PII-070

Pharmacokinetic/Pharmacodynamic Analysis of Apixaban to Determine Dosing Regimens for Pediatric Patients with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma Treated with Asparaginase: Analysis from the PREVAPIX Study

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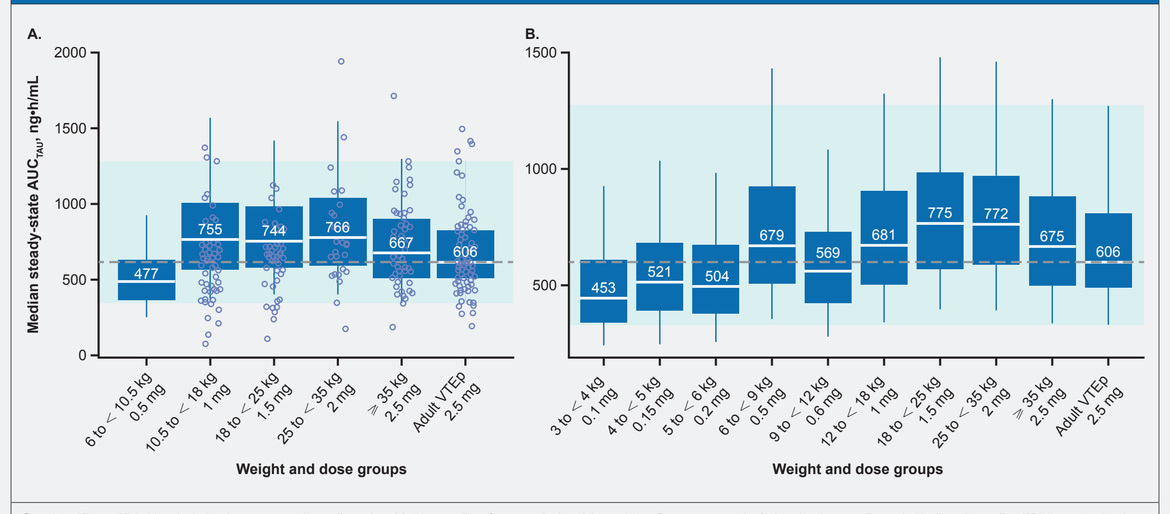
Key statement

Apixaban steady-state exposures in pediatric patients were consistent with exposures observed in adults, supporting target exposures for pediatric patients aged 1 year to < 18 years, and supporting dose extrapolation for pediatric patients aged 28 days to < 1 year

Figure 4. (A) Dose Confirmation: Comparison of Exposure Between Pediatric Patients Aged 1 to < 18 Years and the Adult VTEp Population from the AMPLIFY-EXT Study, and (B) Dose Recommendation: Comparison of Exposure Between Pediatric Patients Aged 28 Days to < 18 Years by Weight Tiers and the Adult VTEp Population from the AMPLIFY-EXT Study



Grey dotted line and light blue shaded regions represent the median, 5th and 95th percentiles of exposure in the adult population. Boxes represent the 25th and 75th percentiles and white lines the median. Whiskers extend to the 5th and 95th percentiles. Circles represent individual patients.

AUC_{TAU} = area under the concentration time curve over the dosing interval; VTEp = venous thromboembolism prevention.

Introduction

- Apixaban is an orally active, direct selective inhibitor of coagulation factor Xa (FXa),[1] and may be a treatment option for prevention of venous thromboembolism (VTE) in children with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL)
- The pharmacokinetics (PK) and pharmacodynamics (PD) of apixaban have previously been studied in healthy adults and adult patients[2,3]
  - Apixaban has an oral bioavailability of ~50%, which 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 in adults[4]
- Apixaban has been studied using age-appropriate oral formulations using a model developed from 2 Phase 1 pediatric studies (NCT01195727, NCT01707394)
- Dose selection for the pediatric population was targeted to achieve similar plasma exposure as seen in adult patients receiving VTE prevention (VTEp) in pediatric patients

