CLINICAL PHARMACOLOGY REVIEW

NDA/SDN	22128/670 (S-17) (Tablet) and 208984/1 (Solution)
Submission Type	Pediatric efficacy supplement
Applicant Name	Viiv Healthcare
Submission Dates	May 6, 2016 (NDA 208984) June 8, 2016 (NDA 22128)
Generic Name	Maraviroc
Dosage Form (Strength)	Oral solution (20 mg/mL) Tablet (25 mg and 75 mg)
Indication	Treatment of HIV-1
Review Team	Mario Sampson, PharmD, Jenny Zheng, PhD, Jeffry Florian, PhD, Shirley Seo, PhD

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CLINICAL PHARMACOLOGY REVIEW

1 Executive Summary

Maraviroc was approved in 2007 for the treatment of HIV in adults. Adult dosing is dependent on whether concomitant medications contain a CYP3A inhibitor (dose is 150 mg BID), drugs not affecting CYP3A substrates (dose is 300 mg BID), or a CYP3A inducer without a CYP3A inhibitor (dose is 600 mg BID). Maraviroc is labeled to be taken with or without food.

This submission contains a pediatric PK, safety, and efficacy trial A4001031 (study 1031), which was required under PREA PMR 1357-2. In addition, a relative bioavailability (BA) trial A4001034 was submitted to support approval of an oral solution (20 mg/mL). The sponsor is seeking to extend the indication to include pediatric patients ages 2 to less than 18 years of age, and is also seeking approval of new tablet strengths (25 mg and 75 mg) and the oral solution as age-appropriate dosing strengths and formulations for this population.

Maraviroc population PK modeling data in adult and pediatric subjects were submitted; separate models were developed for 1) subjects coadministered concomitant CYP3A inhibitors and 2) subjects coadministered neutral concomitant medications. Based on the modeling, the sponsor proposed maraviroc pediatric dosing (Table 1). (b) (4)

Table 1. Sponsor's proposed maraviroc weight-based pediatric dosing (tablets).

	10- <20 kg	20- <30 kg	30- <40 kg	≥40 kg
Potent CYP3A inhibitor (with or without CYP3A inducer)	50 mg BID	75 mg BID	100 mg BID	150 mg BID
Non-interacting concomitant medications	(b) (4)			

Source: Proposed maraviroc US prescribing information (USPI).

The focus of this review was on pediatric study 1031 and the use of modeling and simulation to support the proposed maraviroc pediatric dosing recommendations. Our recommendations regarding the pediatric dosing regimen are summarized in Table 2 and described in more detail in 1.1.

Table 2. Recommendations regarding the sponsor's proposed maraviroc pediatric dosing regimen.

Concomitant medication classification	OCP recommendation
CYP3A inhibitor ± CYP3A inducer	All weight groups: Agree with sponsor's proposal
Noninteracting medications	10-30 kg: Not recommended ≥30 kg: Agree with sponsor's proposal
CYP3A inducer without CYP3A inhibitor	All weight groups: Not recommended

1.1 Summary of clinical pharmacology findings

1.1.1 Study A4001031 – Pediatric PK, safety, and efficacy study

Study 1031 enrolled treatment-experienced pediatric subjects aged 2 - <18 years of age. Subjects were enrolled into one of four cohorts based on age; subjects aged 6-12 years received either the tablet or solution formulation (Table 3).

Table 3. Cohorts in pediatric study A4001031

Cohort	Age (years)	Maraviroc formulation
1	≥2 - <6	Solution
2	≥6 - <12	Tablet
3	≥6 - <12	Solution
4	≥12 - <18	Tablet

Source: reviewer.

The study was conducted in two stages. The objective of stage 1 was dose finding. Intensive PK was assessed at week 2. Based on the sponsor's finding that response in treatment-experienced adults was associated with an average maraviroc concentration (Cavg) of ≥100 ng/mL, a target Cavg of ≥100 ng/mL was selected. Doses were increased for subjects with below target Cavg values. Dosing was based on body surface area. Protocol doses were increased for all subsequent subjects with neutral background regimens based on preliminary PK data. The objectives of stage 2 of the trial were efficacy and safety. Sparse PK samples were collected approximately every four weeks during stage 2 (weeks 4-48).

One hundred and three subjects were treated with study drug and 101 subjects had PK samples. Fifty subjects contributed intensive PK data in stage 1. Across stages 1-2, 85 subjects with background regimens including CYP3A inhibitors were included in the PK analysis; predominant CYP3A inhibitors used were lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r). Across stages 1-2, there were ten subjects with neutral background regimens and three subjects on background regimens that included CYP3A inducers (without inhibitors).

