Pharmacometrics Review

NDA:	20883 S8-014
DRUG NAME:	ARGATROBAN INJECTION
DOSAGE STRENGTH:	100 mg/mL
APPLICANT:	ENCYSIVE Pharmaceuticals Inc.,
REVIEWER:	Rajanikanth Madabushi, Ph.D.
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SUBMISSION DATE:	Aug 16, 2007
ADDENDUM TO OCP REVIEW:	May 02, 2005

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Executive Summary

The applicant submitted the supplement S014 for NDA 20883 for Argatroban Injection which included PK/PD data from 6 additional pediatric patients to explore the potential for dosing instructions for prophylaxis or treatment of thrombosis in pediatric patients with heparin-induced thrombocytopenia based on the concentration-aPTT relationship developed earlier (see DFSed review Date: 12/15/2005) .

Argatroban plasma concentrations and aPTT measurements in 15 pediatric patients over a wide concentration range of (100 ng/mL – 5000 ng/mL) were available. The key findings are:

1. The concentration-aPTT relationships with and without the 6 additional patients are similar. The previous OCP recommended dosing scheme is supported by the new data.
2. Pharmacokinetics in pediatric patients was reasonably well characterized. Body weight was found to be a significant predictor of clearance. The estimated clearance in a typical 20 kg pediatric patient was 3.1 L/hr (95% CI: 2.2 L/hr - 4.0 L/hr). The mean clearance in four patients with elevated serum bilirubin levels, most likely secondary to cardiac complications was 0.8 L/hr.
3. Effect on aPTT was found to be concentration dependent and the concentration-aPTT relationship was found to be similar in pediatric patients and healthy adults.
4. For pediatric patients an initial dose of 0.75 µg/kg/min of Argatroban injection dose as a continuous infusion is recommended. Dosage adjustment as clinically indicated in step sizes of 0.25 µg/kg/min every 2-4 hr is also recommended. Pediatric patients with hepatic impairment/elevated bilirubin levels most likely secondary to cardiac complications should be dosed 1/4th of the normals.

Recommendation:

The following statements under the " Clinical Pharmacology " and "Dosage and Administration" section of the label are recommended based on the argatroban concentration-response (aPTT) relationship in pediatric patients:

CLINICAL PHARMACOLOGY
SPECIAL POPULATION
Pediatric: Pharmacokinetic parameters of Argatroban were characterized in a population pharmacokinetic/pharmacodynamic analysis with sparse data from [redacted] 15 seriously [redacted] ill pediatric patients [redacted]. Clearance in pediatric patients [redacted] 0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Four (4) pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels. (See DOSAGE AND ADMINISTRATION, *Pediatric HIT/HITTS Patients*.)

Pediatric HIT/HITTS Patients: Initial Dosage: [redacted]

Monitoring Therapy: In general, therapy with Argatroban is monitored using the aPTT. Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1 to 3 hours following initiation of Argatroban in patients without hepatic impairment (see PRECAUTIONS, Hepatic Impairment). Dose adjustment may be required to attain the target aPTT. Check the aPTT 2 hours after initiation of therapy and any dose change to confirm that the patient has attained the desired therapeutic range.

Dosage Adjustment: [redacted]

Background:

The Office of Clinical Pharmacology based on the PK/PD analysis recommended the following in the review of sNDA 20-883 in December 2005: *"The Office of Clinical Pharmacology and Biopharmaceutics, Division of Clinical Pharmacology V, has reviewed the information and data included in sNDA 20-883 package submitted on 29 June 2005 and has found that the there is sufficient pediatric information and data to update the package insert of Argatroban Injection."*

Subsequently, as per sponsor's request, a teleconference was granted by the Agency to discuss sponsor's further perusal of the exclusivity for the pediatric supplement. In the meeting the sponsor reported that 7 additional patients had been enrolled following the SE8-014 submission. The Agency asked the sponsors to submit this additional data to corroborate the dosing recommendations.

The present review pertains to the pharmacometric analyses performed on the full data which includes the 6 additional subjects (with PK/PD data available) enrolled since the previous submission.

Question Based Review

1. Is the pharmacokinetics well characterized in pediatrics?

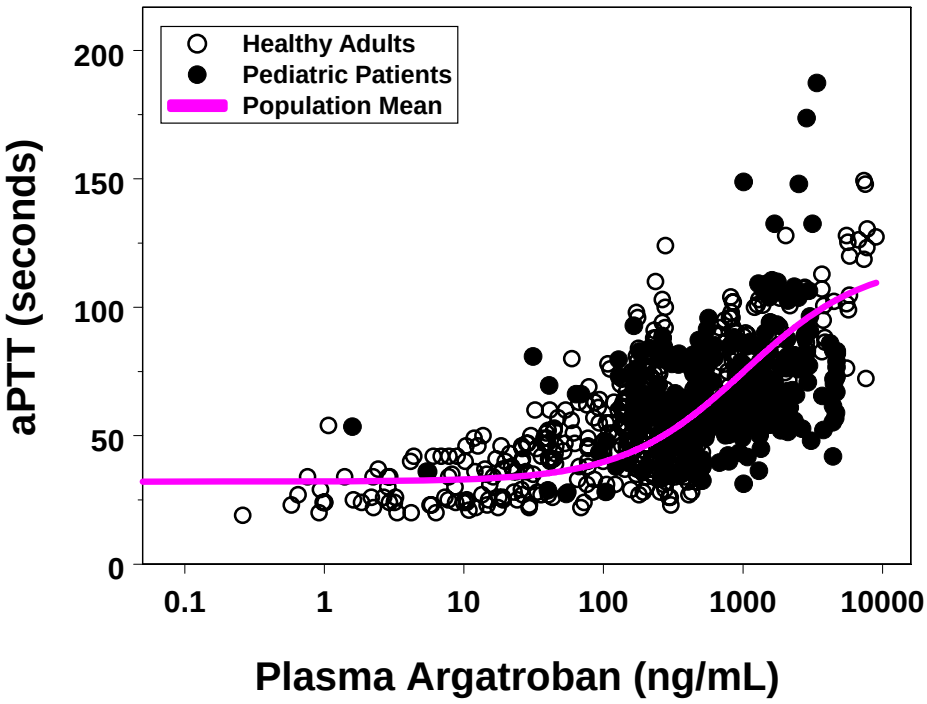
- The most important pharmacokinetic parameter necessary for deriving a dosing regimen is systemic clearance. In the present study, plasma samples at steady-state were collected over a range of doses in 15 seriously ill pediatric patients (166 data points). The concentration - time data were adequate to estimate the systemic clearance reliably.
- The population clearance in pediatric patients (0.15 L/hr/kg) was approximately 50% of healthy adults (0.3 L/hr/kg). This difference is probably due to the fact that, pediatric patients are seriously ill with several co-morbidities.

- The estimated clearance in a typical 20 kg pediatric patient was 3.1 L/hr with 95% confidence intervals ranging from 2.2 L/hr to 4.0 L/hr. Body weight was a significant predictor of clearance. Age was not found to be a predictor for clearance after adjusting for elevated serum bilirubin status.
- The mean clearance in four patients with elevated serum bilirubin levels secondary to cardiac complications was 0.6 L/hr.

