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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 215859
Supporting document/s:	1
Applicant's letter date:	June 22, 2021
CDER stamp date:	June 22, 2021
Product:	Xarelto (Rivaroxaban) Oral Suspension
Indication:	• Venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age, • Thromboprophylaxis in pediatric patients 2 years of age and older with congenital heart disease (CHD) after the Fontan procedure
Applicant:	Janssen Pharmaceuticals Inc.
Review Division:	Division of Non-Malignant Hematology
Reviewer:	Bo Yeon Lee, Ph.D.
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1 Executive Summary

1.1 Introduction

Rivaroxaban (JNJ-39039039, BAY 59-7939, Xarelto®) is a selective inhibitor of the serine protease coagulation Factor Xa (FXa) being developed for the prevention and treatment of thrombo-embolic events. (Reference NDAs 022406 and 202439)

Currently, Xarelto is approved in adult patients for the following indications; 1) to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation, 2) for treatment of deep vein thrombosis (DVT), 3) for treatment of pulmonary embolism (PE), 4) for reduction in the risk of recurrence of DVT or PE, 5) for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery, 6) for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients, 7) to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) (Xarelto USPI, revised 03/2020).

The Sponsor submitted this NDA 245859 for 2 indications in pediatric population: 1) venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age, and 2) thromboprophylaxis in pediatric patients 2 years of age and older with congenital heart disease (CHD) after the Fontan procedure

In support of the clinical development in pediatric population, the Sponsor conducted additional pharmacokinetics studies including protein binding using plasma from pediatric healthy volunteers and substrate characteristics towards fetal CYP3A7. There are no new pharmacology or toxicology studies submitted. There are no outstanding issues from a Pharmacology/Toxicology perspective that would prevent the approval of rivaroxaban for the proposed indications.

1.2 Brief Discussion of Nonclinical Findings

Xarelto® is an approved drug in adult populations and the Sponsor has submitted this NDA to support the clinical development and market authorization of rivaroxaban in pediatric populations.

The nonclinical program reviewed under reference NDAs 202439 and 022406 concluded that rivaroxaban was approvable for the indications listed above in adult patient population. The reference NDAs include nonclinical studies in juvenile, adolescent and adult rats, and the overall nonclinical assessment remains unchanged. In addition, the Sponsor submitted additional PK studies of pediatric protein binding and of substrate characteristics towards a fetal CYP isoform, which showed that the unbound fraction in pediatric plasma was higher than in adult plasma and that rivaroxaban is a poor substrate for the fetal isoform CYP3A7.

Therefore, there are no safety concerns from the nonclinical perspective and rivaroxaban is approvable to be used in pediatric populations for the proposed indications based on the nonclinical assessment of the new PK studies and reviews by nonclinical reviewers of reference NDAs.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study Title: Rivaroxaban: Supplementary Investigations on Binding to Plasma Proteins in Pediatric Human Plasma of Rivaroxaban In Vitro (Study PH-41585) Non-GLP compliant

The Sponsor assessed protein binding of Rivaroxaban in pediatric human plasma (< 2 years old children, 2-6 years old children, and > 6 years old children) using radiolabeled [^{14}C]BAY 59-7939 (rivaroxaban), and the unbound fractions of [^{14}C]BAY 59-7939 was determined.

Plasma samples were pooled to test from < 2 years old children, 2-6 years old children, > 6 years old children, and healthy adult volunteers (represents a control in this study). (see, Table 1) Protein binding of rivaroxaban to human plasma samples was analyzed by the equilibrium dialysis method.

The protein binding assay showed that the binding of rivaroxaban ranged between 95.4 µg/L - 99.9 µg/L. The unbound fractions were determined as 11.1%, 11.2%, and 9.23% in < 2 years old children, 2-6 years old children, and > 6 years old children, respectively. (see, Table 2) The unbound fraction of rivaroxaban was higher in pediatric plasma than in adult plasma, and unbound fraction in plasma from man (control) was 6.82% which is comparable to the reported data 5.07% from reference NDA 022406. (see, Table 3)

Table 1. List of Plasma Samples from Pediatric Population

(Excerpted from submission)

Species	Age	Gender	Race	Ethnicity	Supplier
Pediatric human	8 months	M	Caucasian	European	(b) (4)
	1 year	F	African	African American	
	6 months	F	African	African American	
	5 years	F	African	African American	
	3 years	M	African	African American	
	2 years	F	African	African American	
	9 years	F	Caucasian	N/A	
	8 years	F	Caucasian	N/A	
	7 years	F	Caucasian	N/A	
Man	N/A	male	Caucasian	N/A	(b) (4)

Table 2. Rivaroxaban Binding to Pediatric Human Plasma Proteins.