Objectives

- To characterize apixaban PK and PK/PD relationship between anti-factor Xa (AXA) and apixaban concentration, in pediatric patients with ALL/LL treated with asparaginase
- To assess whether a fixed-dose by weight-tiered regimen for apixaban in pediatric patients aged 1 to < 18 years achieved target exposures
- To identify the optimal apixaban dose for achieving a target apixaban steady-state in patients with cancer aged 28 days to < 1 year

Methods

POPULATION PK (PPK) MODEL

- Data from a Phase 3 pediatric study (NCT02369653) were used to update a previously developed PPK model and to assess the covariate effect of patient type on PK parameters, while retaining previous covariates (**Figure 1**)

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 a base model. The model was re-estimated after including the data from Study CV185155. The model included the effects of the following covariates on PK parameters:
  - Ka: Age group (9 months to < 18 years)
  - F1: Dose and neonatal sprinkle capsule formulation
  - CL/F: Body weight, Johnson MF with FBirth
  - Vc/F: Body weight
  - Q/F: Age

Full Covariate Model

- The effects of subject type (pediatric patient at risk of VTE or ATE, pediatric patient with ALL or LL treated with asparaginase 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 final model for Study CV185155 included the effects of the following covariates on PK parameters:
  - Ka: Age group (9 months to < 18 years), pediatric patient with ALL or LL treated with asparaginase at risk of VTE
  - F1: Dose and neonatal sprinkle capsule formulation
  - CL/F: Body weight, Johnson MF with FBirth
  - Vc/F: Body weight, pediatric patient with ALL or LL treated with asparaginase at risk of VTE
  - Q/F: Age

ALL = acute lymphoblastic leukemia; ATE = atrial thromboembolism; CL/F = apparent clearance; F1 = relative bioavailability; FBirth = fraction of adult activity at birth; Ka = first-order absorption rate constant; LL = lymphoblastic lymphoma; 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 STIMULATIONS

- Stochastic simulations were performed to identify doses of apixaban that matched adult exposures in ~5000 virtual pediatric patients aged 1 to <18 years
  - Age and sex were randomly assigned, and body weight was generated by random sampling from the Centers of 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
- The simulated steady-state AUC_{TAU} in pediatric patients grouped by weight tiers was compared with the target median steady-state of 606 ng•h/mL observed in the adult VTEp population receiving apixaban 2.5 mg twice daily (BID)
- Model-based stochastic simulations were also utilized to support dose extrapolation to pediatric patients with cancer aged 28 days to < 1 year

PK/PD ANALYSIS

- A simple linear regression analysis was performed to estimate the slope on the observed apixaban concentration versus the 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 performed using prediction-corrected visual predictive check (pcVPC) methodology and bootstrap procedures

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
- IIV was estimated in 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 (Vp/F) using an exponential variance model
- Residual variability was estimated using an additive variance model on log concentrations
- In addition to the covariate effects present in the base model, the effects of pediatric patients with ALL/LL at risk of VTE treated with asparaginase on Ka and Vc/F were found to be significant and were included in the final model
  - Apixaban Ka was ~80% lower in pediatric patients with ALL/LL compared with adult patients or pediatric patients at risk of VTE or ATE
  - Apixaban Vc/F was ~26% lower in pediatric patients with ALL/LL compared with adults
- All parameters in the final model were estimated with good precision (% relative standard error < 22% for fixed- and random-effect parameters; **Table 1**)