2. Is the exposure-response relationship well characterized in pediatrics?

- Plasma concentration-anticoagulant response (aPTT) data in 15 pediatric patients (329 data points) was collected over a wide range of concentrations (100 – 5000 ng/mL).
- Effect on aPTT was found to be concentration dependent as shown in Figure 1. The concentration-aPTT relationship was found to be similar in pediatric patients and healthy adults (Figure 1).
- The estimated mean maximum aPTT for pediatric patients was 84 seconds with a confidence interval of 67 seconds to 102 seconds.
- The estimated mean plasma concentration required to produce 50% of the maximum effect was 959 ng/mL with a 95% confidence interval of 536 ng/mL to 1382 ng/mL.

Figure 1: Similar concentration dependent aPTT relationship in pediatric patients and adults.


Healthy Adults
Pediatric Patients
Population Mean
aPTT (seconds)
200
150
100
50
0
0.1
1
10
100
1000
10000
Plasma Argatroban (ng/mL)

3. What is the optimal dosing regimen for pediatrics?

The recommended dosage regimen is based on the argatroban concentration-response (aPTT) relationship:

- Using the plasma concentration-aPTT relationship and taking into account the between-patient variability associated with the estimated parameters, different dosing scenarios were explored using simulations in order to obtain an optimal regimen for pediatric patients with normal bilirubin levels.
- The simulations revealed a starting dose of 0.75 µg/kg/min in pediatric patients was reasonably comparable to 2 µg/kg/min in adults with about 58% of the subjects reaching a target aPTT of 1.5 to 3 times the baseline and aPTT not exceeding 100 seconds. Further, at this starting dose only 1% of the subjects have an aPTT of 100 seconds or more and might need down titration as compared to 2% seen with 2 µg/kg/min in adults. Approximately 40% of the patients receiving a starting dose of 0.75 µg/kg/min might not reach the target if 1.5 – 3 times the baseline.
- A step size adjustment of 0.25 µg/kg/min performed at 2-4 hrs, after checking for aPTT, was found to be most suitable to titrate the remaining 40% of the patients not reaching the therapeutic levels with a starting dose of 0.75 µg/kg/min.

Reviewer's Methods

Data

- The PK and PK/PD data was obtained from Study 013 which included 110pediatric patients for the SE8-014 submission and 6 new patients submitted in the current IND. The PK and PD data from five healthy adult studies (n=52 providing 1223 PK and PD observations) administered infusion doses ranging from 1 µg/kg/min to 40 µg/kg/min were used for model development.

- Of the 6 new pediatric patients, one patient (Patient # 142) was identified by the sponsor to be associated with elevated bilirubin levels along with underlying cardiac complication. In total 4 patients were coded for elevated bilirubin status.
- Of the 16 subjects with PK/PD data, patient 102 received a single intravenous bolus dose and had only 2 concentration measurements taken at 15 min and 75 min post dose respectively. The terminal half-life of argatroban in adults is reported to be ~50 min and expected to be longer in pediatric patients. Furthermore, argatroban follows a biphasic disposition, hence, the concentrations in patient 102 would not provide sufficient information for characterizing the clearance. Furthermore, the reported observations were always over predicted for either of the doses and resulted in 10% increase in the mean clearance of pediatric patients and between-patient variability of the population EC_{50} estimate increased from 57% to 76%. Hence, the patient #102 was considered an outlier and excluded in further analysis.

PK Model

- Reviewer's analysis involved sequential analysis of pharmacokinetics followed by PK/PD modeling to analyze argatroban plasma concentration and aPTT relationship.
- A two-compartment open model described the log transformed concentration-time profile in healthy adults and pediatric patients. The model was parameterized in terms of CL (Clearance from central compartment), V_c (Volume of distribution for central compartment, CL_{ic} (Inter-compartmental clearance) and V_p (Volume of Distribution for peripheral compartment). Inter-individual variability in model parameters was assumed to be log-normally distributed. A simple additive error model was used to account for the residual error.

- Reviewer's final model identified that the mean clearance was different for healthy adults and pediatric patients. Body weight was predictor of clearance and volumes of distribution in adults as well as pediatric patients. Bilirubin status was a significant covariate affecting systemic clearance in pediatric patients. The relationship for obtaining the mean clearance is shown below:

$$CL_{Adult} = CL_{Mean\_Adult} \bullet \left(\frac{WT}{20} \right)$$

$$CL_{Ped} = CL_{Mean\_Ped} \bullet \left(\frac{WT}{20} \right) \bullet \left(1 + \left(BIL_{Factor} \bullet BIL_{Status} \right)\right)$$

BIL_{Factor}: Bilirubin Factor

BIL_{Status}: 0 - Not clinically significant

1 – Significantly elevated secondary to cardiac complications

PD Model

- A simple Emax model parameterized in terms of the effect at baseline aPTT (E0), the maximal increase in aPTT response from baseline (Emax), and the concentration of Argatroban causing 50% of Emax (EC50) described the concentration-anticoagulant relationship in healthy adults and pediatric patients. The inter-individual variability was modeled using an exponential error model while the residual error was modeled using a constant coefficient variation (CCV) model.

$$E = E_0 + \left(\frac{E_{max} \bullet C}{EC_{50} + C} \right)$$

Simulations to explore dosing strategy

- Simulations of 10,000 pediatric patients were performed in SPLUS using the population pharmacokinetic/pharmacodynamic model developed above to derive an optimal dosing strategy. Based on the simulations, percent of patients reaching a target of aPTT 1.5 to 3 times the baseline and not exceeding an aPTT of 100 seconds was calculated for both adults and pediatrics for the range of doses. Similarly, the percent subjects failing to reach the target and the percent subjects having aPTT values beyond 100 seconds was also calculated.

Results and Discussion

PK

A two compartment was used to model healthy adult and pediatric patient data. The key results of the population pharmacokinetic analysis are:

- Individual plots show that a two-compartment open model adequately describes the concentration-time profile in pediatric patients (Figure 2).

Figure 2: Individual concentration-time profiles in pediatric patients.