(Excerpted from submission)

Species	Concentration for protein binding assay [µg/L]	f_u[a] [%]	CV [%]
Human, <2 years and younger	99.9	11.1	3.19
Human, 2 - 6 years old	95.4	11.2	6.88
Human, >6 years and older	99.9	9.23	4.04

CV = coefficient of variation

a = arithmetic mean unbound fraction from three independent experiments at the respective concentration

Table 3. Binding of [14C]BAY 59-7939 to Plasma Proteins in Healthy Adult Volunteers

(Excerpted from Reference NDA 022406, eCTD M4.2.2.3, Study PH-32966)

	Sex	Concentration [mg-eq/L]	fu [%]	fu [%] mean
Human	Male	0.104	4.56	
		1.00	4.61	
		3.14	4.69	
		11.1	6.46	
		32.7	7.16	
		112	7.37	
		278	8.38	
		340	8.13	
	Female	0.109	5.43	
		1.03	5.48	
		3.09	5.63	***5.07
		10.6	7.72	
		32.6	8.55	
		110	8.96	****7.96

*** = mean human male and female, conc. 0.1 - 3 µg/mL

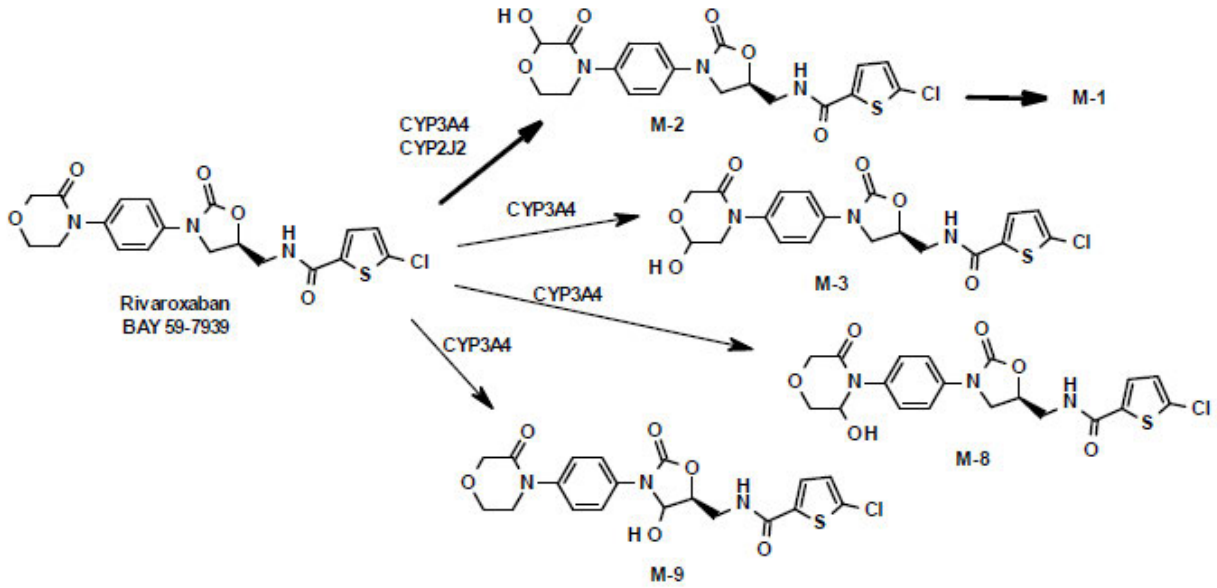
**** = mean human male and female, conc. 10 - 300 µg/mL

Study Title: Rivaroxaban: In Vitro Intrinsic Clearances with Recombinant Human CYP Isoforms (Study PH-41153)

Rivaroxaban was shown to be substrate for CYP2J2, CYP3A4 and 3A5 in adults (reference NDA 022406, eCTD4.2.2.4, PH-32627), and is eliminated via 3 pathways in adults: ~43.5% of the dose is excreted by transporter-mediated as unchanged drug via urine and feces, ~14% of the dose is by hydrolytic cleavage of the amide bonds yielding M-4 and M-7, and 32% of the dose is eliminated via oxidative pathways. CYP2J2 and CYP3A4/3A5-mediated oxidation yield M-2, M-3, M-8, and M-9 (by CYP3A4) and M-2 (by CYP2J2). (see Figure 1).

