant with observed data, suggesting that model structure and covariate effects adequately described observed data (**Figure 3**)

DOSE CONFIRMATION IN PEDIATRIC PATIENTS

- Stochastic simulations of proposed fixed doses by weight tiers demonstrated that apixaban steady-state exposures in pediatric patients were consistent with exposures observed in adult patients receiving apixaban 5 mg BID (**Figure 4A**)

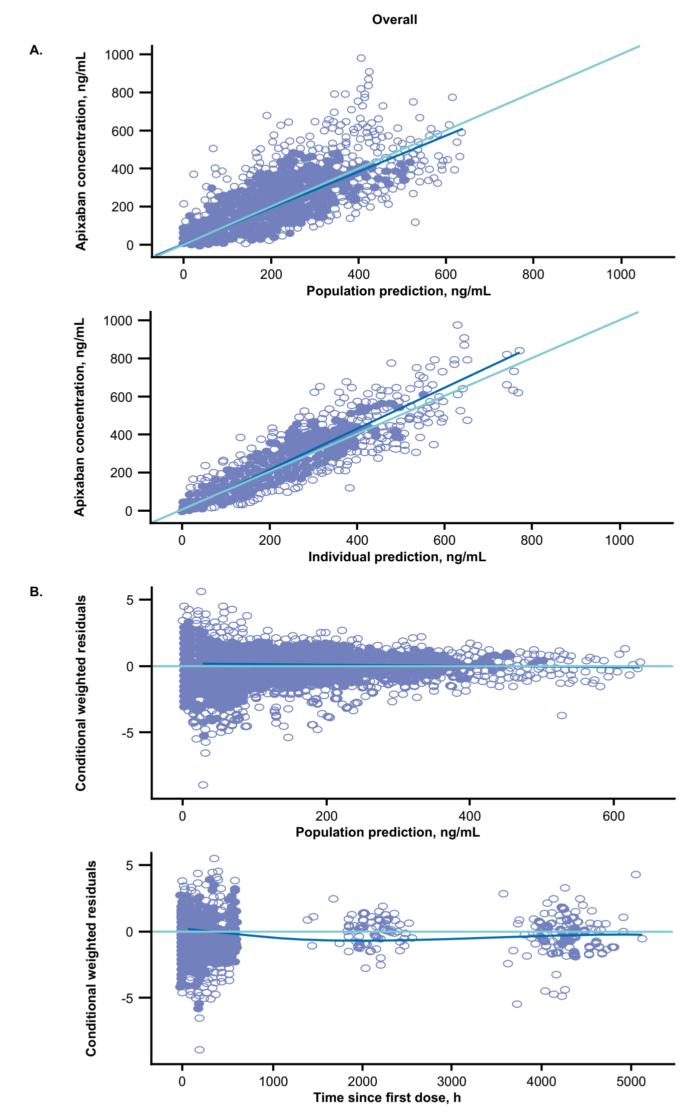
DOSE ADJUSTMENT FOR WEIGHT TIER CHANGE

- Simulated apixaban trough concentrations with weight-based dose adjustment in virtual pediatric patients aged 28 days to < 18 years were consistent with concentrations in the adult population over 12 months, suggesting that the dose adjustment is accurate and may be used for future studies (**Figure 4B**)