Dose adjustments were needed in six subjects with neutral regimens (and one subject in each of the other concomitant medication categories). Reported protocol deviations largely consisted of dosing errors and repeated intensive PK when compliance issues were suspected. In the noncompartmental analysis for the final doses selected in stage 1, Cavg and Cmax values were not significantly different between cohorts, while Cmin values were more variable between cohorts.

Population PK analyses were conducted using the pediatric intensive and sparse PK data from this study in combination with adult PK data. These analyses, comparisons of pediatric and adult exposures, and adequacy of the proposed dosing regimen are discussed in sections 1.1.2 and 1.1.3.

The focus of our review of study 1031 was on the adequacy of the study conduct, bioanalysis, and noncompartmental PK analysis. It appeared that compliance was highly variable, especially

in adolescents (according to pill/volume counts); however, this is likely the case for pediatric studies in general. The maraviroc bioanalytical methods were validated and study samples were analyzed in accordance with the FDA bioanalytical method validation guidance.

Overall, from the review team's perspective, study 1031 is acceptable to support dosing recommendations in labeling (section 2) and for inclusion of pediatric PK data in labeling (section 12.3). Evaluation of the sponsor's proposed pediatric dosing recommendations for coadministration with CYP3A inhibitors or neutral concomitant medications are described in sections 1.1.2 and 1.1.3. Based on the enrollment of only three subjects on regimens containing CYP3A inducers without CYP3A inhibitors, we do not recommend pediatric use of maraviroc in subjects on regimens containing CYP3A inducers without CYP3A inhibitors.

1.1.2 Pediatric maraviroc dosing when coadministered with CYP3A inhibitor concomitant medications

Background

The sponsor evaluated body surface area (BSA)-based maraviroc dosing in study 1031 and proposed body weight-based maraviroc pediatric dosing for inclusion in the USPI (Table 4). Typically, the proposed doses were equivalent to the doses administered to most subjects in pediatric study 1031; the exception is for subjects ≥40 kg where 125 mg BID was administered whereas 150 mg BID is the proposed dose (Table 5).

Table 4. Proposed pediatric weight-based maraviroc dosing for subjects with a CYP3A inhibitor-containing background regimen.

Formulation	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
Tablet	50 mg BID	75 mg BID	100 mg BID	**150 mg BID**
Solution	50 mg (2.5 mL) BID	80 mg (4 mL) BID	100 mg (5 mL) BID	**150 mg (7.5 mL) BID**

Source: Proposed maraviroc USPI.

Table 5. Maraviroc doses administered to pediatric subjects in study 1031 on a CYP3A inhibitor-containing regimen.

	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
N	20	25	22	18
Median	50 mg BID	75 mg BID	100 mg BID	**125 mg BID**
Min	50 mg BID	75 mg BID	75 mg BID	75 mg BID
Max	75 mg BID	75 mg BID	112.5 mg BID	150 mg BID

Source: Reviewer's analysis.

Model development and evaluation

The sponsor developed a population PK model using data from 85 pediatric (intensive and sparse) and 171 adult subjects. Model performance was reported to be acceptable. Bootstrapping was applied to the pediatric study population to generate a dataset of 1000 subjects for simulation, and pediatric exposures were then simulated for the proposed dosing regimen.