Figure 1. Proposed Primary Oxidative Metabolites of Rivaroxaban from In Vitro Studies

(Excerpted from submission)



* Bold arrows are the main metabolic in vivo pathway

The activity of CYP3A4 may differ between pediatric populations and adults due to changes of CYP3A activity during human development. CYP3A4 activity is negligible at birth and increase to ~40% of adult activity within the 2-12 month of age and reach ~120% of adult activity at an age of 12 months, then the activity goes down to adult levels. Also, inverse activities of the fetal isoform CYP3A7 with peak activity at birth and decreasing to negligible levels around 12 months of age is reported (de Wildt et al., 1993, Lacroix et al., 1997, Zane et al., 2017)

The Sponsor conducted an in vitro study to evaluate 1) the metabolic stability of rivaroxaban at a physiologically relevant concentration (0.1 µM) towards CYP2J2, 3A4, 3A5 and 3A7 and 2) a potential contribution of CYP3A7 (isoform of CYP3A4) to the biotransformation of rivaroxaban in the pediatric population.

Clearance of rivaroxaban and the level of the hydroxylated form of rivaroxaban (OH-rivaroxaban) were measured as indicators of enzymatic activity of CYP2J2, 3A4, 3A5 and 3A7 when incubated with rivaroxaban for up to 60 min. (see Table 4, Figure 2A&B). The Sponsor commented that the metabolite formation is only a qualitative measure of enzymatic activity in this study. (Figure 2).

The hydroxylated metabolites were formed by all 4 CYP enzymes (see Table 4, Figure 2B). Intrinsic clearance of rivaroxaban was highest with CYP2J2 (2.49 µL/min/pmol) and then CYP3A4 (0.38 µL/min/pmol), while CYP3A5 and CYP3A7 were 8-fold lower (< 0.05 µL/min/pmol). (see Table 4).

Results show evidence that rivaroxaban is a poor substrate for the CYP3A7, fetal isoform of CYP3A4, and it is unlikely that CYP3A7 will contribute to hepatic clearance of rivaroxaban in the pediatric population.

