CLINICAL PHARMACOLOGY REVIEW

NDA (Supplement)	22128 (S-19) and 208984 (S-2)
Submission Type	Pediatric efficacy supplement
Applicant Name	Viiv Healthcare
Submission Date	May 1, 2020
Brand (Generic) Name	Selzentry (Maraviroc)
Dosage Form (Strength)	Oral solution (20 mg/mL) Tablet (25 mg and 75 mg)
Indication	Treatment of HIV-1
Review Team	Jenny Zheng, Justin Earp, Su-Young Choi

Contents

1. Executive Summary

Maraviroc (MVC) is a CCR5 co-receptor antagonist indicated in combination with other antiretroviral agents for the treatment of CCR5-tropic HIV-1 in patients 2 years of age and older weighing at least 10 kg. The applicant submitted this efficacy supplement to extend the age down to birth (full term) for pediatric patients weighing at least 2 kg as summarized in Table 1.

The applicant provided the following reports to support the proposed dosing recommendations:

- Final report for study IMPAACT 2007 (b) (4), a Phase I safety and PK study of MVC in neonates born to HIV-1 positive mothers at risk for acquiring HIV-1 infection (conducted on behalf of VHC by DAIDS).
- A population PK modeling and simulation (M&S) report (PMAR-2007) that summarizes the model and PK parameters with variability from neonatal participants.
- A M&S report (PMAR-1030) providing simulated PK exposures for the proposed doses based on combined data from study IMPAACT 2007, study A4001031, and relevant adult studies.

Study IMPACCT 2007 contains PK data of MVC in neonates from birth to 6 weeks who received noninteracting concomitant medications. The currently approved MVC dosages for pediatric patients from >2 years to 18 years of age were based on Study A4001031, which was a PK, safety, and efficacy study in treatment-experienced pediatric subjects. In Study A4001031, the majority of subjects received

MVC with concomitant potent CYP3A inhibitors. No MVC PK data are available for children from 6 weeks to <2 years of age. The dosage recommendation for this age group is based on interpolation using PK data from neonates (<6 weeks old), children above 2 years of age, and adults.

Table 1: The Approved Dosage and the Applicant's Proposed Dosage for MVC in Pediatrics (blue font highlights the proposed changes)

	Current		Proposed	
	With potent CYP3A inhibitors	With no interacting drugs	With potent CYP3A inhibitors	With no interacting drugs
2 to <4 kg	Not approved		(b) (4)	30 mg BID
4 to <6 kg				40 mg BID
6 to <10 kg				100 mg BID
10 to < 14 kg	50 mg BID	Not recommended	50 mg BID	150 mg BID
14 to <20 kg	50 mg BID	Not recommended	50 mg BID	200 mg BID
20 to < 30 kg	75 mg (tablet)or 80 mg (oral solution) BID	Not recommended	75 mg (tablet)or 80 mg (oral solution) BID	200 mg BID
30 to <40 kg	100 mg BID	300 mg BID	100 mg BID	300 mg BID
≥ 40 kg*	150 mg BID*	300 mg BID*	150 mg BID*	300 mg BID*

*Approved dose in adults

* In adults, 600 mg BID is approved when MCV is co-administered with a potent CYP3A inducer. However, the use of MCV with a potent inducer is not recommended in pediatric patients due to the lack of supporting data.

Upon reviewing these reports, the Clinical Pharmacology Review Team has determined that the proposed MVC dosage for pediatric patients with noninteracting drugs is acceptable for children of at least 2 kg. However, the team does not agree with the applicant's recommended MVC dosage in pediatric subjects who are <2 years of age, <10 kg, and are receiving concomitant potent CYP3A inhibitors. No PK data are available in this population and MCV exposures and effects of potent CYP3A inhibitors cannot be reliably predicted using an M&S approach (see Section 4.2 for further details). Table 2 summarizes the dosage recommendations by the Agency. To be noted, no changes to the currently approved dosing recommendations for children ≥2 years of age in weight bands ≥30 kg are being proposed, and MVC is not recommended in pediatric patients who are receiving potent CYP3A inducers.

Table 2: MVC Dosage Recommended by the Agency in Pediatric Patients Weighing at least 2 kg

Concomitant Medications	Dosage of SELZENTRY Based on Weight							
	2 kg to <4 kg	4 kg to <6 kg	6 kg to <10 kg	10 kg to <14 kg	14 kg to <20 kg	20 kg to <30 kg	30 kg to <40 kg	**≥40** kg
Potent CYP3A inhibitors (with or without a CYP3A inducer)	Not recommended			50 mg BID	50 mg BID	75 mg (tablet) or 80 mg (oral solution) BID	100 mg BID	150 mg BID
Noninteracting concomitant medications	30 mg BID	40 mg BID	100 mg BID	150 mg BID	200 mg BID	200 mg BID	300 mg BID	300 mg BID

blue font shows the new recommended dosage, underline shows the difference between the Agency recommendation and the Applicant proposal

1.1 Summary of Clinical Pharmacology Findings

1.1.1 Study IMPAACT 2007 –

IMPAACT 2007 was a Phase I, multi-center, open label, intensive PK study to evaluate the safety and PK of MVC solution when administered with a single or combination antiretroviral drug (ARV) regimen for prevention of perinatal HIV transmission to infants exposed to HIV-1. This study was conducted in full-term infants (gestational age at least 37 weeks) up to 3 days old, weighing at least 2 kg, born to mothers living with HIV-1. A total of 47 infant participants were enrolled in 1 of 2 sequential dosing cohorts stratified by EFV exposure:

Cohort 1: infants received two single doses of (~8 mg/kg) MVC oral solution (within 3 days of birth and at Week 1)
- Stratum 1A: n=8 infant participants without *in utero* exposure to maternal EFV
- Stratum 1B: n=7 infant participants with *in utero* exposure to maternal EFV

Cohort 2: infants received repeated doses (~ 8 mg/kg BID) of MVC oral solution
- Stratum 2A: n=16 infant participants without any exposure to maternal EFV either *in utero* or while breastfeeding.
- Stratum 2B: n=16 breastfeeding infant participants with exposure to maternal EFV both *in utero* and after birth while breastfeeding

Intensive PK samples were collected predose and up to 24 hours (± 2 hours) postdose on Day 1 for Cohort 1; and predose and up to 12 hours (± 1 hour) postdose at Week 1 and Week 4 for Cohort 2. An additional sparse PK sample was collected at Week 1 (pre-dose, 1-2 and 22-26 hours post dose) for Cohort 1 and at Week 6 (single random sample) for Cohort 2.

The applicant selected the MVC PK target of a Cavg value of ≥75 ng/mL in the study. This target was based on the multivariate analysis of predictors of response (binary success failure endpoint of viral load >50 copies/mL) evaluation including exposure and other predictors of response at 48 weeks from the adult HIV-1 treatment-naïve study (A4001026) where MVC was dosed at 300 mg BID. The dose would be considered a failure if the MVC PK target was not met in 2 or more of the 6 infant participants at the Entry/Day 1 and Week 1 visits. For Cohort 2, the dose would be considered a failure if the MVC PK target

was not met in 3 or more of the 12 infant participants in Stratum 2A or 2B at both PK assessments (Weeks 1 and 4).

Table 3 summarizes MVC exposures observed in Study IMPACCT 2007. The results indicated that the PK target of Cavg ≥75 ng/mL was achieved in all participants in Cohort 1 at Entry/Day 1 and most participants in Cohort 2 at Week 1 (18/25, 72%) and Week 4 (16/25, 64%). The PK dose finding criteria was met in Cohort 1 but not in Cohort 2 at both Week 1 and Week 4. High PK variability was observed in all strata and cohorts, which is consistent with the high PK variability observed for other ARVs in neonates (e.g., nelfinavir, nevirapine). In addition, MVC exposures were not reduced by maternal exposure to EFV and was generally comparable between infant participants with and without maternal exposure to EFV.

Table 3: Summary of Geometric Mean (GM) MVC Exposures in Neonates following Single and Multiple (BID) Dose Administration of ~8 mg/kg MVC (IMPAACT 2007)

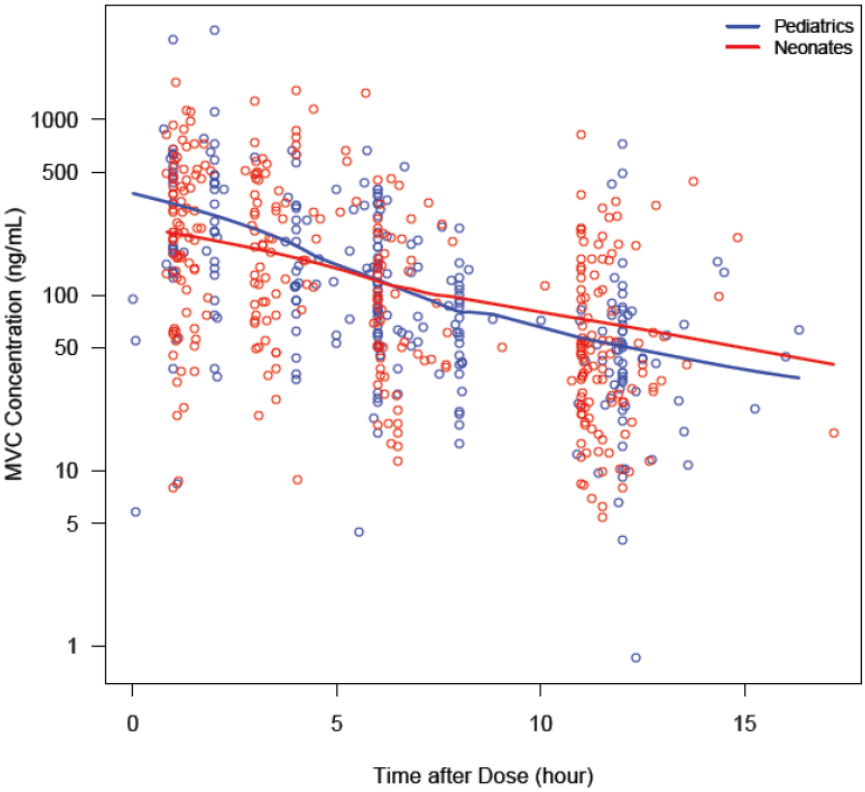
Analysis Set	Median weight (range) (kg)	GM Cavg (95% CI) (ng/mL)	GM Cmax (95% CI) (ng/mL)	GM Ctau (95% CI) (ng/mL)	PK target met[a] n/N(%)
Entry/Day 1 (single-dose, Cohort 1)					
Cohort 1 (N=13)	3.30 (2.48-3.97)	292.46 (179.71, 475.95)	380.05 (195.94, 737.14)	N/A	13/13 (100)
Stratum 1A (n=6)	3.23 (2.48-3.84)	227.76 (81.9, 633.35)	225.59 (53.9, 944.1)	N/A	6/6 (100)
Stratum 1B (n=7)	3.44 (2.80-3.97)	362.36 (203.18, 646.23)	594.29 (344.43, 1025.39)	N/A	7/7 (100)
Week 1 (multiple-dose, Cohort 2)					
Cohort 2 (N=25)	3.10 (2.40-3.94)	101.37 (68.02, 151.07)	261.58 (165.48, 413.48)	22.71 (12.15, 42.44)	18/25 (72)
Stratum 2A (n=13)	2.97 (2.64-3.84)	102.32 (57.05, 183.52)	278.68 (141.35, 549.43)	22.7 (10.3, 50.04)	10/13 (77)
Stratum 2B (n=12)	3.25 (2.40-3.94)	100.34 (52.84, 190.53)	244.23 (118.42, 503.71)	22.72 (7.37, 70.03)	8/12 (67)
Week 4 (multiple-dose, Cohort 2)					
Cohort 2 (N=25)	3.73 (2.27-4.54)	115.42 (82.33, 161.81)	295.45 (218.96, 398.65)	42.67 (24.85, 73.29)	16/25 (64)
Stratum 2A (n=13)	3.50 (3.17-4.18)	128.75 (74.07, 223.79)	357.3 (234.7, 543.92)	40.19 (15.68, 103.03)	9/13 (69)
Stratum 2B (n=12)	3.87 (2.27-4.54)	102.53 (64.88, 162.04)	240.47 (151.23, 382.36)	45.54 (23.46, 88.38)	7/12 (58)

a. Number of participants to achieve PK target Cavg ≥75 ng/mL

Source: The Applicant's Clinical Overview, Page 27, Table 8

MVC exposures following single dose or repeated BID dose administration of ~8 mg/kg (range: 6.13 to 10.13 mg/kg; 20-40 mg) MVC to infant participants were within the range of those observed in the Phase II pediatric study (≥2 years of age and >10 kg) through at least 48 weeks (Figure 1). In addition, MVC Cavg in neonates are generally comparable to exposures observed in Phase IIb/III adult studies following administration of MVC 300 mg BID (GM Cavg: 95 ng/mL) with relative lower Cmin in Week 1 and Week 4 following multiple doses as compared to adults (GM Cmin: 55 ng/mL in adults).

Figure 1: MVC Concentrations versus after Time after Dose Profiles in Pediatric Participants (A4001031) and Neonates (IMPAACT 2007) with Noninteracting Drugs



Source: The Applicant's Clinical Overview, Page 32, Figure 1

Reviewer's comments
While the applicant used a Cavg value of 75 ng/mL to make decisions to proceed to cohort 1 to cohort 2, FDA's decision on the approval of the dosing regimen is primarily based on the comparison of MCV exposures between the proposed pediatric patient group and adults/older pediatric patients.