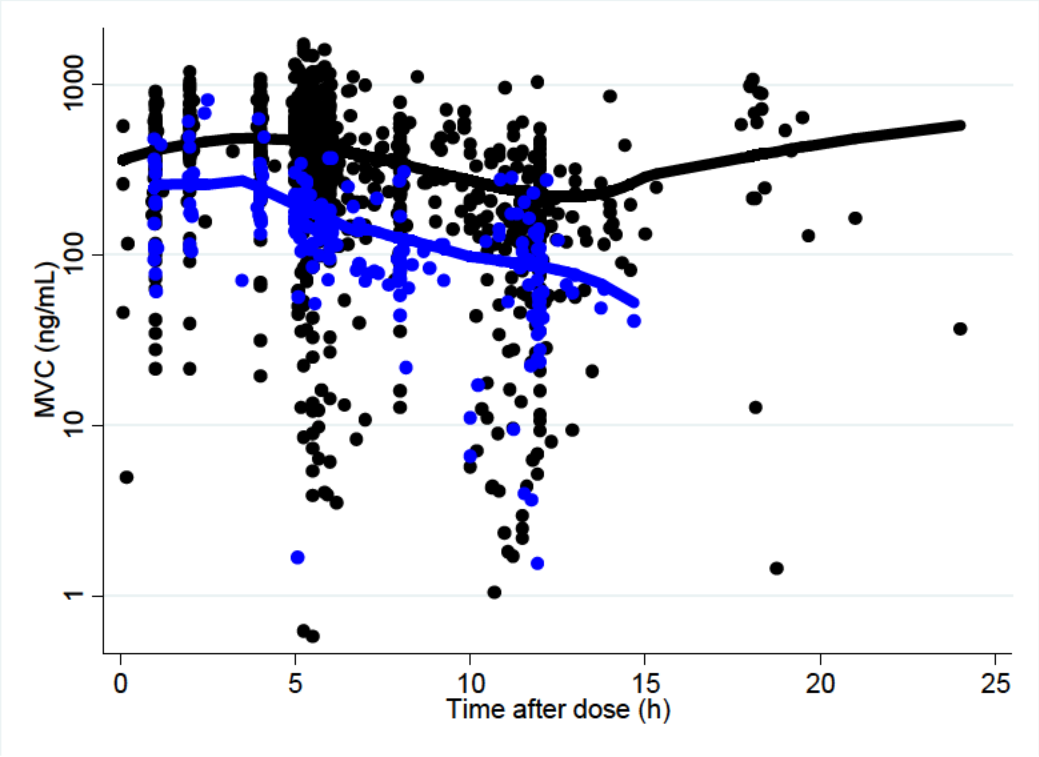
Reviewer's analyses

Analyses conducted using the model parameters submitted by the sponsor

We compared simulated pediatric exposures for the proposed dosing regimen to adult exposures. Predicted exposures were lower for pediatric subjects coadministered DRV/r relative to LPV/r (Figure 1). Only in the 10 - <20 kg group was the interquartile range (IQR) of exposures for pediatric subjects on DRV/r below the adult IQR. However, the rate of virologic failure was numerically higher in the LPV/r versus the DRV/r group (17/68 [25%] versus 2/14 [14%]).

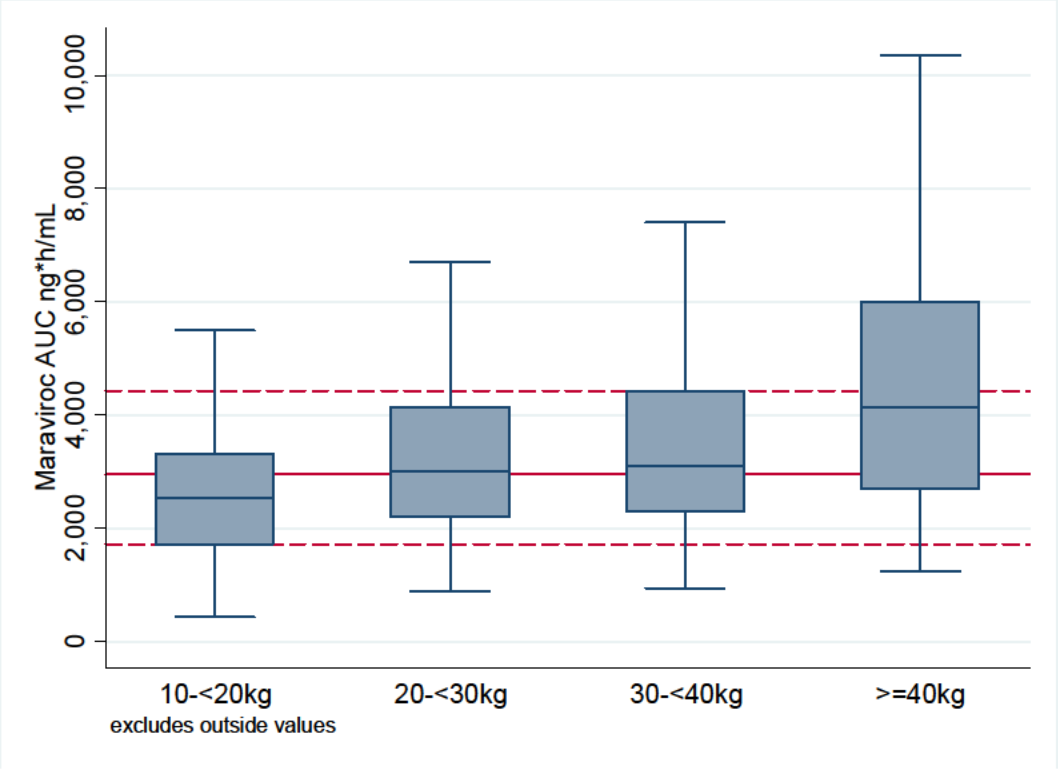
Overall, the IQR of pediatric exposures was within the adult IQR with the exception of the ≥40 kg group, where the pediatric median was 40% higher (Figure 2). The adult reference group was 342 TE adults on inhibitor regimens that comprise the adult PK parameters in the maraviroc USPI (the label has data from 375 subjects; we excluded 23 on unboosted regimens, three on TPV [classified as noninteracting], and seven with absent protease inhibitor). Cmax values for all pediatric subjects were lower than the mean adult Cmax associated with postural hypotension.