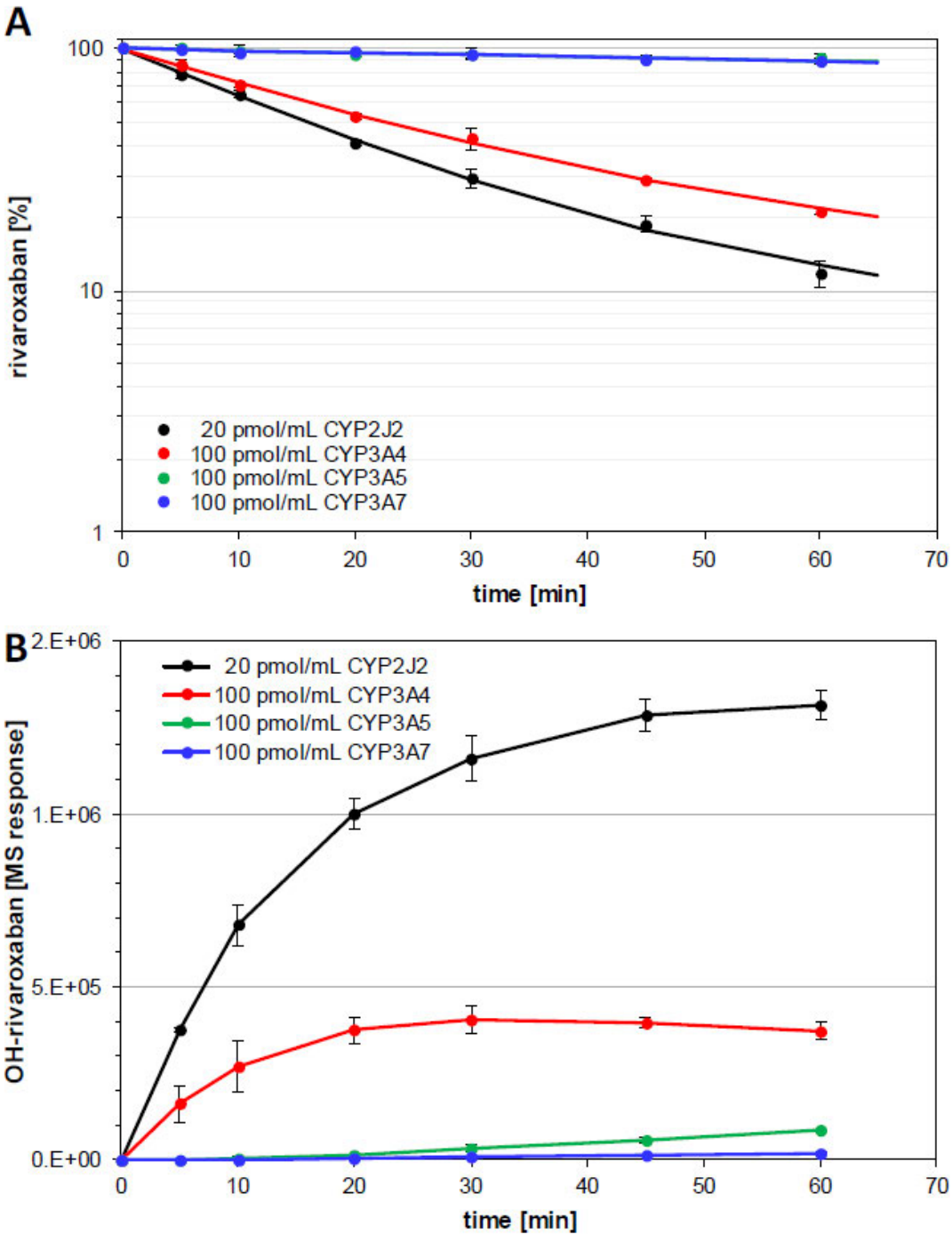
Table 4. Clearance and Metabolite Formation of 0.1 µM Rivaroxaban with CYP2J2, 3A4, 3A5, and 3A7

(Excerpted from submission)

	Time [min]	rivaroxaban mean ± SD [%]	OH-rivaroxaban mean ± SD [MS response]	CL_{int} [µL/min/pmol]
20 pmol/mL CYP2J2	0	100.0 ± 0.0	- ± -	2.49
	5	77.7 ± 2.3	374 742 ± 7 247	
	10	65.0 ± 1.6	679 122 ± 59 727	
	20	40.7 ± 1.0	1 000 024 ± 44 470	
	30	29.0 ± 2.5	1 161 145 ± 66 930	
	45	18.7 ± 1.5	1 285 999 ± 47 565	
	60	11.8 ± 1.5	1 314 396 ± 40 483	
100 pmol/mL CYP3A4	0	100.0 ± 0.0	- ± -	0.38
	5	85.4 ± 4.0	161 266 ± 52 110	
	10	71.1 ± 1.9	271 331 ± 73 944	
	20	52.5 ± 1.0	374 316 ± 38 068	
	30	42.4 ± 4.5	403 732 ± 41 591	
	45	28.8 ± 0.5	396 724 ± 14 027	
	60	21.3 ± 0.6	373 845 ± 23 298	
100 pmol/mL CYP3A5	0	100.0 ± 0.0	- ± -	<0.05
	5	100.8 ± 1.9	- ± -	
	10	97.5 ± 5.0	5 778 ± 3 336	
	20	94.0 ± 1.7	14 199 ± 2 610	
	30	94.7 ± 4.9	33 026 ± 10 601	
	45	90.8 ± 3.4	59 175 ± 7 167	
	60	91.1 ± 4.9	84 576 ± 2 539	
100 pmol/mL CYP3A7	0	100.0 ± 0.0	- ± -	<0.05
	5	99.2 ± 1.1	- ± -	
	10	96.2 ± 0.6	- ± -	
	20	97.5 ± 1.6	1 891 ± 3 276	
	30	93.8 ± 2.5	7 311 ± 1 857	
	45	90.8 ± 2.2	14 730 ± 3 346	
	60	88.5 ± 2.2	19 359 ± 3 295	