1.1.2 Pediatric Maraviroc Dosing when Coadministered with Noninteracting Concomitant Medications

PK modeling of all pediatric data (A4001031 and IMPAACT 2007) combined with adult data was performed to assist in interpretation of the data and provide an assessment regarding interpolation/extrapolation of MVC PK for different dosing scenarios. In this analysis, there were 54 pediatric subjects (10 from Study A4001031, and 44 from Study IMPACCT 2007) across the age cohorts who received MVC in the absence of interacting drugs. A semi-physiological model, which included maturation functions for hepatic (e.g. CYP3A ontogeny) and renal elimination, had been developed for the MVC population (See Section 4.2 for details). MVC simulations without potent CYP3A inhibitors for various doses across WHO-recommended weight bands were simulated.

Table 4 shows the simulated MVC steady-state exposures (Cavg, Cmax, and Cmin) with noninteracting drugs (b) (4) Table 5 shows the simulated MVC steady-state exposures (Cavg, Cmax, and Cmin) with noninteracting drugs (b) (4) for infants 6 weeks to <2 years of age. Table 6 shows the simulated MVC steady-state exposures (Cavg,

Cmax, and Cmin) with noninteracting drugs for 3 to <4 kg and 4 to <6 kg (b) (4) conducted by the review team.

The simulation shows that the ratio of predicted median exposures for the proposed doses for pediatrics relative to adult ranged from 0.95 to 1.90-fold across all the weight-bands for Cavg, from 0.89 to 2-fold for Cmax and from 1.01 to 1.84-fold for Cmin. The predicted exposures for pediatrics were not greater than the Cavg and Cmax prediction range for adults receiving CYP3A inhibitors at the approved 150 mg BID dose (median Cavg: 338 ng/mL, median Cmax: 487 ng/mL). The result indicated that the proposed dosage by the Applicant is acceptable.

Table 4: Predicted MVC Exposures at Steady-State with Noninteracting Drugs Based on the Final Model with IMPAACT 2007 data for the Proposed Doses for Neonates from birth to 6 Weeks of Age by Weight Bands vs. Adults

Dose (mg)	Adult	2 to <3 kg	3 to <4 kg	4 to <5 kg	5 to <6 kg
	300	30	30	40	40
Cavg (ng/mL)					
GM (CV%)	95 (53)	161 (65)	127 (65)	147 (65)	114 (62)
Median (90%PI)	98 (40-208)	163 (58-415)	128 (46-326)	149 (53-373)	116 (43-287)
% >75 ng/mL	69	89	82	87	77
Ratio to Adult		1.66	1.31	1.52	1.18
Cmax (ng/mL)					
GM (CV%)	188 (84)	275 (83)	218 (82)	256 (81)	201 (81)
Median (90%PI)	178 (61-671)	270 (86-920)	220 (67-705)	252 (80-852)	196 (64-650)
Ratio to Adult		1.52	1.24	1.42	1.10
Cmin (ng/mL)					
GM (CV%)	55 (64)	102 (74)	80 (74)	92 (76)	70 (73)
Median (90%PI)	57 (20-140)	105 (33-287)	82 (26-231)	94 (29-265)	72 (23-199)
Ratio to Adult		1.84	1.44	1.65	1.26

Note: Ratio to adult is median exposures.
The Applicant's Clinical Overview, Page 37, Table 13

Table 5: Predicted MVC Exposures at Steady-State with Noninteracting Drugs Based on the Final Model with IMPAACT 2007 Data [redacted] (b) (4)

Dose (mg)	Adult	3 to <6 kg	6 to <10 kg	10 to <14 kg	14 to <20 kg
	300	40	100	150	200
Cavg (ng/mL)					
GM (CV%)	95 (53)	97 (68)	147 (69)	152 (57)	181 (52)
Median(90%PI)	98 (40-208)	98 (34-260)	148 (52-403)	157 (61-341)	186 (78-384)
% >75 ng/mL	69	66	86	90	96
Ratio to Adult		1.00	1.51	1.60	1.90
Cmax (ng/mL)					
GM (CV%)	188 (84)	178 (87)	290 (91)	312 (86)	371 (82)
Median (90%PI)	178 (61-671)	176 (53-628)	285 (82-1095)	302 (96-1120)	356 (121-1302)
Ratio to Adult		0.99	1.60	1.70	2.00
Cmin (ng/mL)					
GM (CV%)	55 (64)	58 (80)	83 (83)	84 (71)	101 (66)
Median (90%PI)	57 (20-140)	59 (17-179)	84 (24-264)	87 (28-225)	104 (36-259)
Ratio to Adult		1.04	1.47	1.53	1.82

Note: Ratio to adult is median exposures.
The Applicant's Clinical Overview, Page 35, Table 11

Table 6: Predicted MVC Exposures at Steady-State with Noninteracting Drugs [redacted] (b) (4) **The simulations were performed by by the Agency with the applicant's final PPK model.**

Dose (mg)	Adult	3 - <4kg	4 - <6kg
	300	30	40
Cavg (ng/mL)			
GM (CV)	95 (53)	90 (68)	95 (66)
Median	98	93	96
Ratio to Adult		0.95	0.98
Cmax (ng/mL)			
GM (CV)	188 (84)	166 (89)	174 (86)
Median	178	159	172
Ratio to Adult		0.89	0.97
Cmin(ng/mL)			
GM (CV)	55 (64)	55 (75)	57 (77)
Median	57	58	58
Ratio to Adult		1.01	1.01

1.1.3 Pediatric Maraviroc Dosing when Coadministered with Potent CYP3A Inhibitor Concomitant Medications

No MVC PK data is available for pediatric subjects who are < 2 years of age, <10 kg, and are receiving concomitant potent CYP3A inhibitors. Separate models were used to describe data with and without potent CYP3A inhibitors because the original model that accounts for drug-drug interaction (DDI) could not predict exposures in the noninteracting scenario, which results in challenges for utilizing noninteracting data for neonates to predict MVC exposure for subjects receiving concomitant CYP3A Inhibitors. This is further complicated by the CYP3A maturation that takes place <1 year because It is unknown if the magnitude of DDI effect is changed by the maturation of CYP3A expression. Therefore, the review team does not recommend MVC in pediatric subjects who are < 2 years of age, <10 kg, and are receiving concomitant potent CYP3A inhibitors.

2. Recommendations

The Office of Clinical Pharmacology review team finds the application acceptable and recommends approval only for pediatric patients receiving concomitant noninteracting drugs. However, the team does not recommend MVC in pediatric patients who are < 2 years of age, <10 kg, and are receiving concomitant potent CYP3A inhibitors due to no available PK, efficacy, and safety data and an inability to reliably predict PK in this population.

3. Labeling recommendations

The following clinical pharmacology related sections of the USPI were updated: Section 2.4, Section 8.4 and Section 12.3.

- Section 2.4: MVC dosage recommendation for pediatric patients < 30 kg when coadministered with noninteracting concomitant medications is included.
- Section 8.4:
    - Study design for IMPAACT 2007 is included;
    - The dosing recommendation for pediatric patients 6 weeks to <2 years of age, concomitantly receiving noninteracting medications, was based on population PK analysis;
    - There are insufficient data to make dosing recommendations for use of SELZENTRY in pediatric patients concomitantly receiving potent CYP3A inhibitors and weighing less than 10 kg.
- Section 12.3:
    - PK results of IMPAACT 2007 are included;
    - The results of the population PK analysis for pediatric patients 6 weeks to <2 years of age, concomitantly receiving noninteracting medications, are described.

4 Individual Study Reviews

4.1 Study IMPAACT 2007 – Neonate Safety and PK study

Title: Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

Study Centers: 9 Centers in 4 countries: Kenya (1 center), South Africa (2 centers), Thailand (1 center), and US (5 centers)

Trial Period:
Duration of Clinical Phase: June 5, 2017 through November 20, 2019
Duration of Bioanalytical Phase: August 30, 2019 through September 19, 2019
Date of Final Report: December 11, 2019

Trial Objectives:
To evaluate the PK of MVC solution, during the first 6 weeks of life, when administered with antiretroviral (ARV) prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
To evaluate the safety and tolerability of MVC solution, during the first 6 weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
To determine an appropriate dose of MVC solution within the first 6 weeks of life.

Trial Design: This was a Phase I, multi-center, open label, intensive PK study to evaluate the safety and PK of MVC solution when administered with a single or combination ARV regimen for prevention of perinatal HIV transmission to infant participants exposed to HIV-1. This study was conducted in full-term infant participants up to 3 days old and at least 2 kg at birth, born to mothers living with HIV-1. Total of 47 infant participants were enrolled in 1 of 2 sequential dosing cohorts stratified by EFV exposure:

Cohort 1: infants received 2 single doses of (~8 mg/kg) MVC oral solution (within 3 days of birth and at Week 1)
- Stratum 1A: n=8 infant participants without *in utero* exposure to maternal EFV
- Stratum 1B: n=7 infant participants with *in utero* exposure to maternal EFV

Cohort 2: infants received repeated doses (~ 8 mg/kg BID) of MVC oral solution
- Stratum 2A: n=16 infant participants without any exposure to maternal EFV either *in utero* or while breastfeeding.
- Stratum 2B: n=16 breastfeeding infant participants with exposure to maternal EFV both *in utero* and after birth while breastfeeding

MVC was administered by oral syringe using weight-band-based dosing. Infant participants' weight at each visit was used to determine the dose (Table 7). However, if a dose change was indicated based on an infant participant's current weight during the intensive PK sampling visits (Week 1 and Week 4), the dose change was only implemented after the intensive PK sampling was completed.

Table 7: Weight-Based Dosing for Infant Participants Receiving ~8 mg/kg MVC

Weight Band (kg)	Dose (mg)	Volume to Administer (mL)

2.00 to 2.54	20	1
2.55 to 3.14	25	1.25
3.15 to 3.84	30	1.5
3.85 to 5.04	40	2
5.05 to 6.00	50	2.5

Source: The Applicant's Study Report for IMPAACT 2007, Page 24, Table 3
MVC oral solution formulation (20 mg/kg) was used.

Prohibited medications (for both infant participants and breastfeeding participant mothers)

- Potent CYP3A inhibitors such as: atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, saquinavir, cobicistat, boceprevir, telaprevir, elvitegravir, ketoconazole, itraconazole, clarithromycin
- Potent CYP3A inducers such as: EFV (Strata 1A and 2A only), etravirine, rifampin, St. John's Wort, carbamazepine, phenobarbital, and phenytoin
- Other: isoniazid, MVC (for mother during pregnancy)

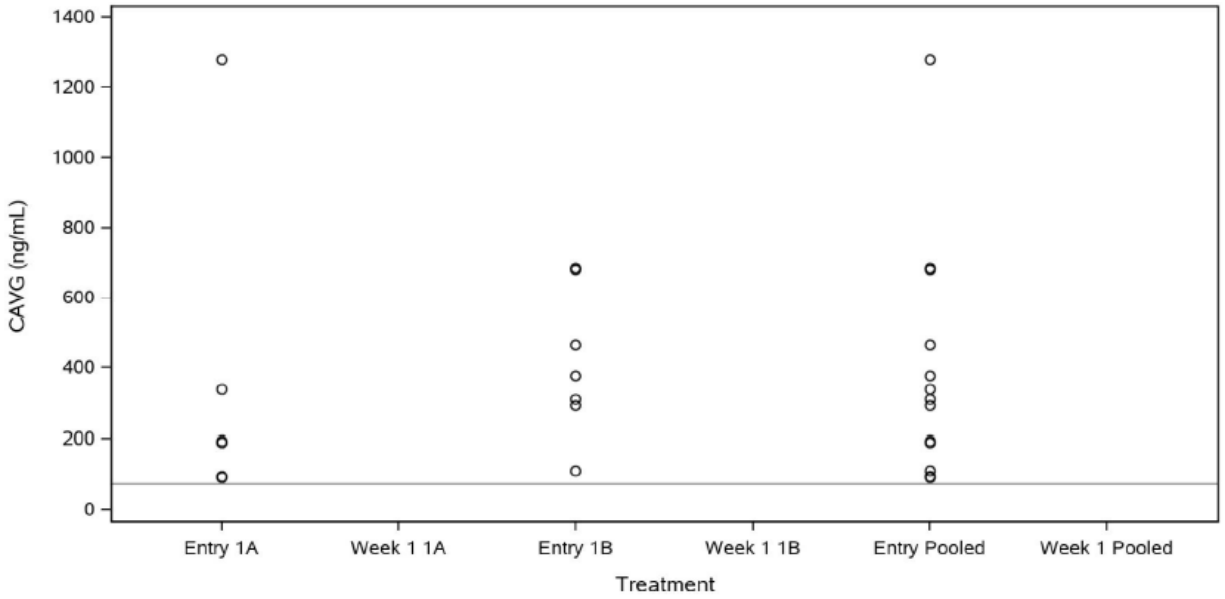
PK Sampling: Intensive PK samples were collected predose and up to 24 hours (± 2 hours) postdose on Day 1 for Cohort 1; and predose and up to 12 hours (± 1 hour) postdose at Week 1 and Week 4 for Cohort 2. An additional sparse PK sample was collected at Week 1 (pre-dose, 1-2 and 22-26 hours post dose) for Cohort 1 and at Week 6 (single random sample) for Cohort 2.