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

Parameter Label	Parameter	Estimate* (%RSE)†	IIV Estimate* (%RSE)†
Ka: First-order absorption rate constant (1/h)	θ_1	0.527 (6.85)	0.604 (11.0)
CL/F: Apparent total clearance (L)	θ_2	4.70 (2.87)	0.397 (5.35)
Vc/F: Apparent central volume of distribution (L)	θ_3	32.7 (3.38)	0.277 (18.9)
Q/F: Apparent intercompartmental clearance (L/h)	θ_4	1.45 (9.18)	0.938 (15.3)
Vp/F: Apparent peripheral volume of distribution (L)	θ_5	21.0 (9.12)	1.10 (8.90)
F1: Shape factor for reduction in F1 at dose > 2.5 mg (−)	θ_6	0.889 (9.84)	
F1: LOGIT max reduction in F1 at dose > 2.5 mg (−)	θ_7	−0.461 (6.98)	
Vc/F: Exponent of (WT/67.4) for Vc/F (−)	θ_8	0.840 (1.46)	
CL/F: Exponent of (WT/67.4) for CL/F (−)	θ_9	0.669 (3.35)	
Q/F: Exponent of (AGE/25) for Q/F (−)	θ_{10}	0.719 (9.26)	
Ka: Effect of age 9 months to 18 years on Ka (−)	θ_{11}	1.53 (21.7)	
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 patients with ALL on Ka (−)	θ_{16}	−1.67 (10.4)	
Vc/F: Effect of pediatric patients with ALL on Vc/F (−)	θ_{17}	−0.564 (20.8)	
Covariance between IIV of Vc/F and CL	$\omega_{3.2}$	0.317 (9.80)	
Covariance between IIV of Vc/F and Vp/F	$\omega_{5.4}$	0.957 (12.2)	
Additive RV on Log conc (−)	$\sigma_{1.1}$	0.316 (0.993)	

The labels for effect of pediatric patients with ALL on Ka or Vc/F refer to pediatric patients with ALL or LL 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; AGE50 = patient age (50); AGE/25 = age of reference subject (25 years); F1 = relative bioavailability; 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; LL = lymphoblastic lymphoma; 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:

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

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

$$Vc/F_i = \theta_3 \bullet \left(\frac{BBWT_i}{67.4}\right)^{\theta_8} \bullet e^{\theta_{17\,(if\;PTYPE=ALL)}} \bullet e^{\eta_{Vc,i}}$$

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

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

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

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

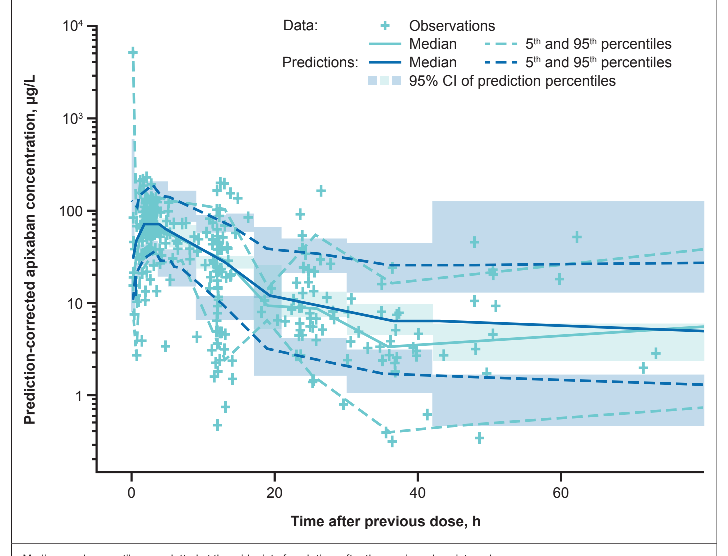
$$F1_i = TVF1_i \bullet \theta_{14} \bullet FFORM$$

- Goodness-of-fit plots indicated good model performance (**Figure 2A** and **2B**)
- The pcVPC for pediatric patients with ALL/LL at risk of VTE suggested that model structure and covariate effects adequately described observed data, as indicated by the 5th, median, and 95th percentiles lying within the 95% confidence interval of the predicted profile (**Figure 3**)
  - Similar results were found for healthy adults, and for pediatric patients at risk of VTE or atrial thromboembolism (ATE; data not shown)
- Apixaban CL/F increased with age, reaching adult clearance values in adolescents aged ⩾ 12 years[6] (data not shown)

DOSE CONFIRMATION AND EXTRAPOLATION IN PEDIATRIC PATIENTS

- Stochastic simulations of proposed fixed doses by weight tiers showed that apixaban steady-state exposures in pediatric patients were consistent with exposures observed in the adult VTEp population receiving apixaban 2.5 mg BID, thus confirming that the approach used to provide target exposures for pediatric patients aged 1 year to < 18 years was accurate (**Figure 4A**)
- A comparison of simulated exposures in patients aged 28 days to < 18 years with the adult VTEp population receiving apixaban 2.5 mg BID supported dose extrapolation for patients aged 28 days to < 1 year and new proposed fixed dose by weight tier regimens for patients aged 1 year to < 18 years (**Figure 4B**)

Figure 3. Prediction-Corrected Visual Predictive Check for Pediatric Patients with ALL/LL at Risk of VTE Using the Final Model



Medians and percentiles are plotted at the midpoint of each time after the previous dose interval.