Figure 1. Pediatric maraviroc concentration time profiles in subjects with LPV/r- and DRV/r-containing regimens.



Source: Plotted by reviewer. Black = LPV/r; blue = DRV/r; thick lines = lowess.

Figure 2. Comparison of maraviroc AUC between HIV-infected TE pediatric and adult subjects using the sponsor's model parameters.



Source: Plotted by reviewer. Pediatric exposures were predicted using model parameters obtained when the model was run by the sponsor. Reference values are 342 TE adults on inhibitor regimens. Solid red line = median AUC in TE adults; dotted red lines = 25th and 75th percentile of AUC in TE adults.

Analyses conducted using the model parameters obtained when the sponsor's model was run at the FDA

We found minor parameter estimate differences and lack of model minimization (as was also observed by the sponsor) after running the sponsor's model.We used the simulation dataset provided by the sponsor, simulated concentrations using model parameters obtained by FDA, and compared simulated exposures to adults. We obtained similar results as the sponsor when comparing maraviroc pediatric and adult exposures.

Reviewer's assessment

We agree with the proposed maraviroc pediatric dosing regimen for subjects with background therapy containing CYP3A inhibitors.

Maraviroc exposures were lower in pediatric subjects on DRV/r-containing regimens versus LPV/r. However, we concluded that dosing need not depend on presence of LPV/r versus DRV/r

because despite lower maraviroc exposures in the DRV/r-containing group, virologic response rates were numerically higher.

Compared to TE adults on an inhibitor-containing regimen, pediatric subjects weighing ≥40 kg and administered maraviroc 150 mg BID are predicted to have exposures that are 40% higher. While the exposure would overall be higher than that in adults, we consider slightly higher exposures compared to adults to be acceptable for the following reasons. First, pediatric Cmax values in all patients are expected to fall below the Cmax value (1351 ng/mL in adults administered ≥600 mg alone) associated with postural hypotension in adults. Second, 150 mg is easier to administer because there is a 150 mg tablet, while 125 mg (the dose given to most subjects ≥40 kg in the pediatric study) would require administration of one 75 mg and two 25 mg tablets. This may improve adherence by reducing complexity of the regimen and pill burden. Third, HIV treatment regimens commonly utilize the adult dose in pediatrics weighing ≥40 kg and sometimes lower weights as well. Fourth, based on allometric scaling, it is expected that utilizing the adult dose in such pediatric patients would always result in slightly higher exposures of a magnitude similar to that described above. As such, the predicted higher exposures in pediatric patients weighing ≥40 kg with maraviroc 150 mg BID are considered acceptable.

1.1.3 Pediatric maraviroc dosing when coadministered with non-interacting concomitant medications

Background

The sponsor proposed pediatric maraviroc dosing of (b) (4) Seven of 10 subjects enrolled with neutral regimens had a final dose that was equivalent to the proposed dose.