Bioanalytical assay assessment: MVC PK samples were assayed at the University of Alabama Birmingham. The samples were analyzed using a validated analytical method for MVC based on protein precipitation, followed by HPLC/MS/MS analysis.

Clinical and Analytical Site Inspection: Office of Study Integrity and Surveilance (OSIS) arranged an inspection of Study IMPAACT 2007 conducted at Rush University Medical Center, Chicago, IL. No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. OSIS also decided that an inspection on the analytical site at University of Alabama at Birmingham, Birmingham, AL is not warranted at this time because the site was inspected in February 2020.

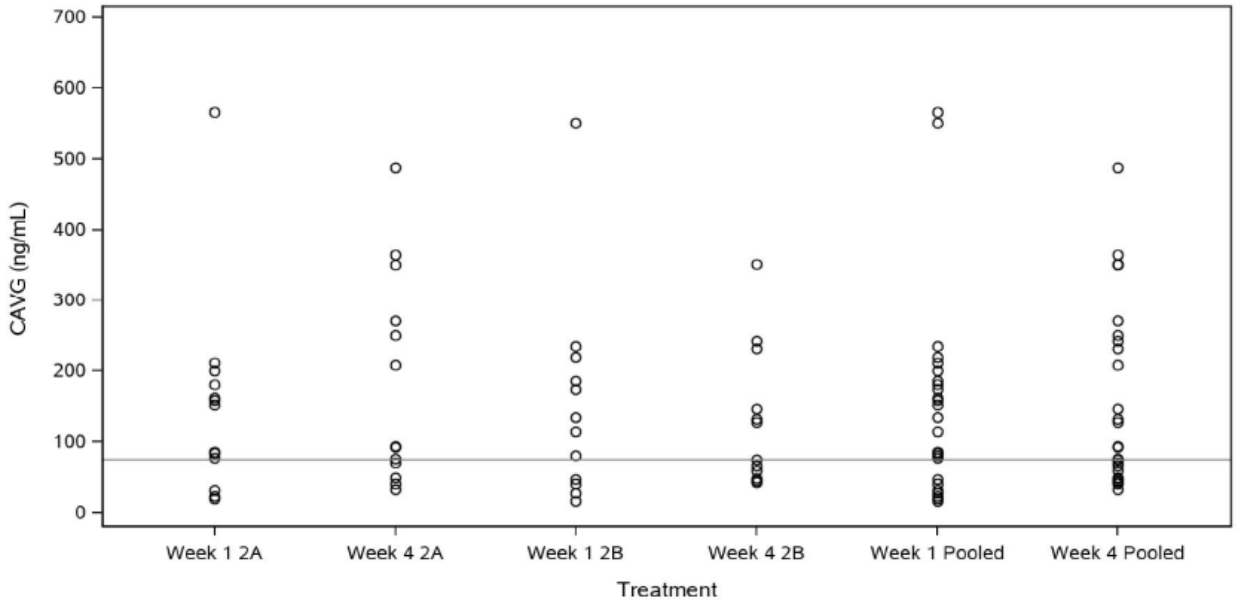
PK results: Figure 2 and 3 show MVC Cavg in Cohort 1 following MVC single dose administration and MVC Cavg in Cohort 2 following MVC repeat dose administration, respectively. Table 8 and Table 9 show Pooled MVC PK parameters for Cohort 1 and Cohort 2, respectively. The results indicated that MVC exposure is higher and apparent clearance (CL/F) is lower at birth as compared to Week 1 and Week 4, probably due to immature CYP3A expression and renal function at birth.

Figure 2: Summary of Plasma MVC Cavg by Strata/Visit (Cohort 1) Following MVC Single Dose Administration



Source: The Applicant's Study Report for IMPAACT 2007, Page 48, Figure 3

Figure 3: Summary of Plasma MVC Cavg by Strata/Visit (Cohort 2) Following MVC Repeat Dose Administration



Source: The Applicant's Study Report for IMPAACT 2007, Page 51, Figure 6

Table 8: MVC PK Parameters for Cohort 1: Day 1 (Pooled Results) Following MVC Single Dose Administration

	MVC Single Dose (Day 1)	
	GM (CV%)	Median (range)
Cavg (ng/mL)[a] (n=13)	292.5 (95.6)	311.0 (93.5-1278.6)
Cmax (ng/mL) (n=13)	380.1 (152.5)	510.2 (29.9-1618.4)
Tmax (hrs) (n=13)	2.5 (93.3)	1.8 (1.1-12.8)
t1/2 (hrs)[b] (n=12)	5.5 (±3.1)[c]	4.1 (3.3-12.5)
AUC (ng.hr/mL)[d] (n=13)	3509.7 (95.6)	3734.0 (1122.5-15343.4)
CL/F (L/hr)	10.0 (134.2)	12.0 (2.0- 26.7)
Vd/F (L)	64.8 (153.6)	76.1 (10.3- 174.2)

a. Cavg calculated for BID dosing
b. t1/2 values should be interpreted with caution due to the limited number of PK samples in the elimination phase
c. For t1/2 arithmetic mean ± SD is shown instead of GM (CV%)
d. AUC for Cohort 1 represents AUCifp (AUC from 0 to infinity), or if AUCifp is missing, AUCall (AUC from 0 to last observation)
Source: The Applicant's Study Report for IMPAACT 2007, Page 48, Table 13 and Page 234, Table 5.2

Table 9: MVC PK Parameters for Cohort 2: Week 1 and Week 4 (Pooled Results) Following MVC Repeat Dose Administration

	MVC Repeat Dose (Week 1)		MVC Repeat Dose (Week 4)	
	GM (CV%)	Median (range)	GM (CV%)	Median (range)
Cavg (ng/mL)[a] (n=25)	101.4 (124.3)	134.7 (17.1-565.7)	115.4 (97.7)	93.6 (32.9-488.2)
Cmax (ng/mL) (n=25)	261.6 (155.7)	283.8 (34.4-1468.4)	295.5 (83.3)	304.2 (76.5-793.4)
Tmax (hrs) (n=25)	2.0 (61.4)	1.6 (0.8-6.2)	1.9 (70.9)	1.5 (0.0-11.4)
t1/2 (hrs)[b] (n=22)	3.8 (±2.2)[c]	3.5 (2.0-12.3)	12.1 (± 29.7)[c]	3.9 (2.0-143.9)
AUC (ng.hr/mL)[d] (n=25)	1216.4 (124.3)	1615.9 (204.9-6788.2)	1385.0 (97.7)	1123.0 (395.0-5858.5)
CL/F (L/hr) (n=25)	20.9 (123.4)	15.8 (3.0-122.0)	20.2 (98.0)	22.6 (4.3-63.3)
Vd/F (L) (n=25)	99.4 (115.4)	102.2 (15.6-560.6)	150.9 (103.1)	135.2 (38.0-1977.4)
Ctau (ng/mL) (n=22)	22.7 (298.7)	23.7 (0.0-824.9)	42.7 (213.7)	53.5 (0.0-373.1)

a. Cavg calculated for BID dosing
b. t1/2 values should be interpreted with caution due to the limited number of PK samples in the elimination phase
c. For t1/2 arithmetic mean ± SD is shown instead of GM (CV%)
d. AUC for Cohort 2 represents AUCtau (AUC over dosing interval), or if AUCtau is missing, AUCall
Source: The Applicant's Study Report for IMPAACT 2007, Page 52, Table 14

Conclusion:

- MVC exposure is higher and apparent clearance (CL/F) is lower at birth as compared to Week 1

and Week 4, probably due to immature CYP3A expression and renal function at birth.

- MVC PK data demonstrated that the PK target of Cavg ≥75 ng/mL was achieved in all participants in Cohort 1 at Day 1 and most participants, 15/25 (60%), in Cohort 2 at Week 1 and Week 4.
- MVC PK parameters showed high intra- and inter-participant variability in all strata and cohorts.
- In both cohorts, MVC exposures were comparable between infant participants with and without maternal exposure to EFV.

4.2 Population PK Review

The population PK of MVC in children 2 years and older has been reviewed previously by the office of clinical pharmacology. See the review in DARRTs on 10/07/2016 by Dr. Mario Sampson. The PPK model presented therein is referred to as PMAR-193.

In this submission the applicant has updated their population PK analysis to include further PK data (down to birth for subjects with non-interacting concomitant medications) and improve the model structure. Two separate models were utilized for subjects receiving concomitant CYP3A4 inhibitors and subjects who did not. The applicant's modeling strategy is shown below:

"When it was found that the final PMAR-193 model gave unrealistic simulations for MVC with LPV/r in relation to the fed/fasted dosing state it was decided to use the PMAR-193 model only for the non-interaction scenario. The final model from PMAR-193 was fitted after the following data/parameter changes were made:

- Exclusion of all data and associated parameters for MVC with potent CYP3A inhibitors and potent CYP3A inducers.
- Replacement of interim PK data from A4001031 for the final Week 48 PK data cut.
- Inclusion of neonate MVC PK data from IMPAACT 2007. After a predictive check showed some model misfit when using only literature-based maturation functions these were re-estimated based on available data."

The fact that a common model with a DDI covariate could not explain the PK in both scenarios did not provide confidence that the PK data in patients with non-interacting concomitant meds could be utilized to inform the dose in subjects <2 years of age receiving concomitant medications where no PK was collected. This is further compounded by the fact that the DDI may also not be correctly predicted in this age range owing to the maturation of liver enzymes between birth and two years of age. As such, 1) it was determined that enough PK data were not available to inform the dose in infants less than two years of age receiving concomitant medications and 2) the population PK review herein will only focus on model development and simulations for pediatrics receiving non-interacting concomitant medications.

4.2.1 Applicant's Population PK Analysis in Patients with Non-Interacting Drugs

Areas shaded in grey are copied from the Applicant's Population PK Report.

Data

Adult MVC PK from 20 healthy volunteer studies (482 participants with 11467 PK samples; age range from 18 to 54 years old and body weight (WT) from 46 kg to 109 kg) and 2 MVC mono-therapy studies in HIV-1 infected participants (48 participants with 928 PK samples; age range from 27 to 53 years old and WT from 53 kg to 92.5 kg) were combined with PK data from pediatric studies A4001031 (10 pediatric

participants with 263 samples; age range from 3 to 17 years old and WT range from 16.4 kg to 43 kg) and IMPAACT 2007 (44 neonates with 358 samples; age range from birth to 42 days and WT range from 2.04 kg to 5.24 kg). Three withdrawn neonates (NSID [redacted (b) (6)]) in IMPAACT 2007 were not included in the data set.

Methods

Nonlinear mixed effects modelling (NONMEM) software version 7.4.3 [redacted (b) (4)], was used for modeling (estimation) as well as for simulations. Perl-speaks-NONMEM (PsN) version 4.8.0 as supporting software for the execution of NONMEM was used. The estimation was first-order conditional estimation method with interaction (FOCEI). R version 3.5.2, and R libraries (dplyr, ggplot2, xpose) were used for data manipulations, graphical analysis, creation of simulation data sets, exploratory analysis, post-processing of simulation output, as well as data summaries.

Base Model for MVC with Non-Interacting Drugs

The final PMAR-193 model included a 4-compartment disposition (IV data); two absorption compartments with different absorption rate constants (absorption rate constant of dual input compartment 1 (KA1), absorption rate constant of dual input compartment 2 (KA2)) and lag times on both depot compartments; a general gastrointestinal first pass effect; renal and hepatic clearances parameterized in terms of intrinsic clearance (CLI). Oral dose non-linearity was described with a sigmoidal maximum effect (Emax) (maximal bioavailability (Fmax)) model to represent the saturable non-linearity in transporter effects (P-gp efflux) in the gastro-intestinal tract. Fmax was fixed to 1 (thereby assuming 100% absorption at sufficiently high dose) and all covariate absorption effects placed on dose to reach half Fmax in sigmoidal Fmax absorption model (MG50).

A priori allometric weight scaling was added to all disposition parameters, with CL and inter-compartmental clearance parameters being scaled with weight raised to a power of 0.75, and all volume parameters being scaled directly by weight. In addition, these inter-compartmental clearance and volume scaled parameters were centered on a weight of 70 kg, to facilitate comparison between adult and pediatric participants. The renal clearance (CLR) was fixed to 12 L/hr and scaled allometrically with weight and with a kidney age maturation function. Hepatic extraction (EH) and liver volume (VH) relative to body weight was scaled according to the relationship described in Price et al 2003. A published maturation factor for CYP3A4 on CLI was also applied and the age-dependent relationship between VH and liver blood flow was scaled by an arbitrary liver partition coefficient multiplier (KP) of 0.8 chosen to give values of extraction and plasma flow broadly compatible with previous analysis of MVC IV/oral data.

The parameters from the original PMAR-193 [1] model were re-estimated with the reduced data set for adults and A4001031 data (non-interacting data alone).

A predictive check was performed by simulating 1000 neonates with the covariates sampled from distributions taken from the IMPAACT 2007 study. Thereafter, the IMPAACT 2007 data was included in the analysis data set and parameters were re-estimated.

Model Assumptions for MVC with Non-Interacting Drugs

The maturation functions for renal and hepatic development were based on PMA with fixed maturation half-time (TM50) and Hill parameters taken from literature references (key assumption):

$$AGEEFFECT(renal) = PMA^{3.33}/(PMA^{3.33} + TM50^{3.33}) \quad (1)$$

$$AGEEFFECT(hepatic) = PMA^{3}/(PMA^{3} + TM50^{3}) \quad (2)$$

TM50 was fixed to 55.4 and 73.6 in equation 1 and equation 2, respectively.