Figure 2. Clearance (Figure 2A) and Metabolite Formation (Figure 2B) of 0.1 µM Rivaroxaban with CYP2J2, 3A4, 3A5, and 3A7

(Excerpted from submission)



Overall Nonclinical Assessment

The nonclinical package of reference NDA 202439 included juvenile studies conducted in rats of PND 4-26 (pilot study) and PND 10-105 (pivotal study), corresponding to the human age ranges of neonate to toddler and infant to adolescent, respectively.

Nonclinical assessment of juvenile studies of reference NDA 202439 by Dr. Harlow pointed out 2 things to note:

1) exposure to rivaroxaban was 6- to 10-fold higher in the younger rats, particularly between PND 10 and 15 compared to exposure in ≥31 days old rats, which could be due to a combination of immature renal development in the rat (Zoetis and Hurtt, 2003) and decreased expression of CYP P450 3A4 (Asaoka et al. 2009, DeZwart et al. 2004).
2) expected prolonged thromboplastin time from pharmacological effect of rivaroxaban was not observed in coagulation test, which is suspected that the blood samples were collected prior to administration of rivaroxaban.

Dr. Harlow concluded that data from the coagulation test is inconclusive and the effect of rivaroxaban on coagulation was not fully evaluated. She also commented that any pediatric studies in humans will need to be carefully designed to determine the appropriate levels of rivaroxaban for a therapeutic effect in neonates and infants undergoing rapid changes in their hemostatic, renal and metabolic systems, considering the levels of Factor X in the neonate at birth are about 37-40% of the adult human level (Andrew et al. 1987, Hassan et al. 1990).

In this NDA, the Sponsor provided a nonclinical risk assessment of 2 new PK studies to support clinical development and market authorization in proposed pediatric indications and summary of overall nonclinical program of reference NDAs 202439 and 022406.

The Sponsor estimated safety margins for the pediatric indications in this NDA (see, Table 5) based on pediatric exposures obtained with population PK modeling with bodyweight-adjusted dosing scheme in pediatric populations, resulting in rivaroxaban exposure similar to that observed in adult patients with deep vein thrombosis (DVT) (eCTD 2.7.2. Summary of Clinical Pharmacology Studies- Einstein Jr). Systemic exposure (C_{max} and AUC) in juvenile rats and the estimated safety margin was also provided by the sponsor. (see, Table 6). There was discrepancy in exposure data of 13-week pilot (gavage) toxicity study in juvenile rats shown in Table 6 compared to the study report PH-36598. Note the corrected data and calculated margin of exposure by the reviewer (see, Table 7)

The systemic exposure from 14-week repeat dose toxicology study in juvenile rats (NDA 202439, eCTD 4.2.3.5.4, PH-36347) was ~5-fold lower compared to that of 3-week pilot toxicity study in juvenile rats (NDA 202439, eCTD 4.2.3.5.4, PH-36153). The Sponsor conducted additional 13-week repeat dose toxicology study in juvenile rats (NDA 202439, eCTD 4.2.3.5.4, PH-36598) and explains that the lower systemic exposure was due to vehicle difference (0.5 % Tylose® vs. Solutol HS15®/ethanol/water); When emulsifying vehicle (Solutol HS15®/ethanol/water) which mimics the absorption-

enhancing effects of milk was used, the systemic exposure was not lower but comparable to other juvenile studies.

Overall nonclinical assessment including the review of reference NDAs and newly submitted PK study reports finds no safety concerns from the perspective of Pharmacology & Toxicology for approvability of rivaroxaban in pediatric population for the two proposed indications.