Model development and evaluation

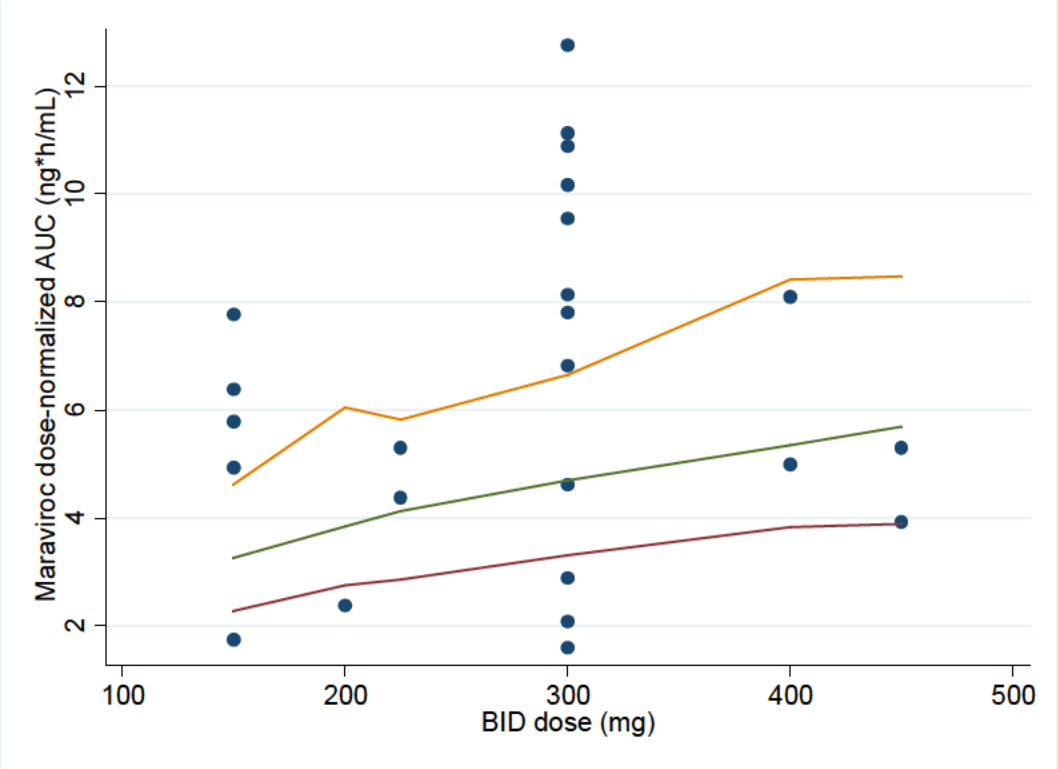
The sponsor developed a model of dose-normalized noncompartmental PK parameters (Cmax and AUC) as a function of dose using intensive PK parameters from 297 adult and 10 pediatric subjects
Separate AUC and Cmax models were developed. Simulations were provided but are not discussed here because the model was not accepted (see Reviewer's assessment).

Reviewer's analyses

Population PK analysis

We ran the sponsor's model and obtained an identical result. There was good agreement between observed and individual predicted values; however, the model underpredicted adult and pediatric variability (Figure 3).

Figure 3. Visual predictive check for pediatric subjects.

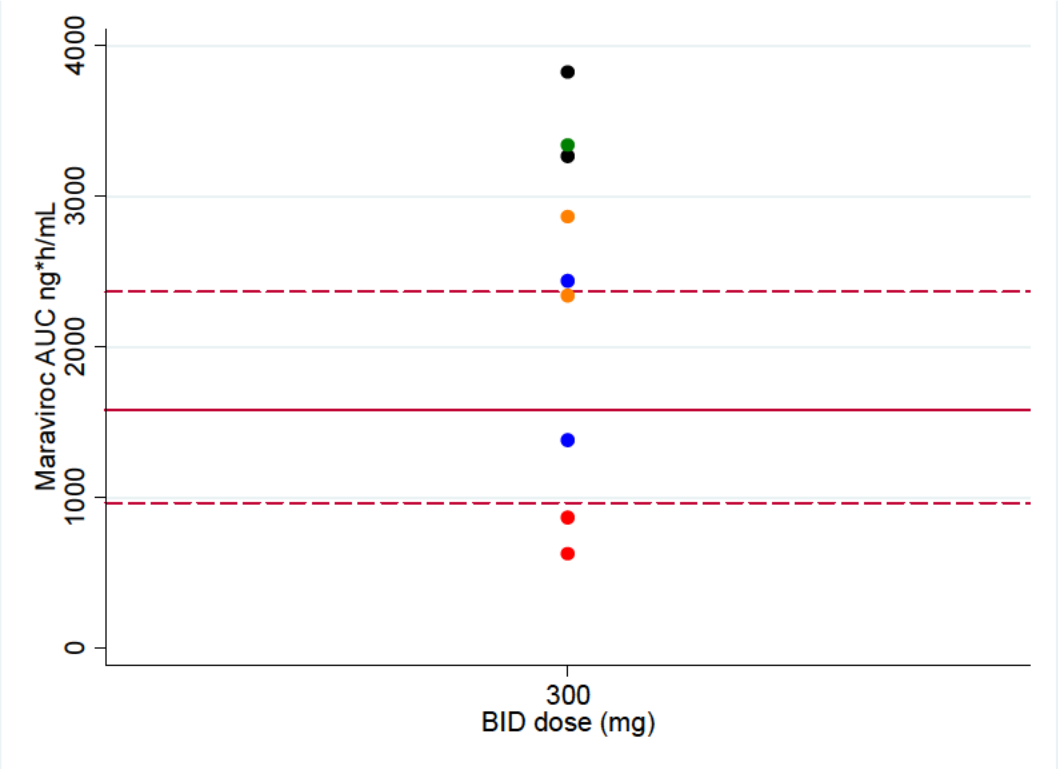


Source: Prepared by reviewer. All data was obtained in the fed state. Circles = observed data; lines = 5th, 50th, and 95th percentiles of 1000 model simulations of the subjects contributing observed data.