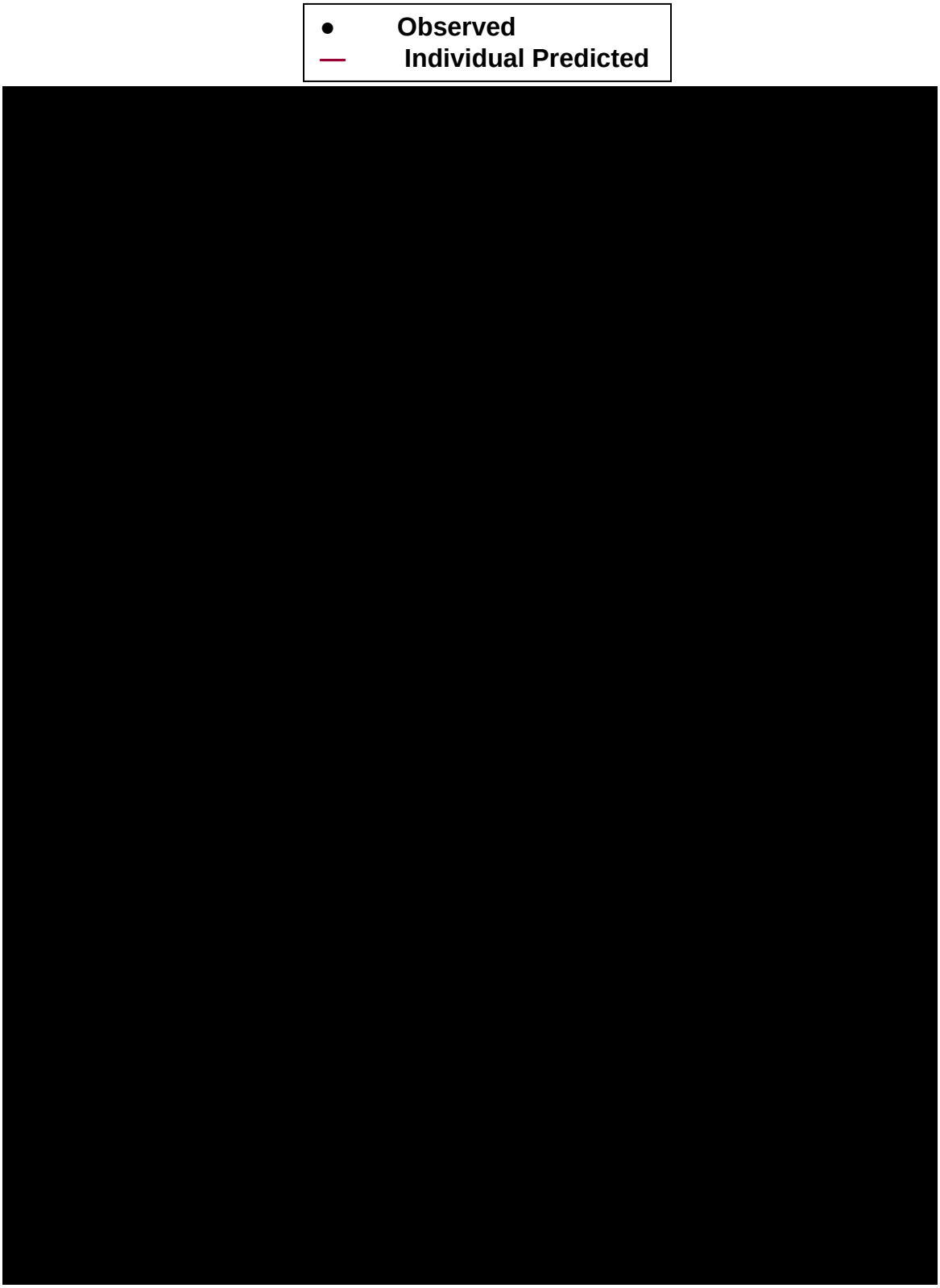
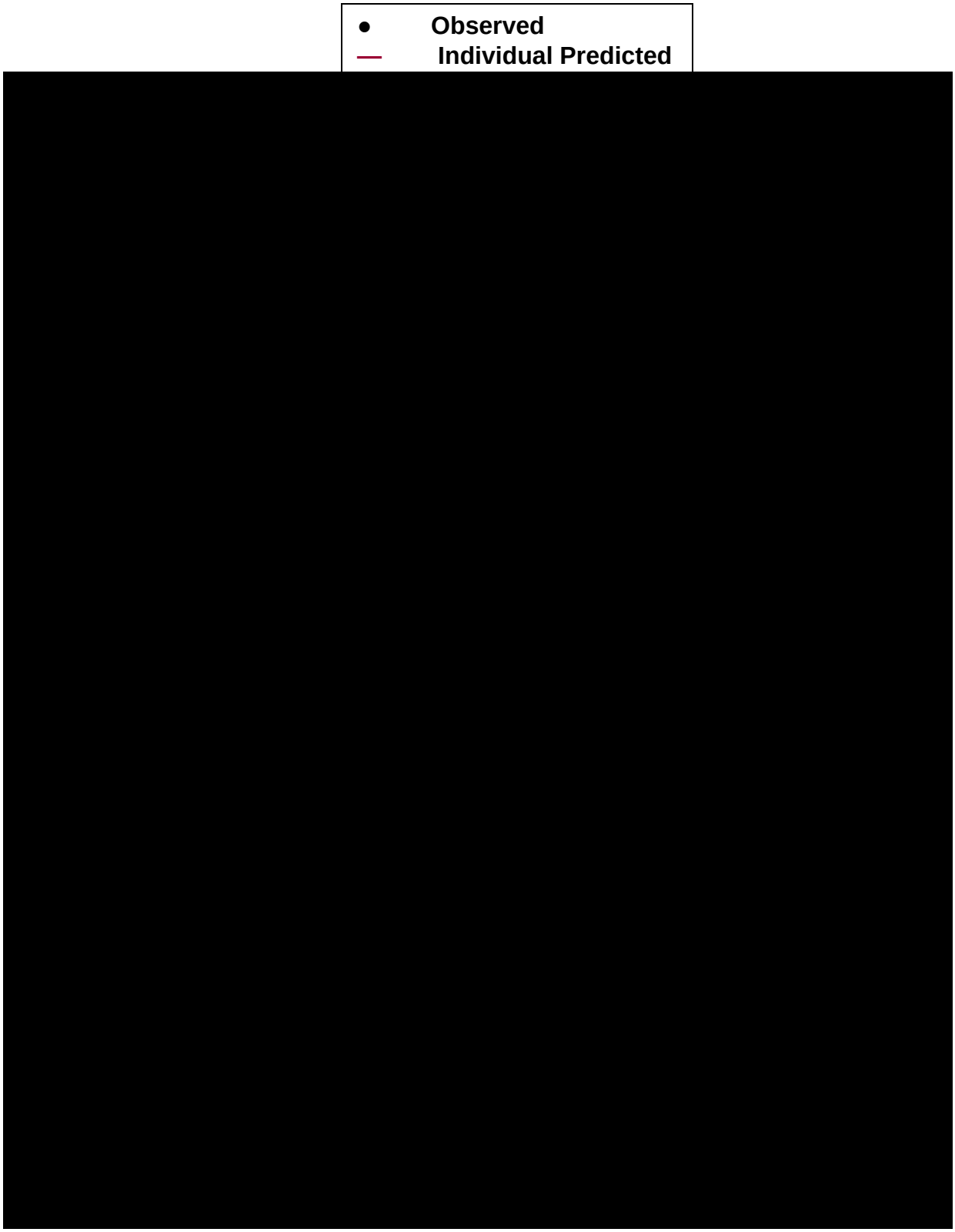


Figure 2: Individual concentration-time profiles in pediatric patients (Continued).



- The slope of the body weight-clearance relationship in the pediatric patients was shallower than that of the healthy adults (Figure 3), as previously observed. This is likely attributed to the fact that the pediatric patients were seriously ill with various underlying co-morbidities. Hence different mean clearances were estimated for pediatric patients and healthy adults.

Figure 3: Clearance is different in pediatric patients and healthy adults. (Note: No covariates included in the model)

- Introduction of body weight reduces the between patient variability on clearance from 72% to 41% as shown in Figure 4.

Figure 4: Body weight reduces between patient-variability from 72% to 41%. (Note: This is not the final PK model)

- It has previously been established in adults that patients with hepatic impairment have slower clearance and require lower doses. Adjustment of the clearance to account of the elevated bilirubin status in pediatric reduces the between-patient variability from 41% to 30% (Figure 5).

Figure 5: Bilirubin status reduces the between-patient variability from 41% to 30%.

- The pharmacokinetic parameters from the final model are shown in the table below (Table 1). The scheme of development leading to final model is shown in Table 2. The diagnostic plots for the final model are shown in the figure below (Figure 6).

Table 1: Between patient variability in clearance for pediatric patients is explained by body weight and bilirubin status.

PK Parameter	Population Mean (%RSE)	Between-Subject Variability (%CV) (%RSE)
CL (L/hr/20kg) ***Adults*** ***Pediatrics*** ***Bilirubin Factor***	 6.29 (3.7) 3.13 (15.6) -0.77 (9.8)	29.72 (28.8)
V (L/20kg)	2.92 (9.6)	42.31 (29.1)
V_p (L/20kg)	1.57 (8.7)	19.36 (91.5)
CL_{ic} (L/hr/20kg)	1.0 (18.5)	39.37 (64.5)
Residual Error (%CV)	33.47 (60.9)	N.E

Table 2: Scheme of development leading to final model.