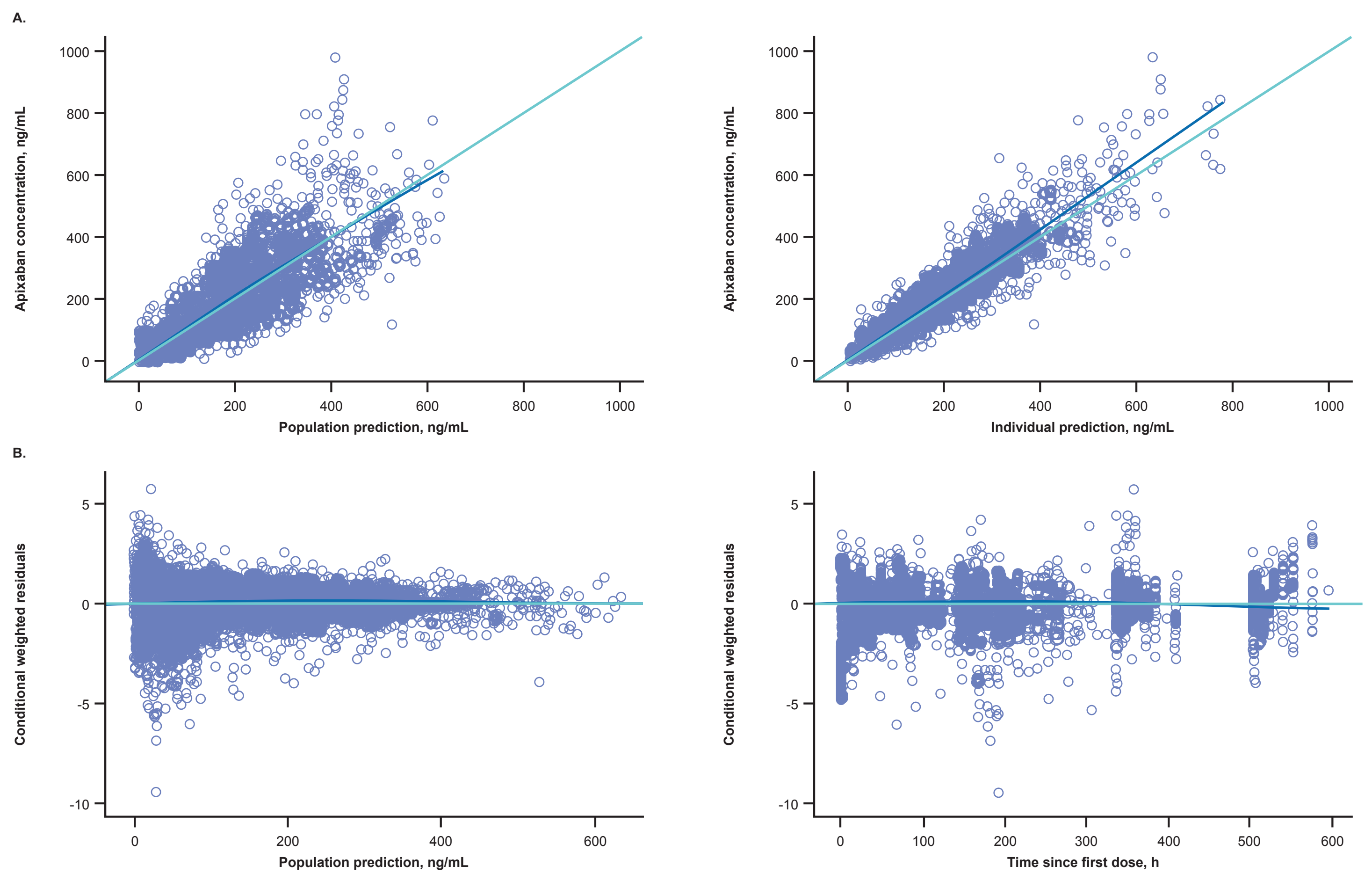
The plots for the healthy adult patients and pediatric patients with ALL or LL at risk of VTE treated with asparaginase were truncated at 80 hours for visualization purposes only (time period where majority of the data occurred).