Comparison of observed intensive PK for pediatric subjects ≥30 kg versus adults

When the 30-40 kg and ≥40 kg weight groups are combined, there are five pediatric subjects ≥30 kg with a total of nine intensive PK assessments at a dose of 300 mg BID. Four of five subjects had maraviroc AUC values that were within or above the adult interquartile range (Figure 4). Pediatric Cmax and Cmin values are also within the adult distribution. Median (min, max) maraviroc Cmax values observed in pediatric subjects weighing ≥30 kg and administered a dose of 300 mg BID were 459 ng/mL (174, 721).

Figure 4. Maraviroc AUC in pediatric subjects ≥30 kg and adults with noninteracting background regimens.



Source: Plotted by reviewer. References lines are adult median (solid line), 25th, and 75th percentiles (dashed lines).

Reviewer's assessment

We agree with the proposed dosage regimen for pediatric subjects weighing ≥30 kg. (b) (4)

(b) (4) we sought to identify weight bands where a sufficient number of pediatric subjects were administered the proposed dose. This was the case only when considering the subset of pediatric subjects weighing ≥30 kg. In these pediatric subjects, observed exposures at a dose of 300 mg BID were sufficiently similar to adults; no subjects had Cmax values that exceeded the mean value in adults associated with postural hypotension. Due to only two subjects enrolled in each of the 10-20 kg and 20-30 kg groups, we do not recommend use in these weight groups.

1.1.4 Pediatric maraviroc dosing when coadministered with CYP3A inducer concomitant medications

PK data were only obtained from three pediatric subjects with CYP3A inducer-based regimens. (b) (4)

2 Recommendations

The Office of Clinical Pharmacology review team finds this application acceptable and recommends approval.

For regimens containing coadministered CYP3A inhibitors, we considered adult maraviroc exposures to be sufficiently similar to predicted pediatric exposures for the proposed dosage regimen. We agree with the sponsor's proposed dosage regimen for regimens containing coadministered CYP3A inhibitors.

For regimens containing noninteracting concomitant medications, there was insufficient data for subjects weighing <30 kg. (b) (4) subjects weighing <30 kg and we do not recommend use in the weight group. Based on the observed intensive pediatric PK data, we agree with the sponsor's proposed dosage regimen for patients weighing ≥30 kg on regimens containing noninteracting concomitant medications.

For regimens containing CYP3A inducers without CYP3A inhibitors, there was insufficient data for any pediatric weight group. (b) (4) we do not recommend maraviroc use in pediatric patients with regimens containing CYP3A inducers without CYP3A inhibitors.

3 Labeling recommendations

The sponsor (b) (4) proposed pediatric dosing regimen. These include:

i) not recommending use in patients <30 kg on neutral regimens
ii) not recommending use in pediatric patients on CYP3A inducer (without inhibitor) regimens.

Also, in section 12, (b) (4) . We instead proposed inclusion of predicted pediatric exposures for the proposed dosing regimen for subjects with regimens containing CYP3A inhibitors. The sponsor accepted this proposal.

4 Individual study reviews

4.1 A4001031 – Pediatric PK, safety, and efficacy study

Link to CSR: \\cdsesub1\evsprod\nda208984\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv1-infection\5352-stud-rep-uncontr\a4001031\a4001031-report.pdf

Methods

Study A4001031 (study 1031) enrolled treatment-experienced pediatric subjects aged 2 - <18 years of age. Subjects were enrolled into one of four cohorts based on age; subjects aged 6-12 years received either the tablet or solution formulation (Table 6).

Table 6. Cohorts in pediatric study A4001034.

Cohort	Age (years)	Maraviroc formulation
1	≥2 - <6	Solution
2	≥6 - <12	Tablet
3	≥6 - <12	Solution
4	≥12 - <18	Tablet

Source: reviewer.

The objectives of stage 1 of the study were dosing finding and intensive PK assessment. The sponsor used a target concentration of Cavg ≥100 ng/mL that was based upon matching adult exposures in addition to the sponsor's conclusion that the probability of treatment response was near-maximal at Cavg ≥100 ng/mL. On days when intensive PK was assessed, maraviroc was recommended to be taken with food; otherwise the recommendation was to take without regard to food. Intensive PK was assessed at week 2. Doses were increased for subjects with Cavg <100 ng/mL and intensive PK was reassessed two weeks later. Initial dosing was based on body surface area and whether CYP3A inhibitors or inducers were present in the background regimen. Preliminary PK was assessed after at least four subjects were enrolled for each concomitant medication category. Based on this assessment, the protocol was amended to increase maraviroc doses for subjects on neutral concomitant medications (Table 7).