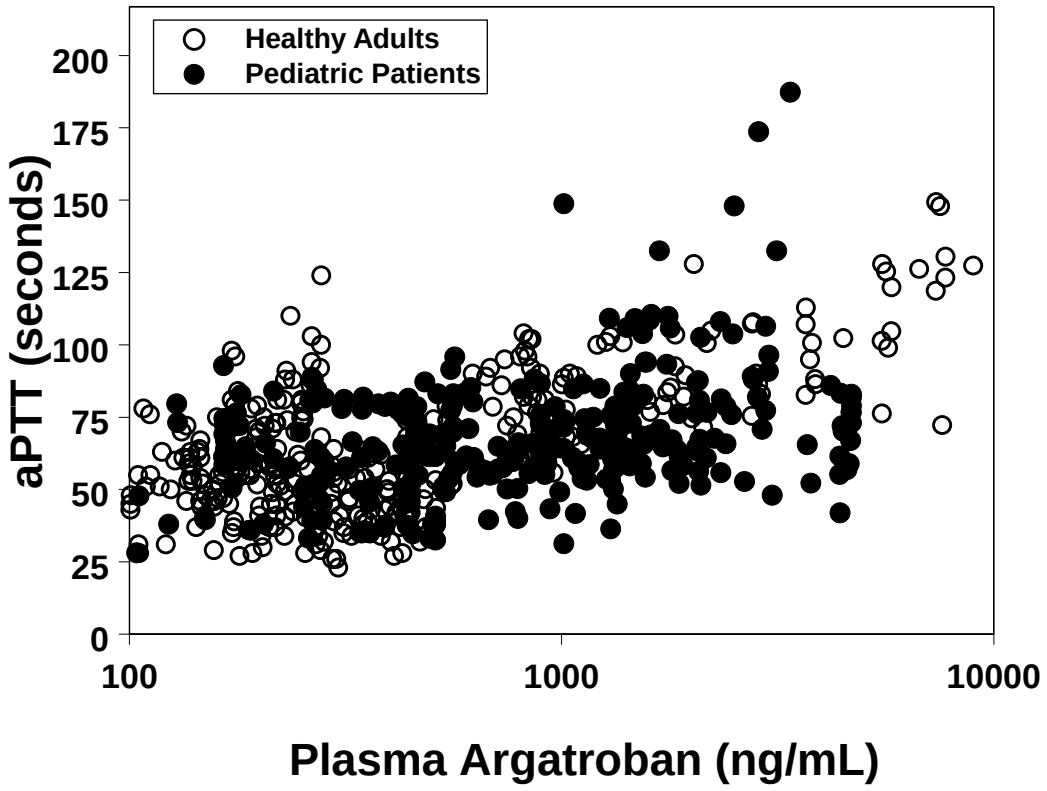
Question	Answer/Comment
Is Body Weight an important covariate for Clearance?	**YES.** Body Weight reduces the between-patient variability from 71% to 40% ($p<0.001$)
Is Elevated Bilirubin Status an important covariate for Clearance?	**YES.** Bilirubin Status reduces the between-patient variability from 41% to 30% ($p<0.001$)

Figure 6: Predicted Concentration (ng/mL) versus Observed Concentration (ng/mL) for the model fit. The population model predicts the concentrations well.

PD

- Graphical analysis of plasma argatroban concentration and the observed aPTT response shows that the effect on aPTT is concentration dependent (Figure 7). Furthermore, it can be seen that the PD in pediatrics is in alignment with adults as seen previously.

Figure 7: Argatroban concentration-aPTT relationship is similar in pediatrics and adults.



- A simple Emax model parameterized in terms of the effect at baseline aPTT (E0), the maximal increase in aPTT response from baseline (Emax), and the concentration of Argatroban causing 50% of Emax (EC50) described the concentration-anticoagulant relationship in healthy adults and pediatric patients. Individual plots show that the Emax model adequately describes the concentration-time profile in pediatric patients (Figure 8).

Figure 8: Individual aPTT-time profiles in pediatric patients.