The renal maturation function differs from that used for MVC with potent inhibitors because a different weight allometric exponent was used (0.632 rather than 0.75) for renal clearance. For non-interacting drugs the parameters for the maturation function on CLI were tested once IMPAACT 2007 data for neonates were added.

Final Model and Assessment of Predictive Performance for MVC with Non-interacting Drugs
The model built with adult and limited pediatric data from A4001031 (without neonate data) was used to perform a predictive check to see how well the neonate data was predicted under the initial assumptions. The predictive check simulated 1000 patients using the relevant covariates associated with Week re-sampled from the IMPAACT 2007 data set. The simulations were then subsetted by Week of observation (Weeks 0, 1, 4 and 6) for a graphical display of observed versus predicted data.

The final models with and without the neonate data were assessed using a pcVPC stratified by adult and pediatric populations.

Simulations
Simulations were performed utilizing the final models with 5000 subjects per age/WT group. Simulated concentrations (individual predictions (IPRED)) incorporating inter-individual variability (IIV) were used to calculate exposure metrics (AUC, Cavg, Cmax, Cmin, and ratio of median exposure values of neonates/pediatrics to adults) at steady-state following twice daily (BID) dosing. Concentration time profiles were simulated following steady-state dosing with time steps of 0.5 hour to 1.5 hours and 1 hour intervals to 12 hours.

Body weight for pediatric patients (term neonates from birth to ≤6 weeks of age, infants from 6 weeks to <2 years of age and children from 2 to <6 years of age) were sampled from a normal distribution with gender specific median, generalized coefficient of variation, and the power in the Box-Cox transformation obtained from the Centers for Disease Control and Prevention (CDC) growth charts. Postmenstrual age (PMA) for all simulated term neonates and infants with age <2 years was calculated by assuming gestational age (GA) of 40 weeks.

For adults, covariates were sampled from a multivariate normal density with covariance of age, weight, and creatinine clearance (CRCL) computed based on adult subjects. The sampled age, weight, and CRCL were truncated to the range obtained from the available adult data with WT >40 kg and CRCL >50 mL/min. For pediatric patients CRCL (only used for
CYP3A inhibitor simulations for age 2 years and above) was sampled from a normal distribution of mean and standard deviation (SD) of adult data; range from 50 to 220 mL/min. For all simulation data sets, approximately 50% subjects were set to Black race.

RESULTS

Final PPK Model for Patients with Non-Interacting Drugs

A summary of the number of participants, PK samples and demographics in the adult healthy volunteer (HV), HIV-1 and pediatric data set with non-interacting drugs is presented in Table 10 and Table 11.

Table 10. Summary of Number of Participants, PK Samples and Demographics in the Adult and Pediatric (Study A4001031) Data Set with Non-Interacting Drugs

	Adult HIV	Adult HV	Pediatrics
Number of Subjects	48	482	10
Number of Plasma Samples	928	11467	263
Sex			
Number (%) Males	46 (95.8)	385 (79.9)	4 (40)
Number (%) Females	2 (4.17)	97 (20.1)	6 (60)
Race			
Number (%) Black	1 (2.08)	17 (3.53)	6 (60)
Number (%) Asian	0	120 (24.9)	0
Number (%) White	46 (95.8)	342 (71)	2 (20)
Number (%) Other	1 (2.08)	3 (0.622)	2 (20)
Formulation			
Number (%) with Tablet	48 (100)	410 (85.1)	7 (70)
Number (%) with Solution	0	72 (14.9)	3 (30)
Food			
Number (%) Fasted	40 (83.3)	466 (96.7)	0
Number (%) Fed	8 (16.7)	16 (3.32)	10 (100)
Body Weight			
Median (Range) (kg)	73.7 (53-92.5)	71 (46-109)	32.1 (16.4-43)
Chronological Age			
Median (Range) (years)	36 (27-53)	28 (18-54)	11.5 (3-17)

Repository artifact ID FI-1888318.

HV = healthy volunteer, HIV = human immunodeficiency virus type 1

(Source: Applicant's Population PK Simulation Report, Table 4)

Table 11. Summary of Number of Neonates, PK Samples and Demographics (by Week) in IMPAACT 2007

	Week 0	Week 1	Week 4	Week 6	Total
Number of Subjects	15	42	26	22	44
Number of Plasma Samples	61	152	124	21	358
Sex					
Number (%) Males	6 (40)	22 (52.4)	15 (57.7)	13 (59.1)	23 (52.3)
Number (%) Females	9 (60)	20 (47.6)	11 (42.3)	9 (40.9)	21 (47.7)
Race					
Number (%) Black	12 (80)	33 (78.6)	20 (76.9)	16 (72.7)	35 (79.5)
Number (%) Asian	0	3 (7.14)	3 (11.5)	3 (13.6)	3 (6.82)
Number (%) White	3 (20)	6 (14.3)	3 (11.5)	3 (13.6)	6 (13.6)
Number (%) Other	0	0	0	0	0
Body Weight					
Median (Range) (kg)	3.3 (2.04-3.97)	3.2 (2.44-4)	3.72 (2.37-4.54)	4.23 (2.76-5.24)	3.5 (2.04-5.24)
Chronological Age					
Median (Range) (days)	1 (0-3)	8 (5-14)	24.5 (19-32)	38.5 (34-42)	11 (0-42)

Repository artifact ID FI-1888317.
PK = pharmacokinetic

(Source: Applicant's Population PK Simulation Report, Table 5)

The final population PK model (step 9) parameters are shown in Table 12. Standard GOF plots are depicted in Figure 4 and Figure 5.

Table 12. Parameter Estimates for the Base Model for Non-Interacting Drugs without IMPAACT 2007 and Final Model with IMPAACT 2007

Parameter	Base Model (Step 2)		Final Model (Step 9)	
	Estimate (%RSE)	IIV% (%RSE)	Estimate (%RSE)	IIV% (%RSE)
Vc (L) (θ_1)	12.6 FIX		12.6 FIX	
CLI (L/h for 70 kg) (θ_2)	75.9 FIX	36.1 FIX	75.9 FIX	36.1 FIX
Q1 (L/h for 70 kg) (θ_3)	14.7 FIX		14.7 FIX	
Vp1 (L for 70 kg) (θ_4)	31.5 FIX		31.5 FIX	
Q2 (L/h for 70 kg) (θ_5)	29.3 FIX		29.3 FIX	
Vp2 (L for 70 kg) (θ_6)	14.4 FIX		14.4 FIX	
Q3 (L/h for 70 kg) (θ_7)	8.12 FIX		8.12 FIX	
Vp3 (L for 70 kg) (θ_8)	121 FIX		121 FIX	
FABmax (θ_9)	1 FIX		1 FIX	
FAB50 Tablet Fasted (mg) (θ_{10})	101 (8.89)	86.1 (16.8)	101 FIX	90.2 (9.3)
FAB50 Tablet Fed (mg) (θ_{17})	582 (25)	86.1 (16.8)	582 FIX	90.2 (9.3)
FAB50 Solution Fasted (mg) (θ_{19})	79.1 (15.2)	86.1 (16.8)	79.1 FIX	90.2 (9.3)
FAB50 Solution Fed (mg) (θ_{18})	523 (23.9)	86.1 (16.8)	523 FIX	90.2 (9.3)
F1 Tablet Fasted (θ_{11})	0.302 (4.99)	81.6 (5.78)	0.302 FIX	81.7 (4.17)
F1 Tablet Fed (θ_{20})	0.186 (22.8)	81.6 (5.78)	0.186 FIX	81.7 (4.17)
F1 Solution Fasted (θ_{22})	0.434 (10.3)	81.6 (5.78)	0.434 FIX	81.7 (4.17)
F1 Solution Fed (θ_{21})	0.49 (23.8)	81.6 (5.78)	0.49 FIX	81.7 (4.17)
Hill coefficient (θ_{16})	0.652 (15.5)		0.652 FIX	
KA1 Fasted (θ_{12})	0.054 (34.1)	202 (11.3)	0.054 FIX	180 (1.98)
KA1 Fed (θ_{23})	0.383 (25.8)	202 (11.3)	0.383 FIX	180 (1.98)
KA2 Tablet Fasted (θ_{13})	0.662 (10.7)	76.4 (5.47)	0.662 FIX	77.6 (5.09)
KA2 Table Fed (θ_{24})	0.284 (22.7)	76.4 (5.47)	0.284 FIX	77.6 (5.09)
KA2 Solution Fasted (θ_{26})	0.414 (14.6)	76.4 (5.47)	0.414 FIX	77.6 (5.09)
KA2 Solution Fed (θ_{25})	0.0318 (29.7)	76.4 (5.47)	0.0318 FIX	77.6 (5.09)
Alag1 Tablet Fasted (h) (θ_{15})	0.227 (2.49)		0.227 FIX	

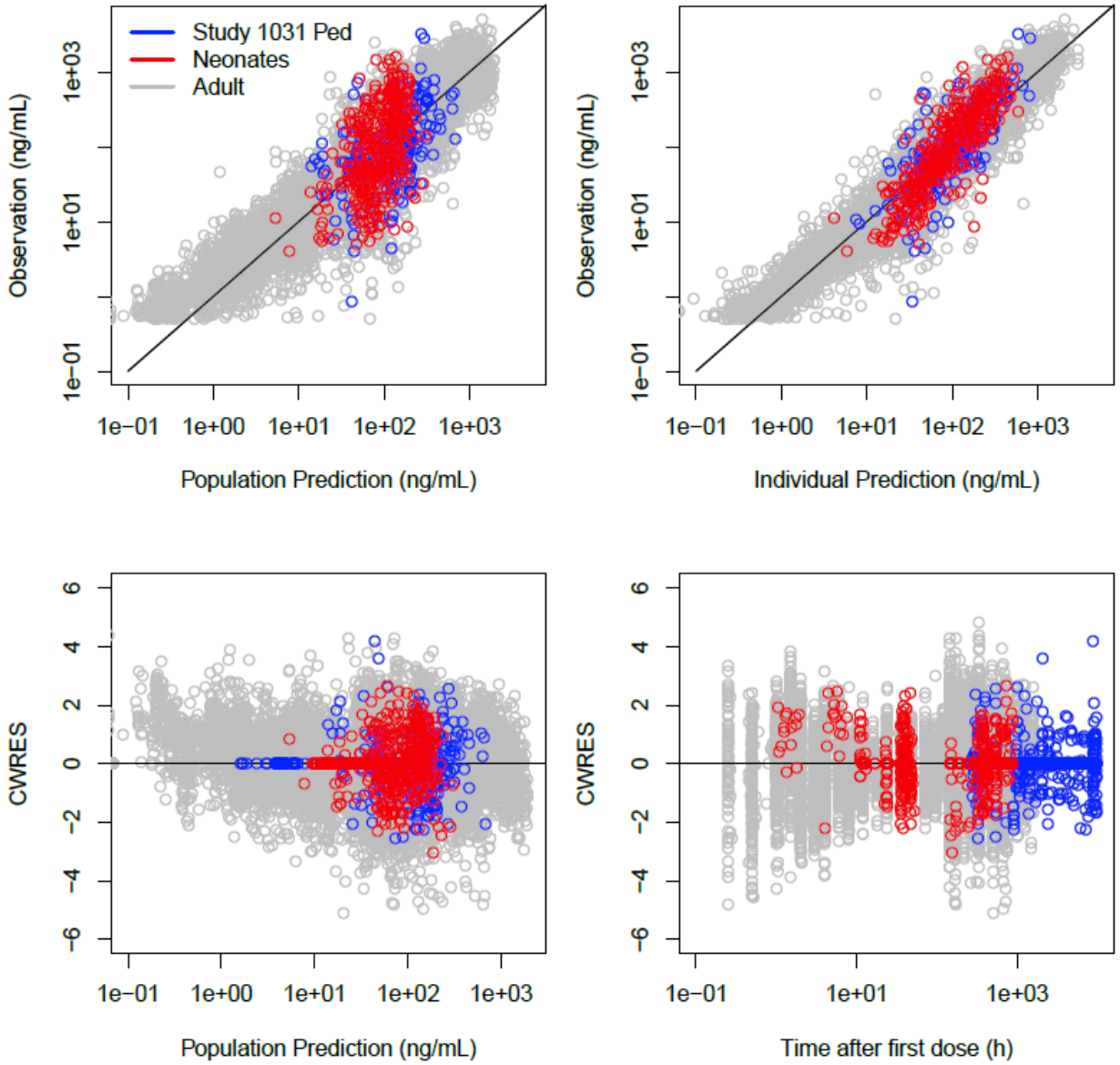
Parameter	Base Model (Step 2)		Final Model (Step 9)	
	Estimate (%RSE)	IIV% (%RSE)	Estimate (%RSE)	IIV% (%RSE)
Alag1 Tablet Fed (h) (θ_{30})	0.235 (3.79)		0.235 FIX	
Alag1 Solution Fasted (h) (θ_{32})	0.158 (8.59)		0.158 FIX	
Alag1 Solution Fed (h) (θ_{31})	0.136 (32.7)		0.136 FIX	
Alag2 Tablet Fasted (h) (θ_{14})	1.69 (1.24)		1.69 FIX	
Alag2 Tablet Fed (h) (θ_{27})	1.18 (3.05)		1.18 FIX	
Alag2 Solution Fasted (h) (θ_{29})	1.79 (1.12)		1.79 FIX	
Alag2 Solution Fed (h) (θ_{28})	0.841 (8.84)		0.841 FIX	
TM50 (week) (θ_{33})	73.6 FIX		60.9 (1.48)	
CLR (L/h for 70 kg)	12 FIX		12 FIX	
Prop RSV adults	44.8 (1.93)	37.8 (21)	44.9 (1.67)	37.6 (21.4)
Prop RSV pediatric rich data	44.8 (1.93)	29.2 (5.54)	44.9 (1.67)	28.9 (2.89)
Prop RSV pediatric sparse data	74.9 (21.5)	48.1 (30.2)	74.8 (17.4)	48.1 (29)
Prop RSV neonates			80.8 (6.79)	13.7 (62.7)