Table 5. Systemic Exposure and Margins of Exposure Compared to Pediatric Exposure

(Excerpted from submission)

Daily dose [mg/kg]	Sex	Total exposure C_{max} [µg/L]	MoE	Total exposure $AUC_{(0-24)}$ [µg·h/L]	MoE	Unbound exposure $C_{max,u}$ [µg/L]	MoE	Unbound exposure $AUC_{0-24,u}$ [µg·h/L]	MoE
Chronic 26-week (gavage) toxicity study in rats (NDA 022406, seq 0000, M4.2.3.2, PH-33611)									
12.5	M	5410	22.9	18000	7.6	68.71	2.6	228.60	0.9
50	M	16700	70.6	75600	31.8	212.09	8.0	960.12	3.6
200	M	25500	107.7	137000	57.5	323.85	12.2	1739.90	6.5
12.5	F	10800	45.6	32400	13.6	137.16	5.2	411.48	1.5
50	F	26300	111.1	114000	47.9	334.01	12.6	1447.80	5.4
200	F	41800	176.6	280000	117.6	530.86	20.0	3556.00	13.3
Chronic 52-week (gavage) toxicity study in dogs (NDA 022406, seq 0000, M4.2.3.2, PH-34235)									
5	M+F	1290	5.5	5990	2.5	134.16	5.1	622.96	2.3
15	M+F	1920	8.1	10200	4.3	199.68	7.5	1060.80	4.0
50	M+F	3100	13.1	22040	9.3	322.40	12.2	2292.16	8.6
Carcinogenicity study in mice (NDA 202439, seq 0000, M4.2.3.4, PH-36243)									
10	M	363	1.5	980	0.4	23.41	0.9	63.21	0.2
20	M	503	2.1	1540	0.6	32.44	1.2	99.33	0.4
60	M	1090	4.6	2520	1.1	70.31	2.7	162.54	0.6
10	F	568	2.4	1710	0.7	36.64	1.4	110.30	0.4
20	F	963	4.1	3290	1.4	62.11	2.3	212.21	0.8
60	F	1020	4.3	4240	1.8	65.79	2.5	273.48	1.0
Carcinogenicity study in rats (NDA 202439, seq 0000, M4.2.3.4, PH-36242)									
10	M	1890	8.0	13400	5.6	24.0	0.9	170.2	0.6
20	M	2310	9.8	15400	6.5	29.3	1.1	195.6	0.7
60	M	2730	11.5	20300	8.5	34.7	1.3	257.8	1.0
10	F	4610	19.5	34700	14.6	58.5	2.2	440.7	1.7
20	F	5480	23.2	47500	19.9	69.6	2.6	603.3	2.3
60	F	7810	33.0	48200	20.2	99.2	3.7	612.1	2.3
Developmental toxicity study in rats (NDA 022406, seq 0000, M4.2.3.5.2, PH-33582)									
10	F	2550	10.8	18900	7.9	32.39	1.2	240.03	0.9
35	F	6590	27.8	77700	32.6	83.69	3.2	986.79	3.7
120	F	12900	54.5	188000	79.0	163.83	6.2	2387.60	9.0
Developmental toxicity study in rabbits (NDA 022406, seq 0000, M4.2.3.5.2, PH-33380) (NDA 022406, seq 0000, M4.2.3.5.2, PH-33368)									
2.5	F	142	0.6	736	0.3	33.23	1.3	172.22	0.6
10	F	294	1.2	2780	1.2	68.80	2.6	650.52	2.4
40	F	881	3.7	13100	5.5	206.15	7.8	3065.40	11.5
120	F	1540	6.5	23900	10.0	360.36	13.6	5592.60	21.0

MoE = margins of exposure (when compared to the human plasma levels)
f_u rat = 1.27 %, f_u human pediatric = 11.2 % (M4.2.2.3/PH 41585 version 2)
Pediatric reference exposures are the highest steady state Cmax (236.66 µg/L, age group 12 to < 18 years) and AUC (2380.96 µg*h/L, age group 2 to < 6 years) obtained by population PK modeling (M2.7.2/Einstein Jr/Table 3-2)

Table 6. Systemic Exposure in Juvenile Rats and Margins of Exposure Compared to Pediatric Exposure

(Excerpted from submission)