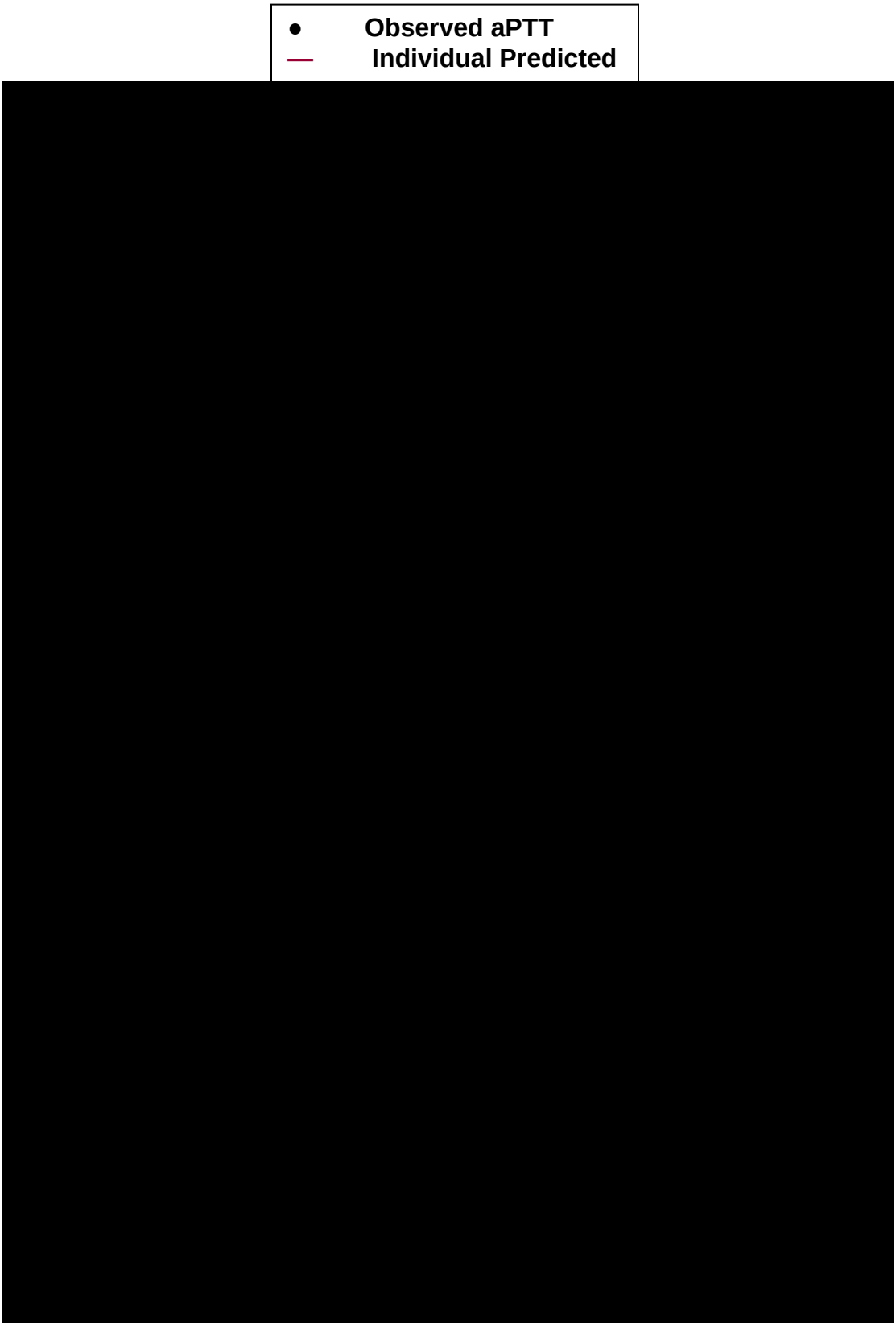
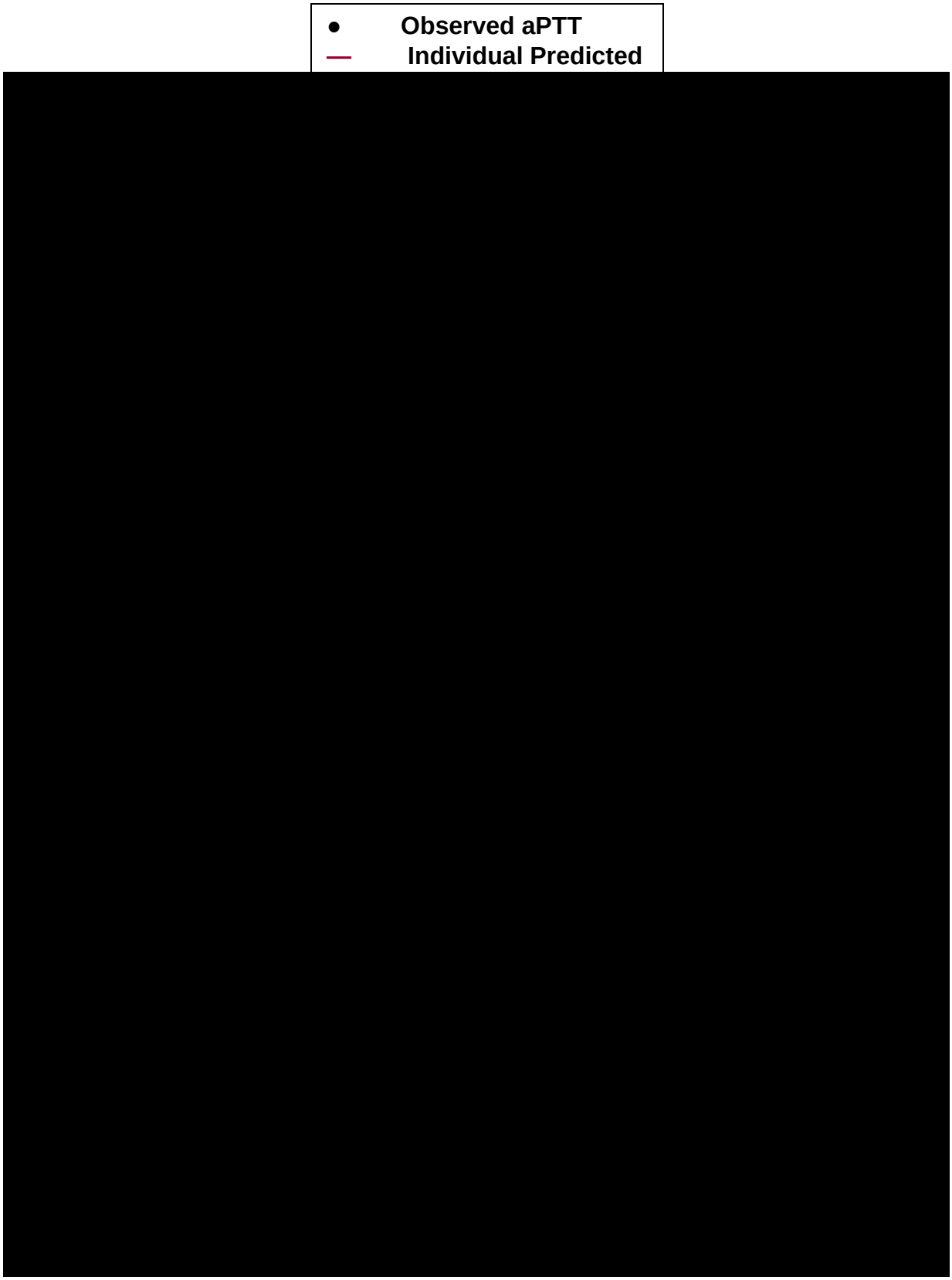


Figure 8: Individual aPTT-time profiles in pediatric patients (Continued).



- The estimated PK/PD parameters are shown in Table 3. The diagnostic plot showing the goodness of fit is shown in Figure 9.

Table 3: Argatroban population PK/PD parameters for healthy adults and pediatric patients.

PK/PD Parameter	Population Mean (%RSE)	Between-Subject Variability (%CV) (%RSE)
E_0 (sec)	31.8 (2.7)	20.86 (25.5)
Emax (sec)	84.4 (13.75)	25.26 (39.0)
EC_{50} (ng/mL)	959 (22.5)	56.75 (31.7)
Residual Error (% CV)	13.75 (12.9)	N.E

Figure 9: Predicted aPTT (seconds) versus Observed aPTT (seconds) for the model fit. The population model predicts the observed aPTT well.

Simulations to explore dosing strategies

To determine how many patients achieved the target aPTT (1.5 to 3 times of baseline and an aPTT not exceeding 100 seconds) with the starting dose, simulations were conducted using SPLUS.

- The relationship between age and bodyweight was generated based on the demographics in the present study is shown below.

$$\mathbf{Weight} = \mathbf{3.46}\mathit{kg} + \left(\frac{\mathbf{88}\mathit{kg} \bullet \mathit{Age}^{1.19}}{\mathbf{11}\mathit{yr} + \mathit{Age}^{1.19}} \right) \bullet \left(\mathbf{1} + \mathit{BSV}\right)$$