PK/PD ANALYSIS

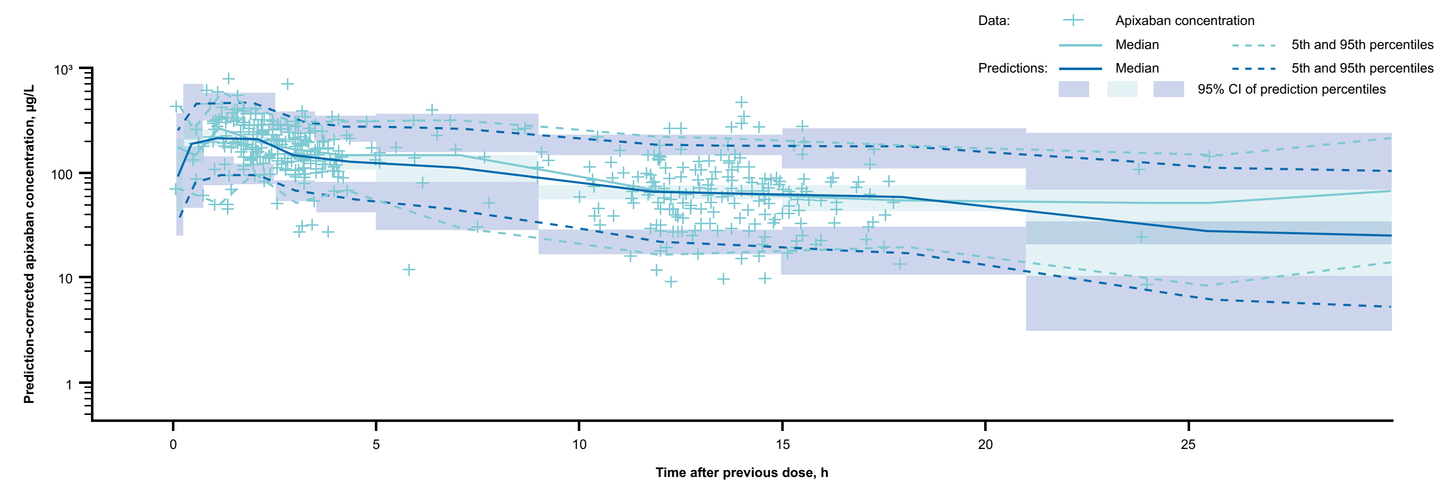
- The apixaban PK–AXA relationship was characterized well using both linear regression and linear mixed-effects modeling
  - The linear mixed-effects model was chosen to characterize the PK-AXA relationship due to a lower Akaike information criterion value (4437 vs 4531) and the linear mixed-effects model resulting in estimation of a very small IIV (~5.3%) on the slope parameter (**Figure 5**)
  - Percent change from baseline in FX level decreased with increasing apixaban concentration (**Figure 6**)

Figure 2. Goodness-of-Fit Plots for the Apixaban Final PPK Model, Overall Data: (A) Apixaban Concentration* and (B) Conditional Weighted Residuals†



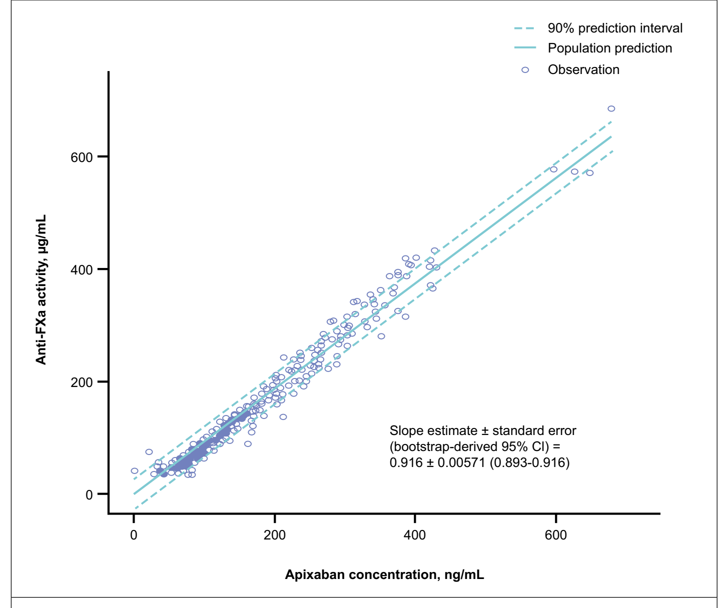
*Teal, line of identity; blue, locally estimated scatterplot smoothing line.
†Teal, y = 0; blue, locally estimated scatterplot smoothing line.
PPK = population pharmacokinetic.