Table 7. Initial maraviroc pediatric dosing.

Body surface area (m^2)	Dose in absence of potent CYP3A inhibitors or inducers (prior to CSP amendment 5)*	Dose in absence of potent CYP3A inhibitors or inducers	Dose with potent CYP3A inhibitors[a]	Dose with CYP3A inducers[c] (in absence of potent CYP3A inhibitors[a])
<0.22	20 mg BID[b]	40 mg BID[b]	10 mg BID[b]	40 mg BID[b]
0.22 – 0.43	50 mg BID	100 mg BID	25 mg BID	100 mg BID
0.44 – 0.72	100 mg BID	200 mg BID	50 mg BID	200 mg BID
0.73 – 1.19	150 mg BID	300 mg BID	75 mg BID	300 mg BID
1.20 – 1.30	200 mg BID	300 mg BID	100 mg BID	375 mg BID
1.31 – 1.73	300 mg BID	300 mg BID	125 mg BID	450 mg BID
>1.73	300 mg BID	300 mg BID	150 mg BID	600 mg BID

Abbreviations: BID=twice a day; BSA=body surface area; CSP=clinical study protocol; CYP3A=cytochrome P450 3A; MVC=maraviroc; OBT=optimized background therapy.
*Original starting doses which were no longer used after CSP amendment 5.
[a] eg, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, ketoconazole, itraconazole, clarithromycin, and telithromycin.
[b] dose available in liquid formulation only.
[c] eg, efavirenz, etravirine, rifampicin, carbamazepine, phenobarbital, and phenytoin.

Source: Study 1031 clinical study report (CSR) pg45.

Stage 1 subjects were rolled over into stage 2 of the study; additional subjects were enrolled directly into stage 2. The objectives of stage 2 were safety, efficacy, and PK. Each subject had a single PK sample collected at all visits through week 48. Intensive PK was reassessed at week 48 for subjects who were rolled over from stage 1.

Results

Study conduct

Seventy-four of 103 treated subjects (72%) completed the study through week 48 (Table 8).

Table 8. Subject disposition.

Number (%) of Subjects	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Screened 285					
Assigned to Study Drug	16	31	13	43	103
Treated	16	31	13	43	103
Treated in Stage 1	13 (81.3)	11 (35.5)	11 (84.6)	21 (48.8)	56 (54.4)
Treated in Stage 2	15 (93.8)	31 (100.0)	12 (92.3)	39 (90.7)	97 (94.2)
Rolled over from Stage 1	12 (75.0)	11 (35.5)	10 (76.9)	17 (39.5)	50 (48.5)
Entered directly into Stage 2	3 (18.8)	20 (64.5)	2 (15.4)	22 (51.2)	47 (45.6)
Completed Week 24[a]	14 (87.5)	30 (96.8)	12 (92.3)	30 (69.8)	86 (83.5)
Completed Week 48[b]	12 (75.0)	26 (83.9)	9 (69.2)	27 (62.8)	74 (71.8)

Source: CSR pg84.

Reported protocol deviations largely consisted of dosing errors and repeated intensive PK when compliance issues were suspected (Table 9).

Table 9. Protocol deviations.

Subject ID	Cohort	OBT group	Deviation
10871006	1	Neutral	Intensive PK was repeated on week 7 because concentrations were high on week 2
10881006		Inhibitor (LPV/r)	Intensive PK repeated on week 6 due to suspected compliance issues
10881008		Inhibitor (LPV/r)	Intensive PK was repeated on week 7 because concentrations were high on week 2
10882002		Inhibitor (LPV/r)	Intensive PK repeated on week 6 due to suspected compliance issues
10882003		Inducer (EFV)	Intensive PK repeated on weeks 7 and 11 due to suspected compliance issues
10201004	2	Inhibitor (LPV/r)	Intensive PK repeated on weeks 7 and 11
10221011		Inhibitor (LPV/r)	150 mg BID incorrectly given on day 1. Corrected to 75 mg BID on day 2.
10221012		Neutral	Intensive PK repeated week 7 after dose change.
10651008		Inhibitor -LPV/r on days 1-145 -LPV/r +ATV on days 146-539	Received 200 BID instead of 100 BID on days 1-11 due to mother's misunderstanding
10201033	3	Inhibitor (LPV/r)	Intensive PK repeated twice on dose of 75 mg on weeks 7 and 9, then again on a dose of 112.5 mg on week 13
10221014		Inhibitor (LPV/r)	Intensive PK repeated on week 7 due to known or suspected compliance issues
10201076	4	Inhibitor (LPV/r)	Rifampicin reportedly used at time of enrollment but was not known to the study team
10201096		Inhibitor (LPV/r)	Subject given 75 mg BID on days 1-29 due to incorrect BSA calculation
10221004		Inhibitor (LPV/r)	Incorrectly received 75 mg BID on days 1-4
10322001		Inhibitor (DRV/r)	Incorrectly dosed with 150 mg BID from weeks ~1-16 though dose should have been 125 mg BID
10451011		Inhibitor+inducer (LPV/r+EFV)	Incorrectly received 100 mg BID from days 1-36 due to incorrect BSA calculation