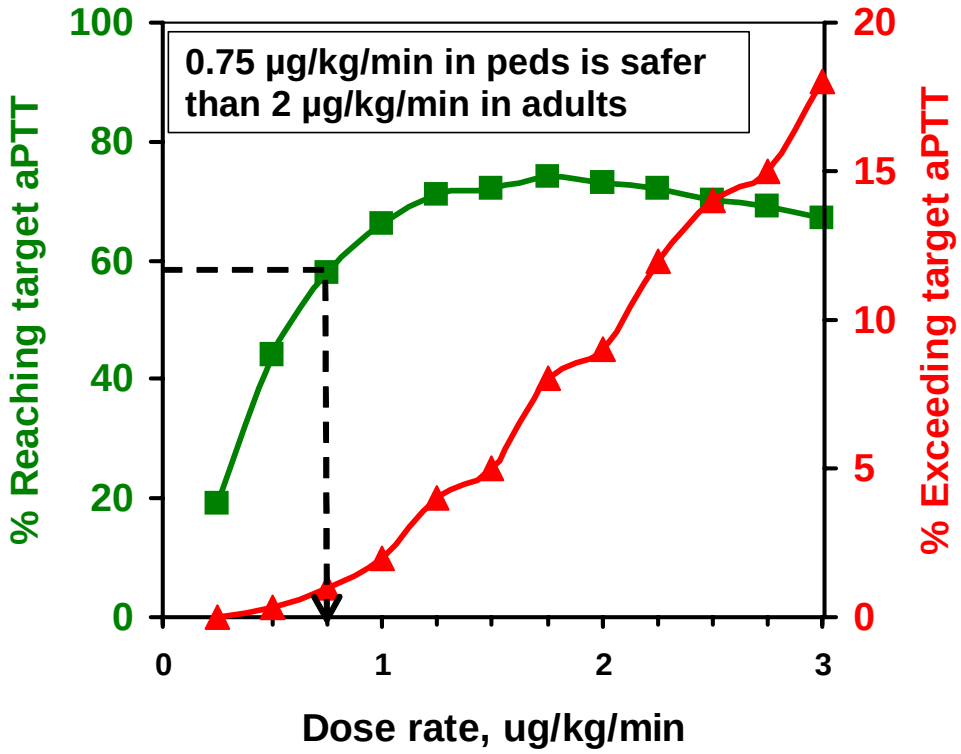
  The between subject variability (BSV) was assumed to be normally distributed with a mean of 0 and variance of 0.0361, reflecting a coefficient of variation of 19%.
- Using the body weight-clearance relationship developed during the population PK analysis, steady state argatroban concentrations were simulated in 10,000 pediatric patients with normal hepatic function.
- The aPTT level corresponding to the steady state plasma concentration was derived utilizing the population PK/PD relationship developed above. Various starting doses ranging from 0.25 µg/kg/min to 4 µg/kg/min were tested across pediatric patients.
- The proportion of subjects reaching a target of aPTT 1.5 to 3 times the baseline and not exceeding an aPTT of 100 seconds was calculated, the proportion of subjects failing to reach the target and the percent subjects having aPTT values beyond 100 seconds were calculated.
- These results were compared with 2 µg/kg/min (approved starting dose in adults) and 10 µg/kg/min (highest approved dose) doses in adults. The results are summarized in Table 4.

Table 4: 0.75 in pediatric patients is comparable to 2 µg/kg/min.

Infusion rate (µg/kg/min)	Patients Below Target (Average %)	Patients Reaching Target (Average %)	Patients with aPTT>100 seconds (Average %)
0.25	81.225	18.710	0.030
0.5	56.130	43.055	0.345
0.75	**38.755**	**58.865**	**1.150**
1.0	28.500	66.610	2.410
1.25	21.055	71.190	3.955
1.5	15.760	73.610	5.535
1.75	12.145	74.040	7.590
2.0	9.755	73.090	9.740
2.25	8.340	71.945	11.405
2.5	6.735	70.775	13.295
2.75	5.605	68.715	15.380
3.0	**4.660**	**66.995**	**17.165**
2.0 (in Adults)	**28.84**	**66.900**	**1.92**
10 (in Adults)	**1.46**	**55.000**	**29.60**

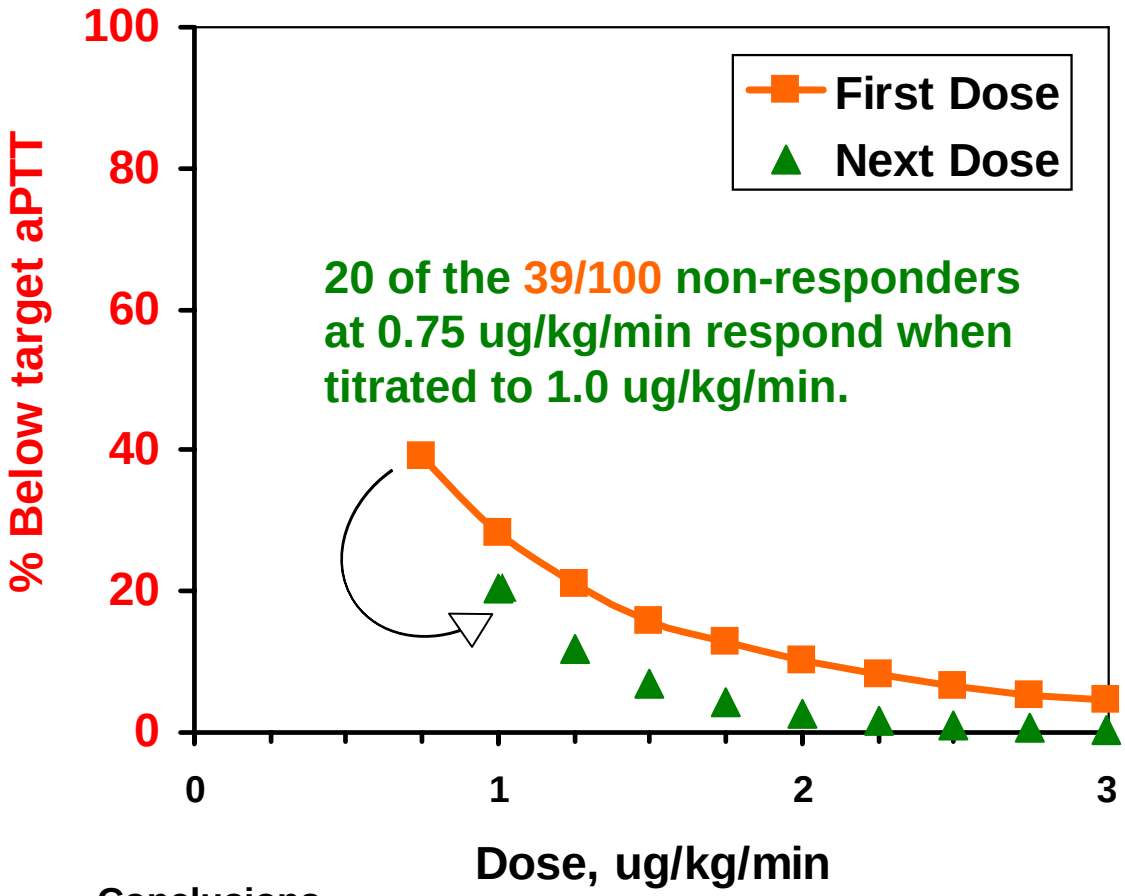
- The effectiveness of a starting dose of 1 µg/kg/min was found to perform similar to 2 µg/kg/min in healthy adults.
- However, risk-to-benefit was minimal with a 0.75 µg/kg/min (Figure 10). The risk was half with a starting dose of 0.75 µg/kg/min compared to 1 µg/kg/min. The starting dose of Study 013 was 1 µg/kg/min and during the study three patients died due to hemorrhage or disseminated intravascular coagulation. ***Hence a starting dose of 0.75 µg/kg/min is a conservative and safe dose.***

Figure 10: 0.75 µg/kg/min is a reasonable and safe starting dose in pediatric patients.



- Dosing the patients not reaching the target with the next higher dose increased the percent of patients falling in the target. With a step size of 0.25 µg/kg/min, 51.2% of the non-responders with a starting dose of 0.75 µg/kg/min attained the target with next dose. Hence, increments of 0.25 µg/kg/min for titrating up the 39% of patients below target were considered reasonable (Figure 11).

Figure 11: 0.25 µg/kg/min is a reasonable incremental dose.