ALL = acute lymphoblastic leukemia; CI = confidence interval; LL = lymphoblastic lymphoma; VTE = venous thromboembolism.

PK/PD ANALYSIS

- The apixaban PK–AXA relationship was characterized well using both linear regression and linear mixed-effects modeling
  - The linear regression model was chosen to characterize the PK/PD relationship due to a lower Akaike information criterion value (1163.663 vs 1169.366) and the linear mixed effects model resulting in estimation of a very small IIV (~4.34%) in the slope parameter
- The final model was evaluated using a visual predictive check, which confirmed that the model adequately captured the relationship and variability within the data set (**Figure 5**)

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

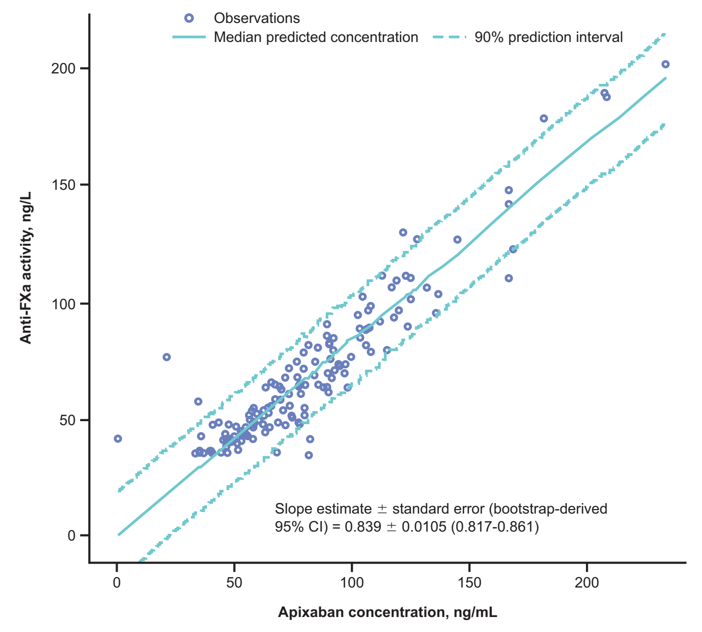


*Teal, line of identity; blue, locally estimated scatterplot smoothing line.

†Teal, y = 0; blue, locally estimated scatterplot smoothing line.

PPK = population pharmacokinetic.

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



FXa = coagulation factor Xa; PD = pharmacodynamic; PK = pharmacokinetic.

Discussion and Conclusions

- **Apixaban PK in pediatric patients with ALL/LL at risk of VTE treated with asparaginase was described using a 2-compartment model with first-order absorption, dose-dependent F1, and first-order elimination (including covariates Ka, F1, CL/F, Vc/F, and Q/F)**
  - **In pediatric patients with ALL/LL at risk of VTE treated with asparaginase, apixaban Ka was ~80% lower than adult patients or pediatric patients at risk of VTE or ATE, and apixaban Vc/F was ~26% lower than adult patients; apixaban CL/F increased with body weight**
- **Apixaban PK/PD in pediatric patients with ALL/LL at risk of VTE treated with asparaginase was well characterized by a simple linear regression model with zero intercept and a slope parameter**
- **Steady-state exposures in pediatric patients were consistent with adult exposures, and weight-tiered doses were predicted to achieve steady-state exposures similar to those of adults receiving apixaban 2.5 mg BID for prevention of VTE**

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.

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