Daily dose [mg/kg]	Sex	Total exposure C_{max} [µg/L]	MoE	Total exposure $AUC_{(0-24)}$ [µg·h/L]	MoE	Unbound exposure $C_{max,u}$ [µg/L]	MoE	Unbound exposure $AUC_{0-24,u}$ [µg·h/L]	MoE
3-week pilot (gavage) toxicity study in juvenile rats (NDA 202439, seq 0000, M4.2.3.5.4, PH-36153)									
6	M	1570	6.6	8570	3.6	19.94	0.8	108.84	0.4
20	M	2050	8.7	24700	10.4	26.04	1.0	313.69	1.2
60	M	3390	14.3	25900	10.9	43.05	1.6	328.93	1.2
6	F	1220	5.2	8890	3.7	15.49	0.6	112.90	0.4
20	F	1980	8.4	12300	5.2	25.15	0.9	156.21	0.6
60	F	3780	16.0	33900	14.2	48.01	1.8	430.53	1.6
14-week pivotal (gavage) toxicity study in juvenile rats (NDA 202439, seq 0125, M4.2.3.5.4, PH-36347)									
6	M	259	1.1	2160	0.9	3.29	0.1	27.43	0.1
20	M	500	2.1	3420	1.4	6.35	0.2	43.43	0.2
60	M	419	1.8	4600	1.9	5.32	0.2	58.42	0.2
6	F	510	2.2	3360	1.4	6.48	0.2	42.67	0.2
20	F	695	2.9	4760	2.0	8.83	0.3	60.45	0.2
60	F	975	4.1	7530	3.2	12.38	0.5	95.63	0.4
4-week (gavage) toxicokinetic study in juvenile female rats (NDA 202439, seq 0125, M4.2.3.5.4, PH-36480)									
	PND								
60	10 [a]	5790	24.5	48500	20.37	73.53	2.8	615.95	2.3
60	21 [a]	2590	10.9	20200	8.48	32.89	1.2	256.54	1.0
60	30 [a]	841	3.6	11100	4.66	10.68	0.4	140.97	0.5
60	37 [b]	4100	17.3	35700	14.99	52.07	2.0	453.39	1.7
13-week pilot (gavage) toxicity study in juvenile rats (NDA 202439, seq 0125, M4.2.3.5.4, PH-36598)									
6	M	1570	6.6	8570	3.6	19.94	0.8	108.84	0.4
20	M	2050	8.7	24700	10.4	26.04	1.0	313.69	1.2
60	M	3390	14.3	29000	12.2	43.05	1.6	368.30	1.4
6	F	1220	5.2	8890	3.7	15.49	0.6	112.90	0.4
20	F	1980	8.4	12300	5.2	25.15	0.9	156.21	0.6
60	F	3780	16.0	33900	14.2	48.01	1.8	430.53	1.6

MoE = margins of exposure (when compared to the human plasma levels)
f_u rat = 1.27 %, f_u human pediatric = 11.2 % (M4.2.2.3/PH 41585 version 2)
Pediatric reference exposures are the highest steady state Cmax (236.66 µg/L, age group 12 to < 18 years) and AUC (2380.96 µg*h/L, age group 2 to < 6 years) obtained by population PK modeling (M2.7.2/Einstein Jr/Table 3-2)
PND = Postnatal day
Vehicles: [a] Tylose® 0.5 %
[b] Solutol HS 15®/ethanol/water

Table 7. Corrected Data of Systemic Exposure and Margin of Exposure from 13-week Toxicity Study in Juvenile Rats (PH-36598)

Daily Dose (mg/kg)	Sex	Total Exposure				Unbound Exposure			
		C_{max} (µg/L)	MoE	AUC_{0-24h} (µg*h/L)	MoE	C_{max} (µg/L)	MoE	AUC_{0-24h} (µg*h/L)	MoE
6	M	1700	7.2	14700	6.2	21.59	0.8	186.69	0.7
20		2270	9.6	22200	9.3	28.83	1.1	281.94	1.1
60		3800	16.1	39500	16.6	48.26	1.8	501.65	1.9
6	F	3160	13.4	18300	7.7	40.13	1.5	232.41	0.9
20		4790	20.2	47900	20.1	60.83	2.3	608.33	2.3
60		5770	24.4	61500	25.8	73.28	2.8	781.05	2.9

MoE = margins of exposure (when compared to the human plasma levels)
f_u rat = 1.27 %, f_u human pediatric = 11.2 % (M4.2.2.3/PH 41585 version 2)
Pediatric reference exposures are the highest steady state Cmax (236.66 µg/L, age group 12 to < 18 years) and AUC (2380.96 µg*h/L, age group 2 to < 6 years) obtained by population PK modeling (M2.7.2/Einstein Jr/Table 3-2)

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