Conclusions

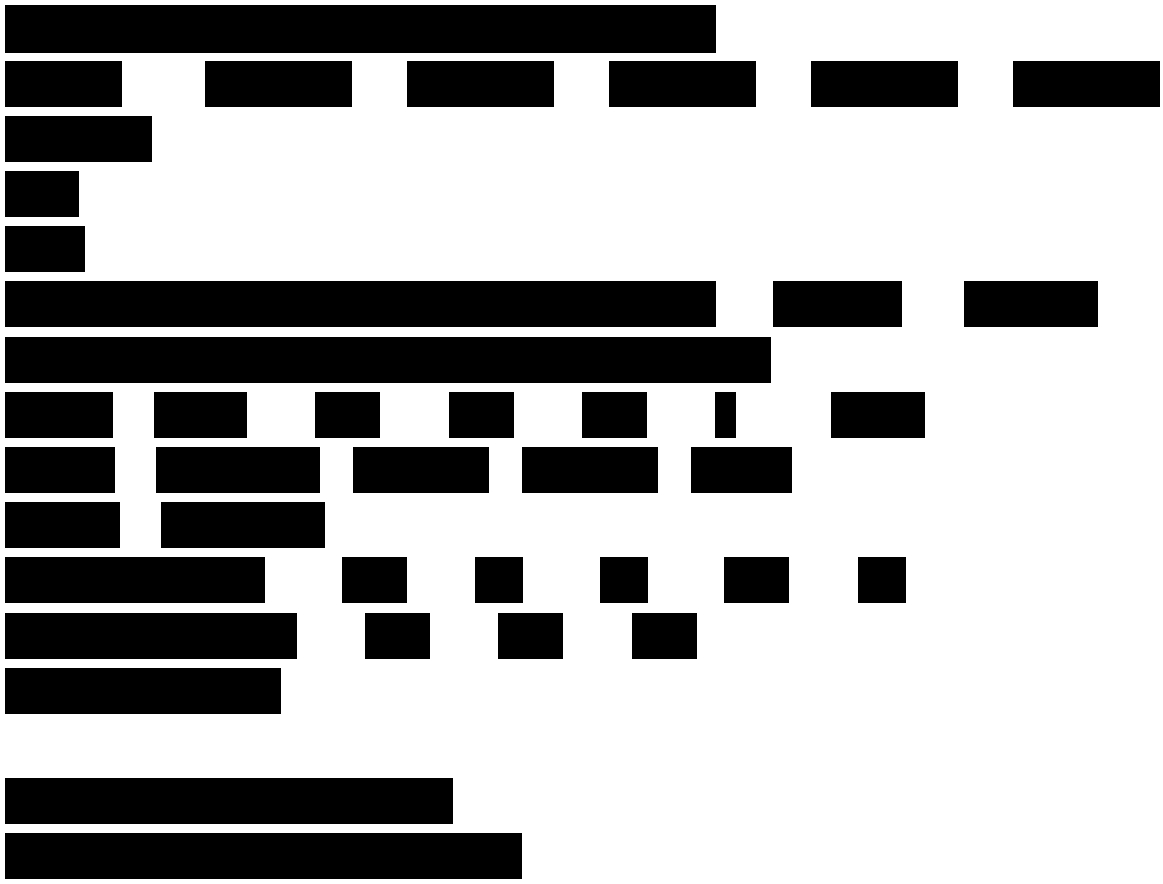
- In the present study, plasma samples corresponding to steady-state levels of argatroban were collected over a range of doses in seriously ill pediatric patients (N=15, 166 data points). The concentration - time data was adequate to characterize systemic clearance.
- The clearance in pediatric patients was found to be different from healthy adults. The clearance in pediatric patients was approximately 50% of healthy adults.
- The estimated clearance in a typical 20 kg pediatric patient was 3.1 L/hr with 95% confidence intervals ranging from 2.2 L/hr to 4.0 L/hr. Body weight was a significant predictor of clearance.
- The mean clearance in four patients with elevated serum bilirubin levels secondary to cardiac complications was 0.6 L/hr.

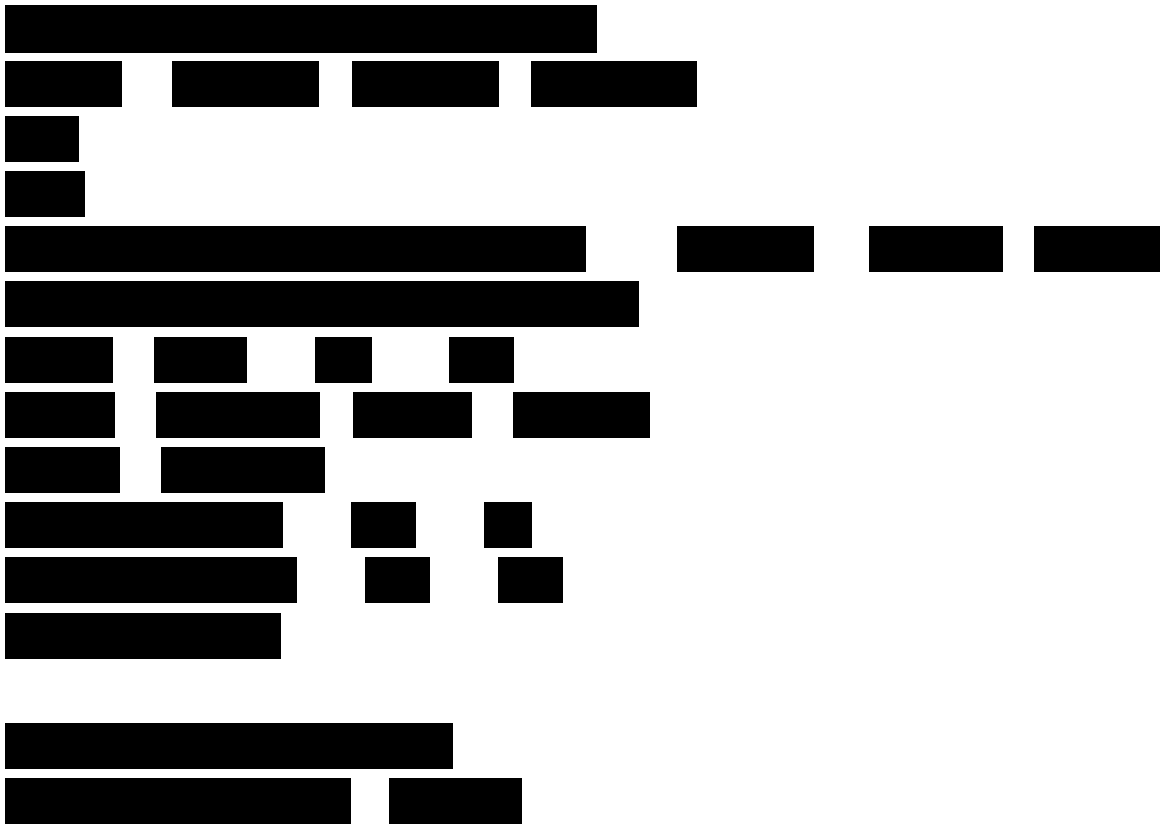
- Plasma concentration-anticoagulant response (aPTT) data in pediatric patients (N=15, 329 data points) was collected over a wide range of concentrations (100 – 5000 ng/mL).
- After the adjustment for clearance in pediatric patients, the concentration-aPTT relationship was found to be similar in pediatric patients and healthy adults.
- A dose of 0.75 µg/kg/min in pediatric patients is a reasonable and safe starting dose with about ~60% of the subjects reaching a target aPTT of 1.5 to 3 times the baseline and aPTT not exceeding 100 seconds.
- A step size of 0.25 µg/kg/min is most suitable to titrate remaining 39% of the patients not reaching the therapeutic levels with a starting dose of 0.75 µg/kg/min.
- About 1% of patients reach aPTT levels above 100 seconds in the simulations.