Repository artifact ID FI-1761603. Lines 1–2 substituted.
Note: Step 2 (CP1:ST-1888470) without IMPAACT 2007
Step 9 (CP1:ST-1888991) with IMPAACT 2007

Vc = central volume, CLI = intrinsic clearance, V1, V2, V3 = peripheral compartmental volumes, Q1,Q2,Q3 = inter-compartmental clearance, CLR = renal clearance, F1 = fraction of absorbed dose, FAB = fraction of absorbed dose before first pass extraction delivered from both depot compartments, FABmax = maximal bioavailability, FAB50 = dose at which 50% FABmax, KA = absorption rate constant, Alag = absorption lag time, TM50 = maturation half-time, Prop = proportional, RSV = residual error, IIV = interindividual variability, RSE = relative standard error

(Source: Applicant's Population PK Simulation Report, Table 6)

Figure 4. Basic Goodness of Fit for the Final Model with Non-Interacting Drugs with IMPAACT 2007

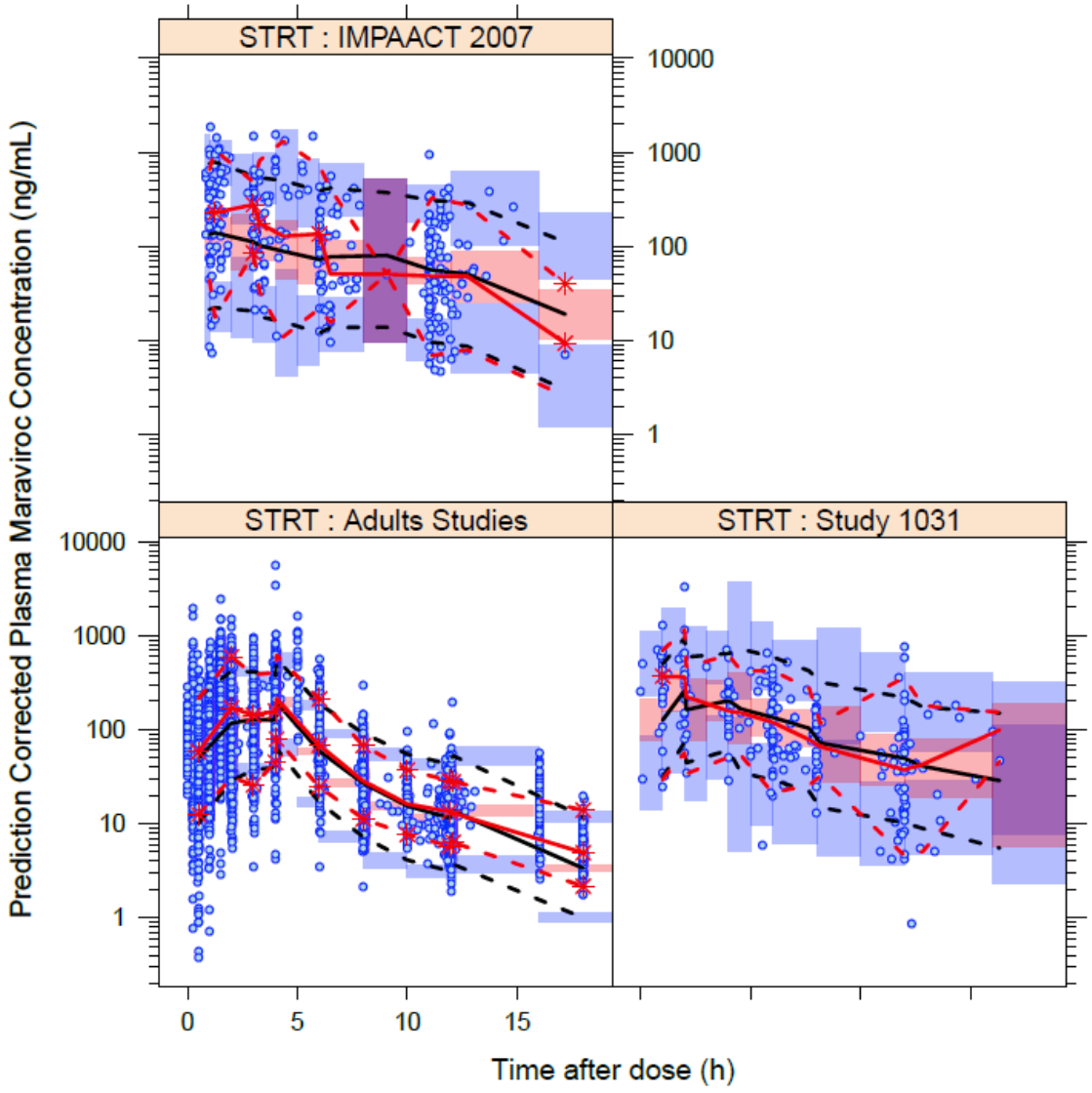


Repository artifact ID FI-1927542.

Study 1031 Ped = A4001031 pediatrics, CWRES = conditional weighted residual

(Source: Applicant's Population PK Simulation Report, Figure A5.3)

Figure 5. The pcVPC for the MVC Model for Non-Interacting Drugs (with IMPAACT 2007 data) Stratified by Adult, Pediatric and Neonate Populations

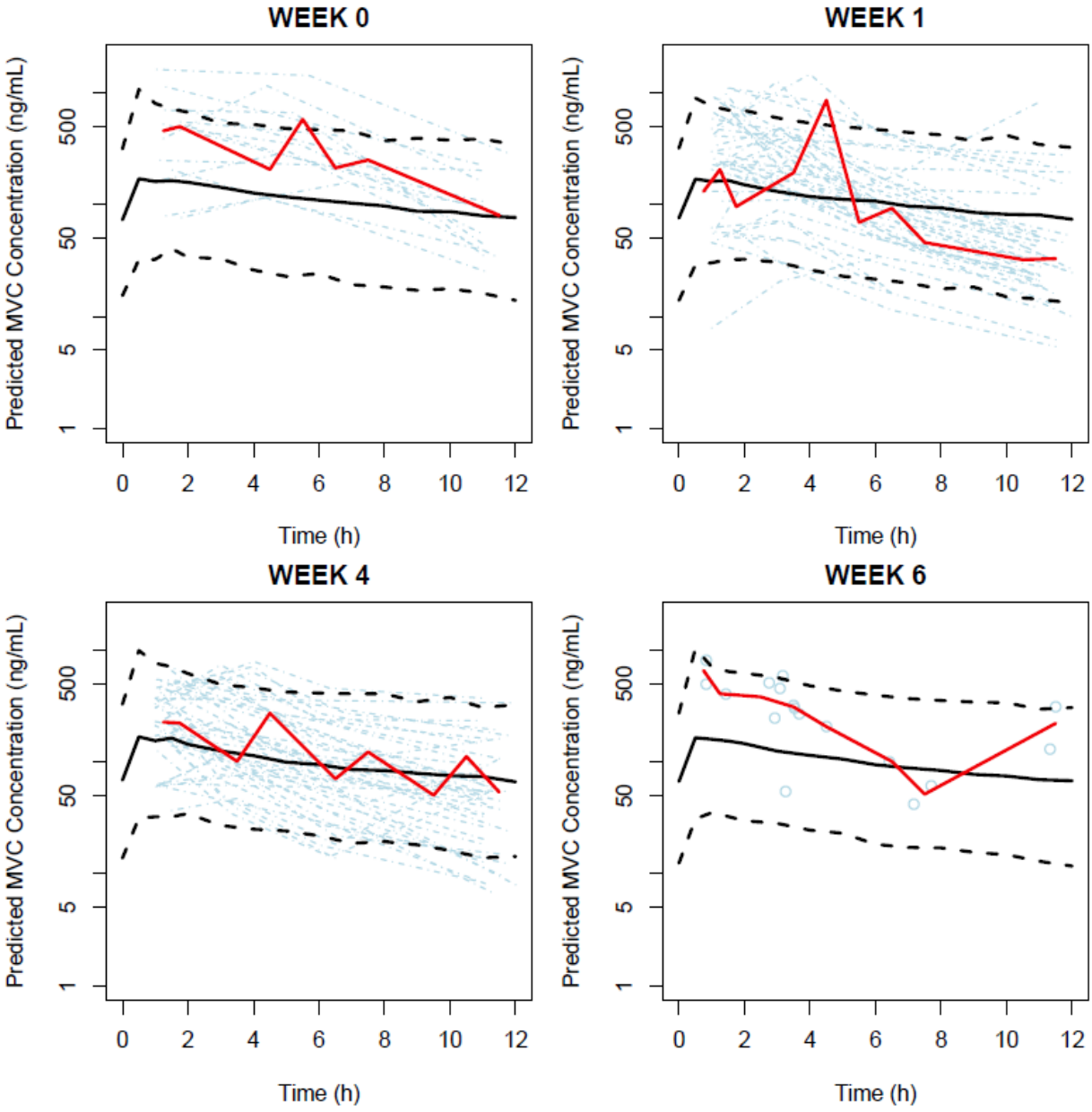


Repository artifact ID FI-1914613.

STRT = stratification, Study 1031 = A4001031, pcVPC = prediction corrected visual predictive check Red and black lines are the 5^{th}, 50^{th} (solid) and 95^{th} percentile of observed and simulated data, respectively. Blue dots are observed data. Shadow areas are 95% CI for the 5^{th}, 50^{th} (red) and 95^{th} percentile prediction intervals based on simulated data.

(Source: Applicant's Population PK Simulation Report, Figure 6)

Figure 6. Predictive Check for IMPAACT 2007 Using the Final Model with IMPAACT 2007 Data



Repository artifact ID FI-1913958.

MVC = maraviroc. Red lines are observed median, blue dash lines are observed individual concentration profiles, black solid and dash lines are predicted median and 90% predictive interval.

(Source: Applicant's Population PK Simulation Report, Figure 7)

Reviewer's Comments:

The applicant's updated population PK model is acceptable to describe the PK in neonates and children older than two years of age. As the model reasonably captures the central tendency of the data it is

reasonable to use the model to interpolate exposures for subjects between 6 weeks and 2 years of age for determining the proposed dosing regimen.

SIMULATION RESULTS

Summaries of covariates for simulations are shown in Table 13 through Table 15.

Table 13. Summary of Covariates for Adult Simulation Data Sets

	Adults
N	5000
Race	
Number (%) of White	2558 (51.16)
Number (%) of Black	2442 (48.84)
Body Weight	
Median (Range) (kg)	71.09 (40.01-118.79)
Chronological Age	
Median (Range) (years)	36.93 (18.01-68.26)
Creatinine Clearance	
Median (Range) (mL/min)	117.82 (50.02-223.7)

Repository artifact ID FI-1746939.

(Source: Applicants Population PK Simulation Report, Table 11)

Table 14. Summary of Covariates of Simulation Data Sets for Neonates ≤6 Weeks

	2 to <3kg	3 to <4 kg	4 to <5 kg	5 to <6 kg
N	5000	5000	5000	5000
Race				
Number (%) of White	2505 (50.1)	2475 (49.5)	2547 (50.94)	2514 (50.28)
Number (%) of Black	2495 (49.9)	2525 (50.5)	2453 (49.06)	2486 (49.72)
Body Weight				
Median (Range) (kg)	2.77 (2-2.99)	3.57 (3-3.99)	4.4 (4-4.99)	5.29 (5-5.99)
Chronological Age				
Median (Range) (years)	0 (0-0.12)	0 (0-0.12)	0.04 (0-0.12)	0.12 (0-0.12)

Repository artifact ID FI-1923498. Line 1 substituted.

(Source: Applicants Population PK Simulation Report, Table 12)

Table 15. Summary of Covariates of Simulation Data Sets for Infants 6 Weeks to <2 Years of Age

	3 to <6 kg	6 to <10 kg	10 to <14 kg	14 to <20 kg
N	5000	5000	5000	5000
Race				
Number (%) of White	2531 (50.62)	2522 (50.44)	2478 (49.56)	2515 (50.3)
Number (%) of Black	2469 (49.38)	2478 (49.56)	2522 (50.44)	2485 (49.7)
Body Weight				
Median (Range) (kg)	5.18 (3.01-5.99)	8.48 (6-9.99)	11.36 (10-13.99)	14.55 (14-18.98)
Chronological Age				
Median (Range) (years)	0.21 (0.12-0.79)	0.71 (0.12-1.96)	1.46 (0.46-1.96)	1.79 (0.79-1.96)

Repository artifact ID FI-1923436. Line 1 substituted.