Figure 3. pcVPC for Pediatric Patients with CAHD at Risk of VTE



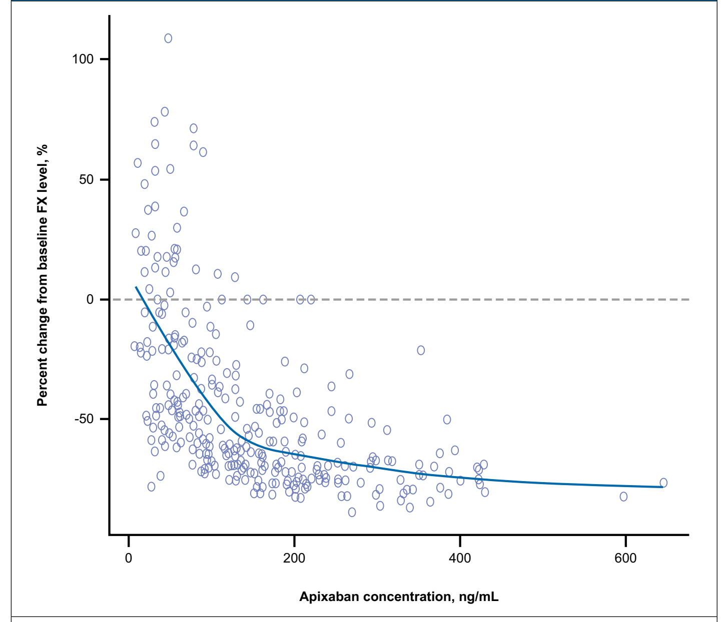
Medians and percentiles are plotted at the midpoint of each time after previous dose interval.
CAHD = congenital or acquired heart disease; CI = confidence interval; pcVPC = prediction-corrected visual predictive check; VTE = venous thromboembolism.

Figure 5. Visual Predictive Check of the Final Apixaban PK/PD Model



CI = confidence interval; FXa = coagulation factor Xa; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 6. Relationship Between Apixaban Concentration and Percent Change from Baseline in Chromogenic FX



The blue line is the locally estimated scatterplot smoothing line.
FX = coagulation factor X.

Discussion and Conclusions

- **A 2-compartment model with first-order absorption, dose-dependent F1, and first-order elimination described apixaban PK in pediatric patients with CAHD at risk of VTE, where CL/F increased with body weight and was ~21% lower in pediatric patients than adults**
  - **Vc/F also increased with body weight; however, the effects on pediatric patients with CAHD at risk of VTE and pediatric patients at risk of VTE or atrial thromboembolism were small (reductions of 16.5% and 2%, respectively)**
- **Apixaban PK/PD was well characterized by a linear mixed-effects regression model fixed to a zero intercept and a slope parameter of 0.916**
- **FX decreased with increasing apixaban concentration**
- **Exposures for dosing regimens in pediatric patients with CAHD matched those in adults**
- **Apixaban dose adjustments in response to increasing body weight maintained exposures in the desired range**

References: 1. Wong PC et al. *J Thromb Haemost.* 2008;6:820-829. 2. Frost C et al. *Br J Clin Pharmacol.* 2013;75:476-487. 3. Cirincione B et al. *CPT Pharmacometrics Syst Pharmacol.* 2018;7:728-738. 4. Eliquis® (apixaban) [US Prescribing Information]. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer Inc; 2021. 5. Centers for Disease Control and Prevention. CDC Growth Charts. Updated December 15, 2022. Accessed February 15, 2023. https://www.cdc.gov/growthcharts/cdc_charts.htm. 6. Garonzik SM et al. *Circulation.* 2021;144:A10571.

Acknowledgments: This study was sponsored by the Bristol Myers Squibb–Pfizer Alliance. Professional medical writing and editorial assistance was provided by Joaquin Jaramillo, MD, of Caudex, and was funded by the Bristol Myers Squibb–Pfizer Alliance. Kristin Burns, Andrew Glatz, Christoph Male, Paul Monagle, Mark Payne, and Olivia Wheaton contributed to clinical data generation. Poster produced in collaboration with the National Heart, Lung and Blood Institute (NHLBI) and Pediatric Heart Network (PHN).

Disclosures: TA-H, PJ, HB, CC, DM, ZW, WC, VP, BM, and SM are paid employees of Bristol Myers Squibb, one of the study sponsors. OO and EL are paid employees of Simulations Plus and were paid consultants to Pfizer and Bristol Myers Squibb in connection with the development of this poster. BH is a paid employee and stockholder of Bristol Myers Squibb, one of the study sponsors.

Presented at the American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2023 Annual Meeting • March 22–24, 2023 • Atlanta, GA, USA

Presenting author: Antoinette.Ajavon-Hartmann@bms.com