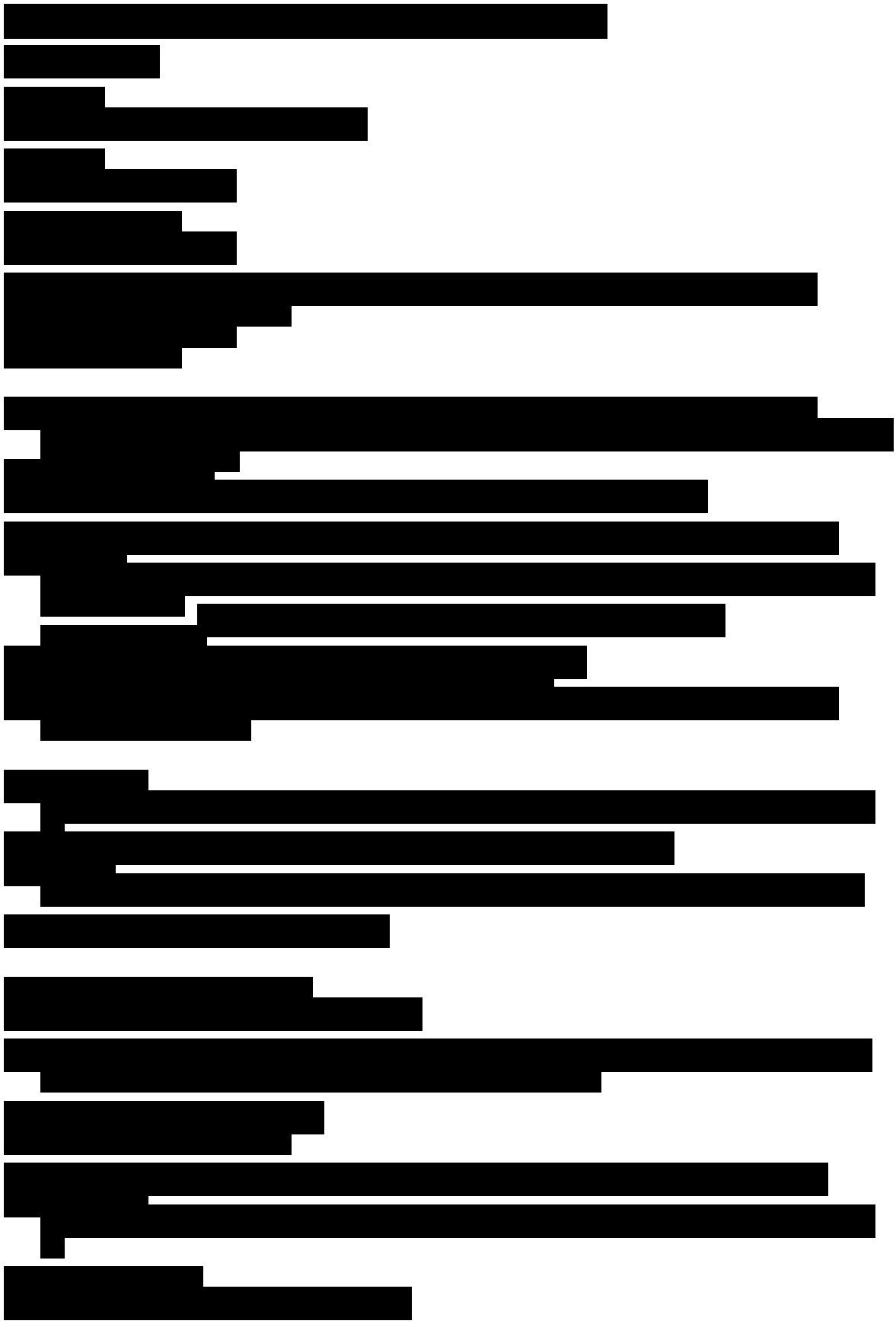
Appendix

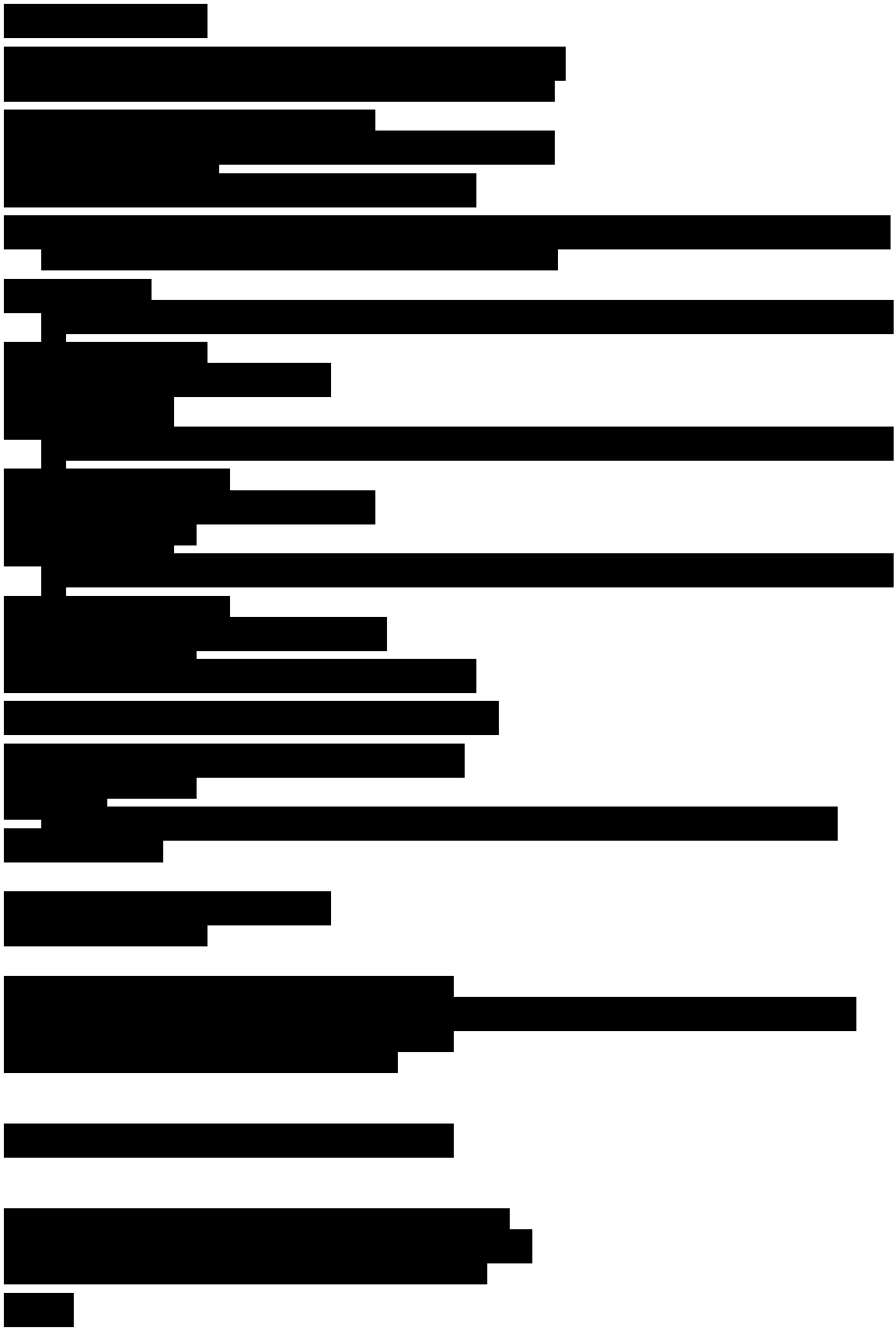
Final Population PK Model:

[redacted]









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