(Source: Applicants Population PK Simulation Report, Table 13)

Simulation Results for Infants 6 Weeks to <2 Years

Table 16 shows predicted MVC median and 90% PI steady-state exposures (AUC, Cavg, Cmax and Cmin) with non-interacting drugs [redacted] (b) (4)

The ratio of the median of the exposure predictions for pediatrics relative to adult predictions for the solution formulation taken with food are shown where the ratios range from 1 to 1.9 across the 4 weight ranges for Cavg and from 0.99 to 2-fold for Cmax along with the median exposures. The proposed doses for these 4 weight band groups achieve the target of Cavg >75 ng/mL in >60% of simulated subjects. The tables also show the proportion of simulated patients in each weight band group that achieve Cavg targets of >75 ng/mL is >80%, with the exception of the 3 to <6 kg group on a 40 mg BID dose where the proportion was 66% and similar to adults on 69% (300 mg BID). The 90% PI for Cmax fall within the observed concentrations from clinical studies.

An additional consideration is to take into account weight bands for infants <2 years that overlap with weight bands in children ≤2 years e.g 10 to <14 kg and 14 to <20 kg. Table 16 shows predictions with 150 mg and 200 mg for children ≤2 years for the same weight bands but where the Cavg ratios are lower in comparsion to infants (1.31 vs 1.6 and 1.59 vs 1.9). The 14 to <20 kg weight band is more likely to occur in children >2 years because this range is above the 75th percentile for CDC growth charts for 2 years old and HIV-1 infected patients are more likely to be underweight. Two children within this weight band, aged 3 and 4 years, were studied in A4001031 on doses of MVC 200 mg BID (NSID [redacted] (b) (6)

Table 16. Predicted MVC Exposures at Steady-State with Non-Interacting Drugs Base on the Final Model with IMPAACT 2007 (b) (4)

	Adult	3 to <6kg	6 to <10kg	10 to <14kg	14 to <20kg
Dose (mg)	300	40	100	150	200
AUC (ng/mL*h)					
Mean (SD)	1289 (645)	1397 (890)	2123 (1373)	2082 (1090)	2435 (1161)
GeoMean (CV%)	1140 (53)	1160 (68)	1760 (69)	1820 (57)	2170 (52)
Median (90%PI)	1171 (481-2498)	1177 (405-3124)	1781 (620-4831)	1883 (734-4086)	2234 (934-4606)
Ratio to Adult		1.01	1.52	1.61	1.91
Cavg (ng/mL)					
Mean (SD)	107 (54)	116 (74)	177 (114)	174 (91)	203 (97)
GeoMean (CV%)	95 (53)	97 (68)	147 (69)	152 (57)	181 (52)
Median (90%PI)	98 (40-208)	98 (34-260)	148 (52-403)	157 (61-341)	186 (78-384)
% >75 ng/mL	69	66	86	90	96
% >100 ng/mL	48	49	73	79	88
Ratio to Adult		1	1.51	1.6	1.9
Cmax (ng/mL)					
Mean (SD)	247 (210)	237 (202)	393 (351)	412 (344)	482 (391)
GeoMean (CV%)	188 (84)	178 (87)	290 (91)	312 (86)	371 (82)
Median (90%PI)	178 (61-671)	176 (53-628)	285 (82-1095)	302 (96-1120)	356 (121-1302)
Ratio to Adult		0.99	1.6	1.7	2
Cmin (ng/mL)					
Mean (SD)	65 (38)	74 (54)	106 (79)	102 (66)	119 (71)
GeoMean (CV%)	55 (64)	58 (80)	83 (83)	84 (71)	101 (66)
Median (90%PI)	57 (20-140)	59 (17-179)	84 (24-264)	87 (28-225)	104 (36-259)
Ratio to Adult		1.04	1.47	1.53	1.82

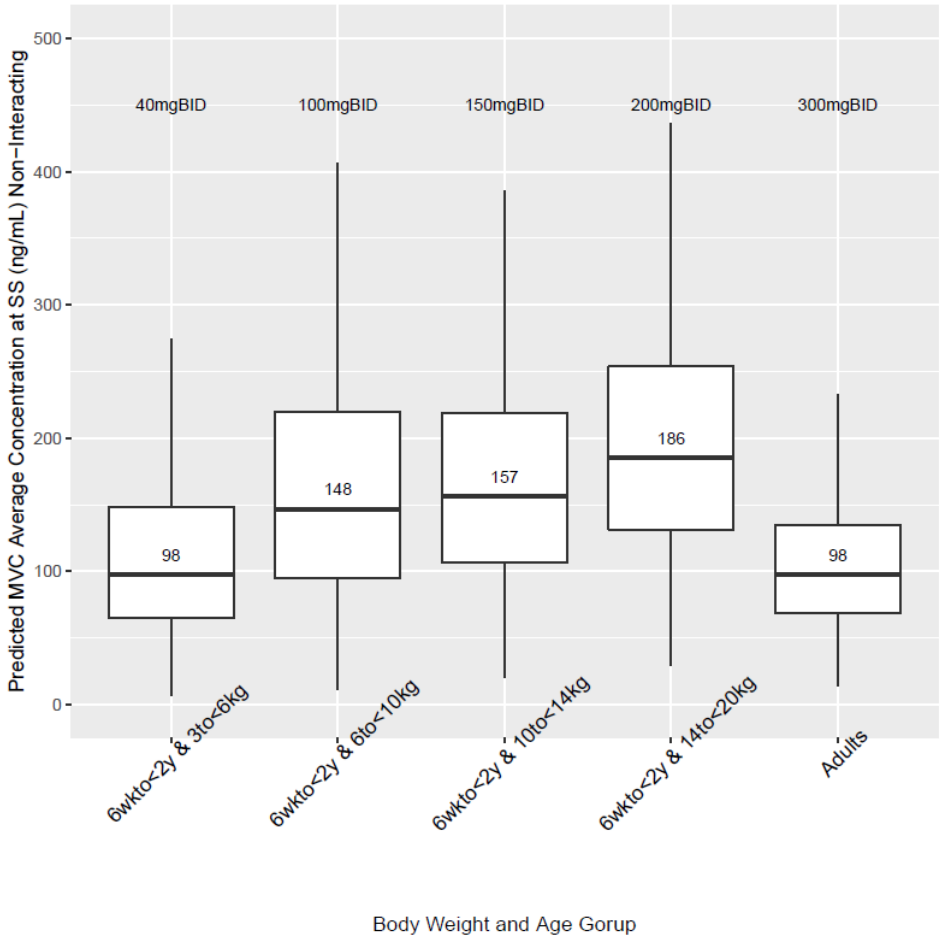
Repository artifact ID FI-1877710. Line 1 substituted.

Ratio to adult is median exposures. MVC = maraviroc, AUC = area under concentration curve, Cavg = average concentration, Cmax = maximum concentration, Cmin = minimum concentration, GeoMean = geometric mean, SD = standard error, CV = coefficient of variation, PI = prediction interval

(Source: Applicant's Population PK Simulation Report, Table 15)

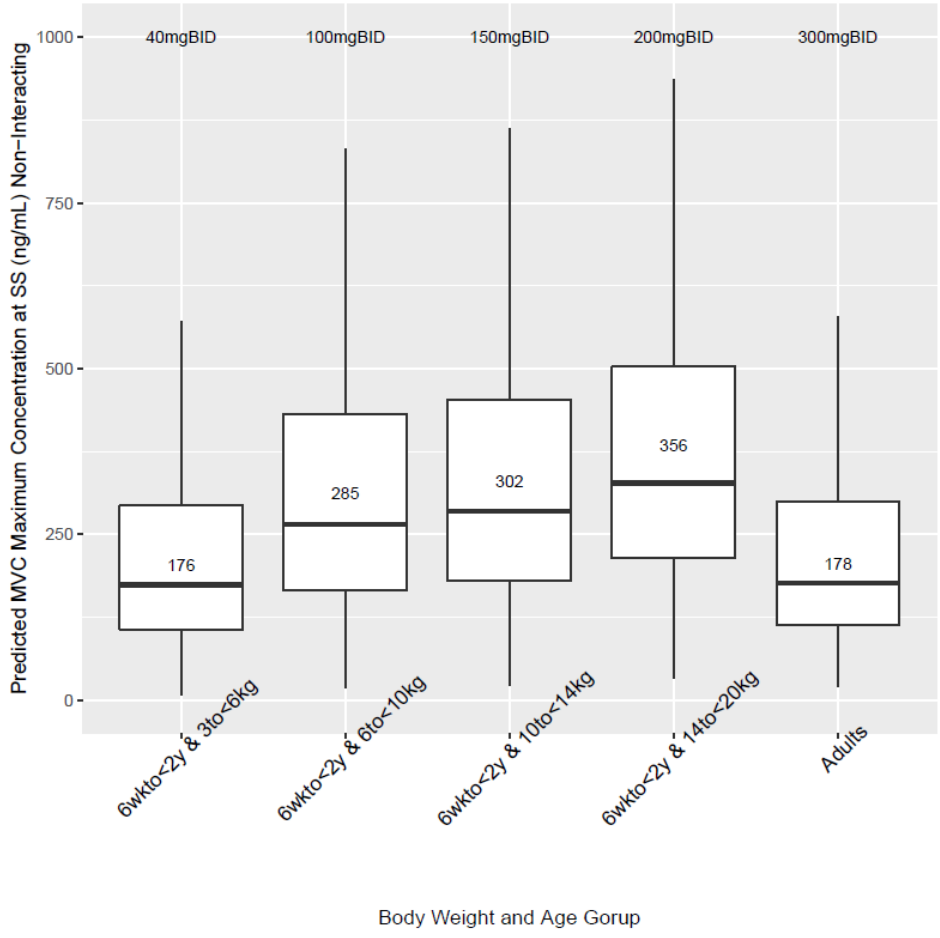
Median exposures across weight bands for 6 weeks to <2 years groups are shown in Figure 7 through Figure 9 for Cavg, Cmax and Cmin.

Figure 7. Distribution of MVC Cavg at Steady-State for Pediatric Patients 6 Weeks to <2 Years of Age [redacted] (b) (4) by Body Weight Bands with Non-Interacting Drugs Based on the Final Model with IMPAACT 2007 Data



(Source: Applicant's Population PK Simulation Report, Figure 9)

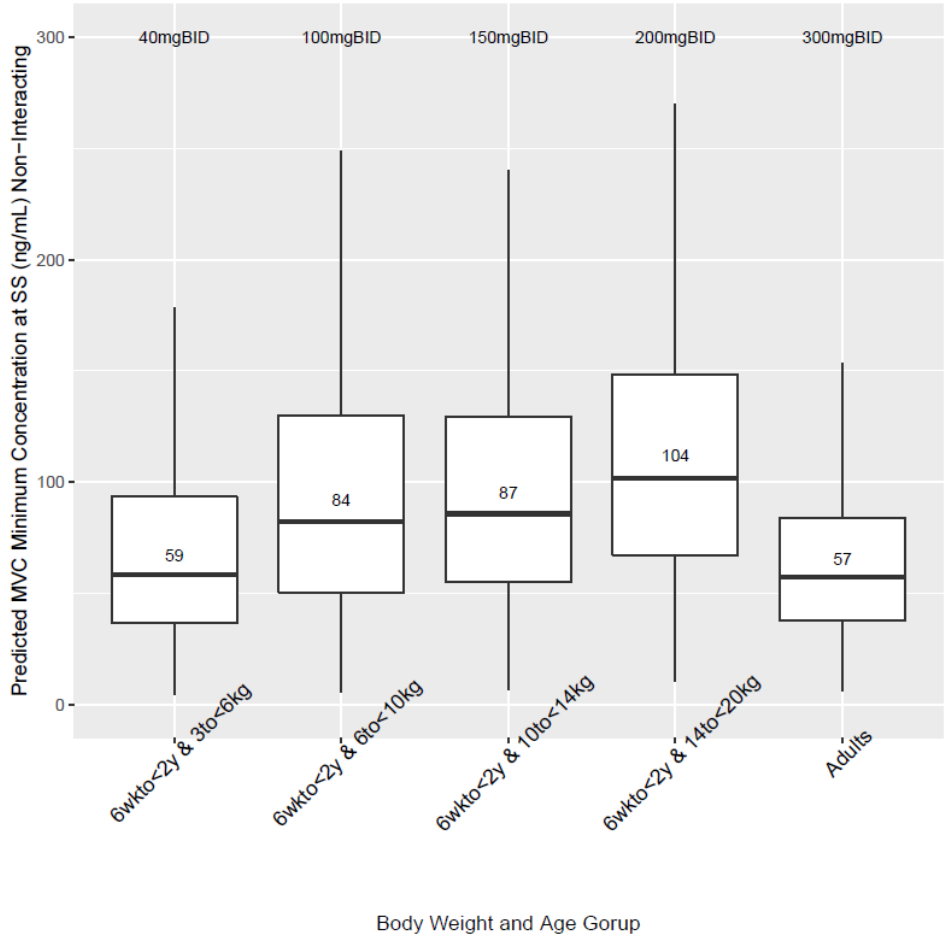
Figure 8. Distribution of MVC Cmax at Steady-State for Pediatric Patients 6 Weeks to <2 Years of Age (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data.



Repository artifact ID FI-1914853.
SS = steady-state, MVC = maraviroc, Cmax = maximum concentration, BID = twice daily, wk = week

(Source: Applicant's Population PK Simulation Report, Figure 10)

Figure 9. Distribution of MVC Cmin at Steady-State for Pediatric Patients 6 Weeks to <2 Years of Age (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data



Repository artifact ID FI-1914857.
SS = steady-state, MVC = maraviroc, Cmin = minimum concentration, BID = twice daily, wk = week

(Source: Applicant's Population PK Simulation Report, Figure 11)

Simulation Results for Neonates (Birth to 6Weeks)
Table 17 shows predicted MVC steady state exposures (AUC, Cavg, Cmax and Cmin) with non-interacting drugs (b) (4)

Median Cavg and Cmax exposure are <2-fold the adult prediction and Cmax 90% PI are similar to adults. The proportion of subjects achieving the Cavg target of >75 ng/mL was above 75% for all weight bands vs 69% for simulated adults.

Table 17. Predicted MVC Exposures at Steady-State with Non-Interacting Drugs Based on the Final Model with IMPAACT 2007 [redacted] (b) (4) for Pediatric Patients ≤6 Weeks of Age by Body Weight Bands vs Adults

	Adult	2 to <3 kg	3 to <4kg	4 to <5kg	5 to <6kg
Dose (mg)	300	30	30	40	40
AUC (ng/mL*h)					
Mean (SD)	1289 (645)	2290 (1405)	1806 (1106)	2083 (1259)	1604 (941)
GeoMean (CV%)	1140 (53)	1930 (65)	1520 (65)	1760 (65)	1370 (62)
Median (90%PI)	1171 (481-2498)	1952 (699-4976)	1540 (553-3914)	1787 (642-4472)	1393 (513-3448)
Ratio to Adult		1.67	1.32	1.53	1.19
Cavg (ng/mL)					
Mean (SD)	107 (54)	191 (117)	150 (92)	174 (105)	134 (78)
GeoMean (CV%)	95 (53)	161 (65)	127 (65)	147 (65)	114 (62)
Median (90%PI)	98 (40-208)	163 (58-415)	128 (46-326)	149 (53-373)	116 (43-287)
% >75 ng/mL	69	89	82	87	77
% >100 ng/mL	48	79	66	75	60
Ratio to Adult		1.66	1.31	1.52	1.18
Cmax (ng/mL)					
Mean (SD)	247 (210)	358 (295)	281 (226)	330 (261)	258 (205)
GeoMean (CV%)	188 (84)	275 (83)	218 (82)	256 (81)	201 (81)
Median (90%PI)	178 (61-671)	270 (86-920)	220 (67-705)	252 (80-852)	196 (64-650)
Ratio to Adult		1.52	1.24	1.42	1.1
Cmin (ng/mL)					
Mean (SD)	65 (38)	126 (85)	99 (68)	114 (79)	86 (58)
GeoMean (CV%)	55 (64)	102 (74)	80 (74)	92 (76)	70 (73)
Median (90%PI)	57 (20-140)	105 (33-287)	82 (26-231)	94 (29-265)	72 (23-199)
Ratio to Adult		1.84	1.44	1.65	1.26

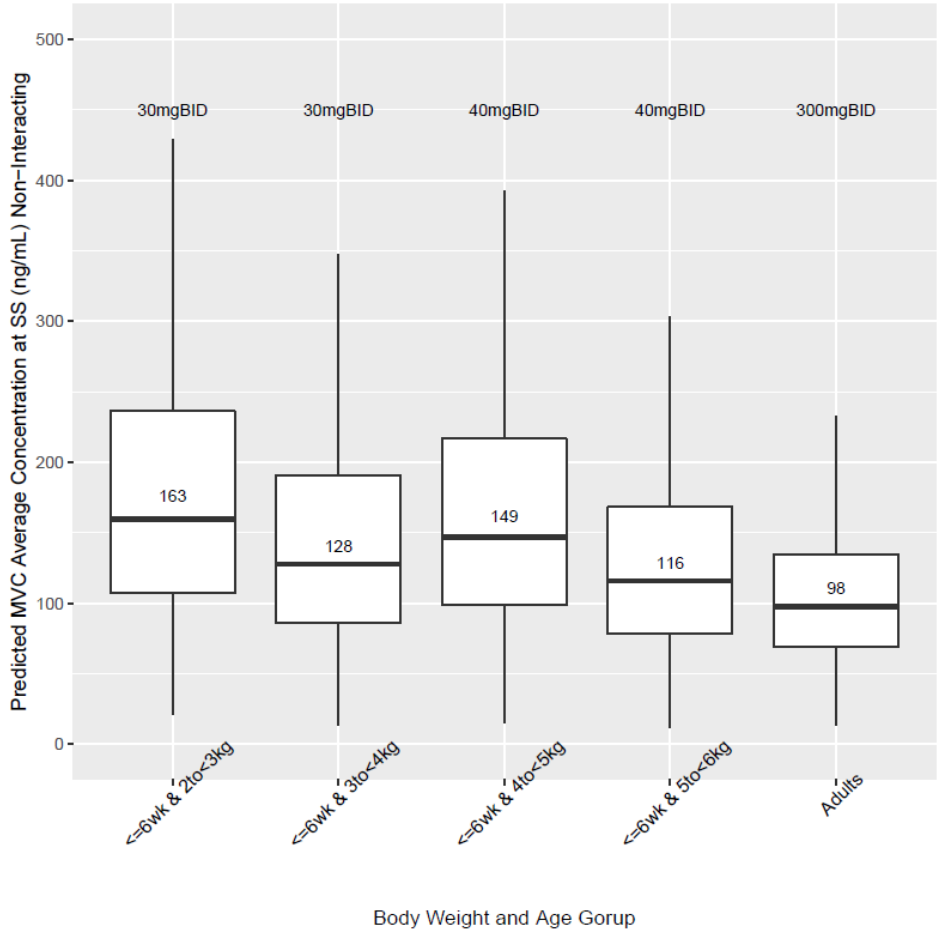
Repository artifact ID FI-1923472. Line 1 substituted.

Ratio to adult is median exposures. MVC = maraviroc, AUC = area under concentration curve, Cavg = average concentration, Cmax = maximum concentration, Cmin = minimum concentration, GeoMean = geometric mean, SD = standard error, CV = coefficient of variation, PI = prediction interval

(Source: Applicant's Population PK Simulation Report, Table 16)

Figure 10, Figure 11, and Figure 2 show Cavg, Cmax and Cmin at steady-state respectively.

Figure 10. Distribution of MVC Cavg at Steady-State for Pediatric Patients ≤6 Weeks of Age (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data

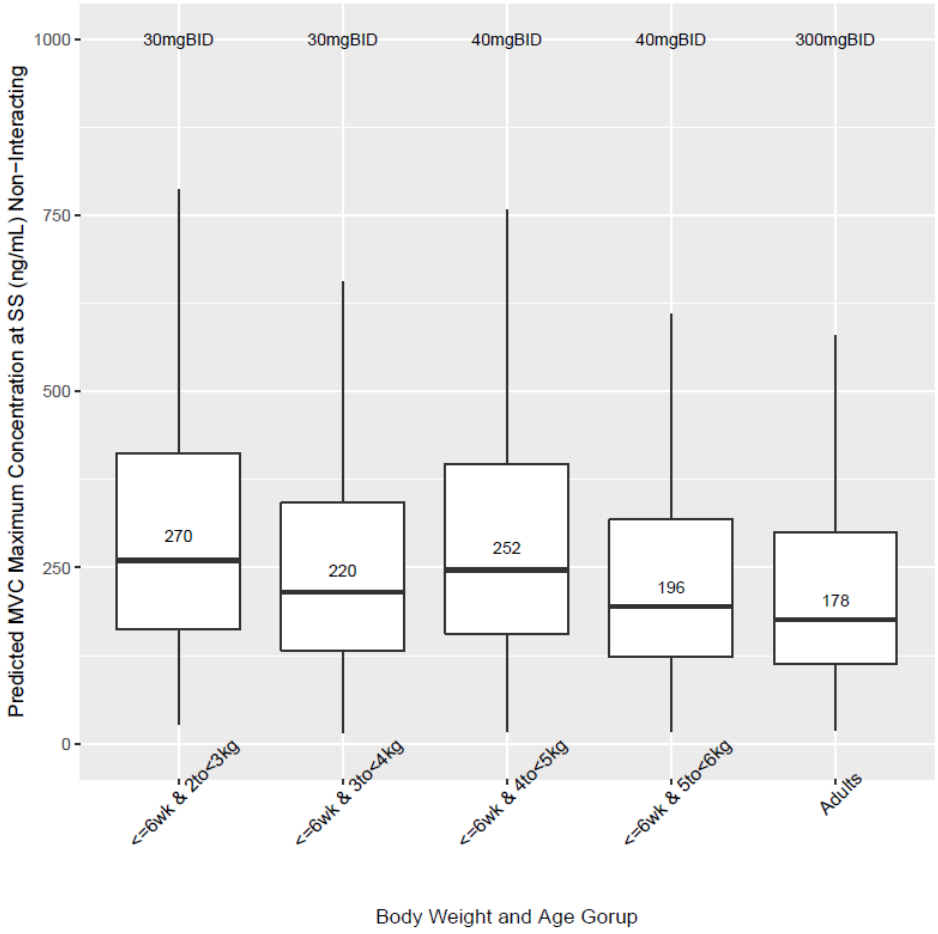


Repository artifact ID FI-1923475.

SS = steady-state, MVC = maraviroc, Cavg = average concentration, BID = twice daily, wk = week

(Source: Applicant's Population PK Simulation Report, Figure 12)

Figure 11. Distribution of MVC Cmax at Steady-State for Pediatric Patients ≤6 Weeks of Age (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data

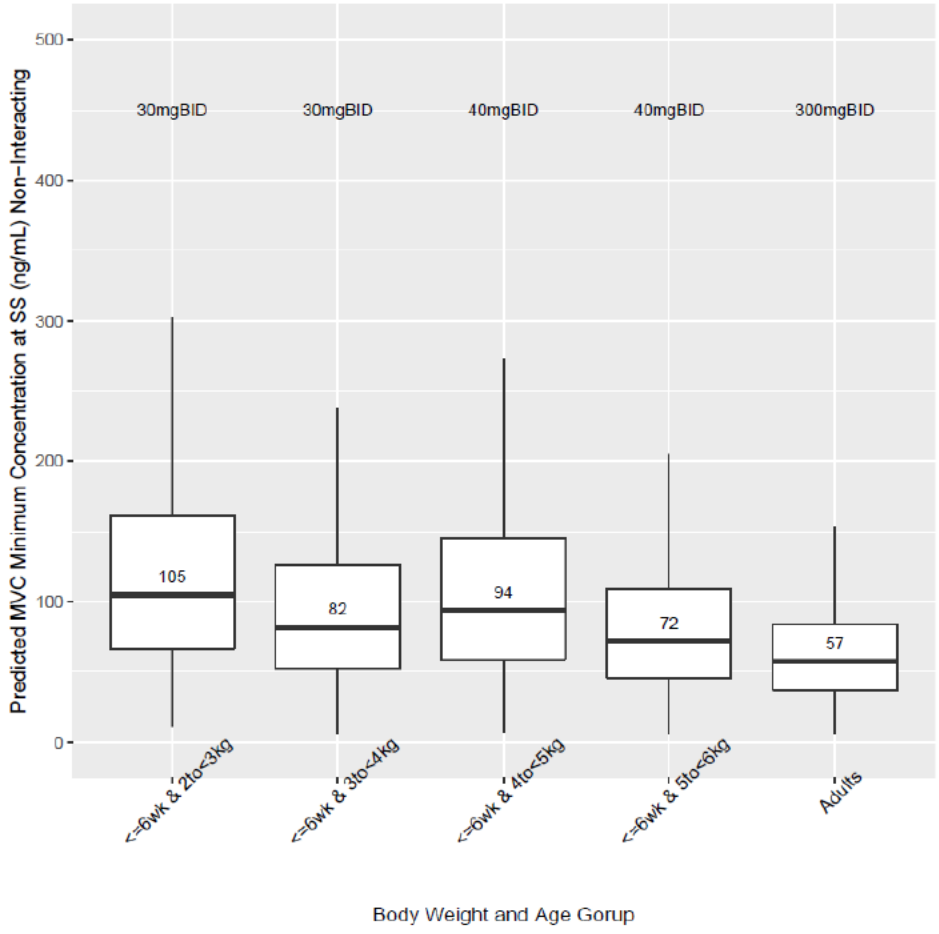


Repository artifact ID FI-1923470.

SS = steady-state, MVC = maraviroc, Cmax = maximum concentration, BID = twice daily, wk = week

(Source: Applicant's Population PK Simulation Report, Figure 13)

Figure 12. Distribution of MVC Cmin at Steady-State for Pediatric Patients ≤6 Weeks of Age [redacted] (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data



Repository artifact ID FI-1923467.
SS = steady-state, MVC = maraviroc, Cmin = minimum concentration, BID = twice daily, wk = week

(Source: Applicant's Population PK Simulation Report, Figure 14)

Simulation Results for Children 2 to <6 Years of Age

Table 18 shows predicted MVC steady-state exposures (AUC, Cavg, Cmax and Cmin) with non-interacting drugs for patients from 2 years and weighing up to 30 kg.

The 300 mg BID dose for 30 to <40 kg patients is an approved dose and was included for comparison with [redacted] (b) (4) doses for lower weight bands. Median ratios for Cavg and Cmax for weight bands for patients from 2 years are within <1.8-fold those predicted for adults on 300 mg BID. The 90% PI for Cmax are within the observed concentration ranges for Phase 3 adults on 300 mg BID and observations in A4001031. With the exception of the low 6 to <10 kg weight band which is unlikely to occur in children from 2 years and older (<3rd percentile for CDC tables) the proportion of subjects achieving the Cavg 75 ng/mL target across the weight bands is >80% [redacted] (b) (4)

Table 18. Predicted MVC Exposures at Steady-State with Non-Interacting Drugs Based on the Final Model with IMPAACT 2007 (b) (4) for Pediatric Patients 2 to <6 Years of Age by Body Weight Bands vs Adults

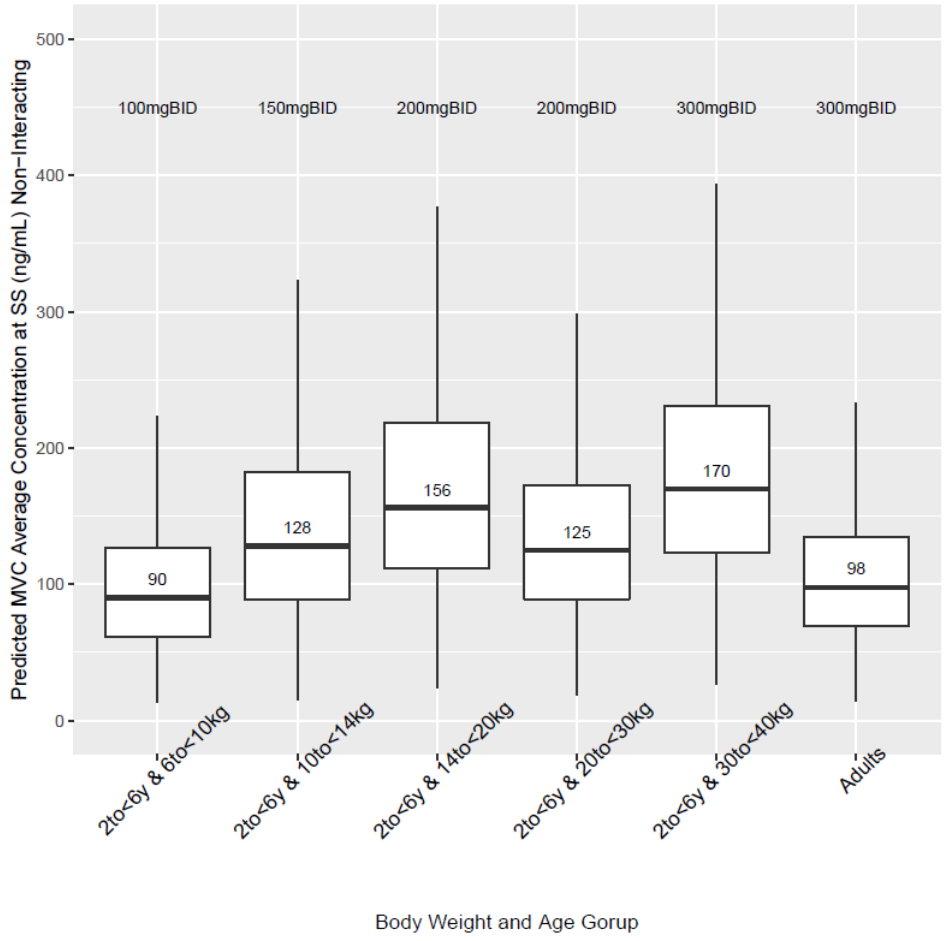
	Adult	6 to <10kg	10 to <14kg	14 to <20kg	20 to <30kg	30 to <40kg
Dose (mg)	300	100	150	200	200	300
AUC (ng/mL*h)						
Mean (SD)	1289 (645)	1194 (626)	1710 (866)	2079 (1020)	1649 (808)	2229 (1043)
GeoMean (CV%)	1140 (53)	1050 (57)	1510 (55)	1850 (53)	1470 (53)	2000 (50)
Median (90%PI)	1171 (481-2498)	1081 (409-2368)	1538 (641-3333)	1877 (788-4011)	1496 (627-3198)	2045 (889-4190)
Ratio to Adult		0.92	1.31	1.6	1.28	1.75
Cavg (ng/mL)						
Mean (SD)	107 (54)	100 (52)	142 (72)	173 (85)	137 (67)	186 (87)
GeoMean (CV%)	95 (53)	87 (57)	126 (55)	154 (53)	122 (53)	167 (50)
Median (90%PI)	98 (40-208)	90 (34-197)	128 (53-278)	156 (66-334)	125 (52-267)	170 (74-349)
% >75 ng/mL	69	63	84	92	84	95
% >100 ng/mL	48	42	68	81	67	85
Ratio to Adult		0.92	1.31	1.59	1.28	1.73
Cmax (ng/mL)						
Mean (SD)	247 (210)	239 (206)	343 (281)	410 (343)	329 (281)	432 (344)
GeoMean (CV%)	188 (84)	179 (87)	261 (84)	313 (83)	250 (84)	336 (79)
Median (90%PI)	178 (61-671)	172 (55-648)	255 (81-913)	299 (101-1090)	236 (82-902)	317 (113-1140)
Ratio to Adult		0.97	1.43	1.68	1.33	1.78
Cmin (ng/mL)						
Mean (SD)	65 (38)	58 (36)	83 (52)	101 (60)	81 (48)	111 (65)
GeoMean (CV%)	55 (64)	48 (69)	69 (69)	86 (65)	69 (66)	95 (64)
Median (90%PI)	57 (20-140)	50 (17-128)	71 (23-188)	89 (31-218)	72 (24-175)	98 (35-233)
Ratio to Adult		0.88	1.25	1.56	1.26	1.72

Repository artifact ID FI-1877708. Line 1 substituted.
Ratio to adult is median exposures. MVC = maraviroc, AUC = area under concentration curve, Cavg = average concentration, Cmax = maximum concentration, Cmin = minimum concentration, GeoMean = geometric mean, SD = standard error, CV = coefficient of variation, PI = prediction interval

(Source: Applicant's Population PK Simulation Report, Table 17)

Figure 13, Figure 14, and Figure 15 show Cavg, Cmax and Cmin at steady-state respectively.

Figure 13. Distribution of MVC Cavg at Steady-State for Pediatric Patients 2 to <6 Years of Age [redacted] (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data

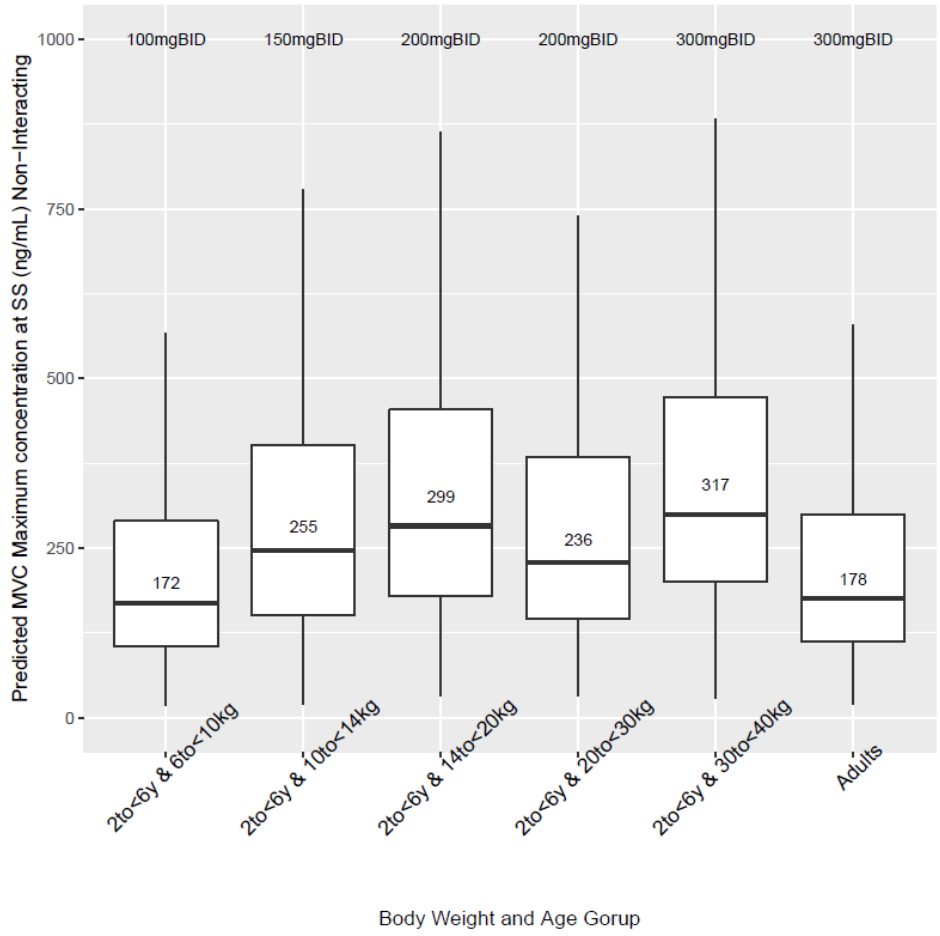


Repository artifact ID FI-1914854.

SS = steady-state, MVC = maraviroc, Cavg = average concentration, BID = twice daily

(Source: Applicant's Population PK Simulation Report, Figure 15)

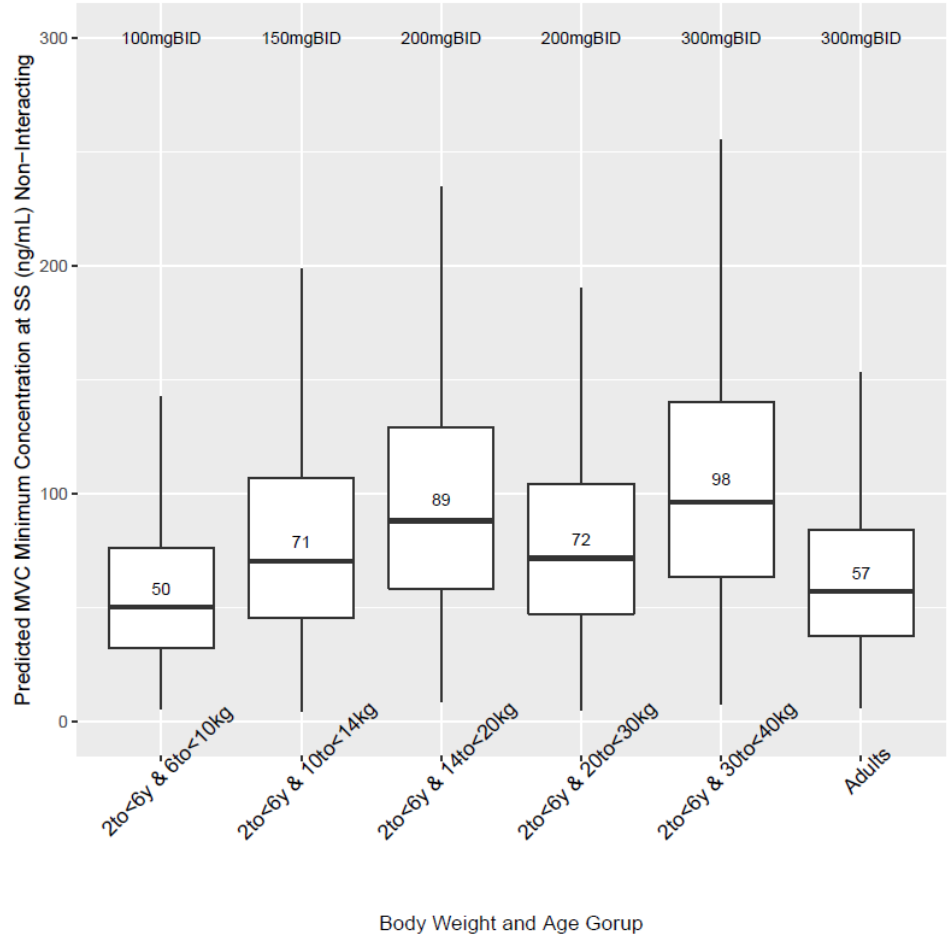
Figure 14. Distribution of MVC Cmax at Steady-State for Pediatric Patients 2 to <6 Years of Age [redacted] (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data



Repository artifact ID FI-1914858.
SS = steady-state, MVC = maraviroc, Cmax = maximum concentration, BID = twice daily

(Source: Applicant's Population PK Simulation Report, Figure 16)

Figure 15. Distribution of MVC Cmin at Steady-State for Pediatric Patients 2 to <6 Years of Age [redacted] (b) (4) by Body Weight Bands with Non-Interactive Drugs Based on the Final Model with IMPAACT 2007 Data



Repository artifact ID FI-1914856.
SS = steady-state, MVC = maraviroc, Cmin = minimum concentration, BID = twice daily

(Source: Applicant's Population PK Simulation Report, Figure 17)

Reviewer's Comments:
The applicant's simulations suggest that exposures in children < 2 years of age are acceptable [redacted] (b) (4) No large deviations from the adult exposures were noted.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HUIMIN ZHENG
10/19/2020 08:06:11 AM

JUSTIN C EARP
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10/19/2020 09:42:12 AM