Source: Prepared by reviewer from CSR section 10.2.

Pharmacokinetics

Fifty-six subjects were treated in stage 1 and evaluable PK data were obtained for 50 subjects. Three subjects had no evaluable PK, data were excluded for two subjects deemed non-compliant, and one subject had evaluable PK but at the incorrect dose (CSR pg 86). In stage 1, 49 of 50 subjects were reported to have met the exposure target on their initial or adjusted maraviroc dose. One subject did not meet the target but had virologic success. Overall, dose adjustments were required for 8 subjects (n=1 on CYP3A inhibitor regimen, n=6 on neutral regimen, n=1 on

inducer regimen). In the noncompartmental analysis for the final doses selected in stage 1, Cavg and Cmax values were not significantly different between cohorts, while Cmin values were more variable between cohorts (Table 10).

Table 10. Noncompartmental analysis of intensive PK data for final stage 1 doses.

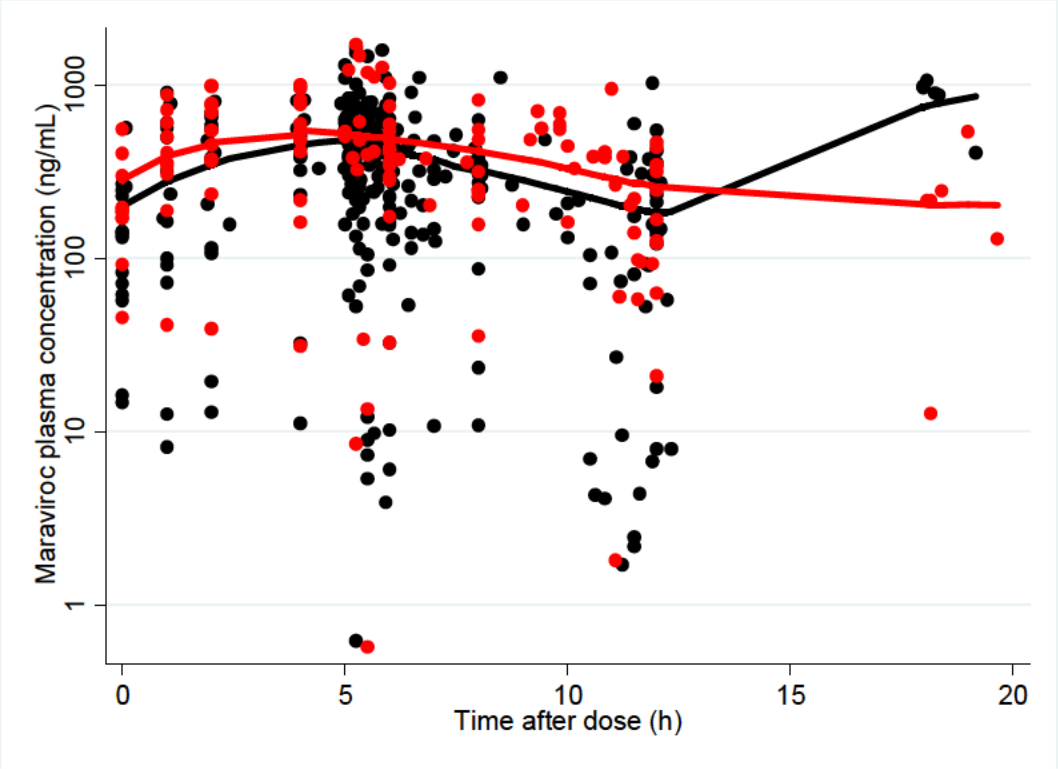
Analysis Set	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Stage 1 subjects enrolled in Stage 2	**n=12 (75%)**	**n=11 (35.5%)**	**n=10 (76.9%)**	**n=17 (39.5%)**	**n=50 (48.5%)**
C_{avg} (geometric mean) (ng/mL)	237.34	260.65	264.45	239.85	248.47
C_{avg} (median) (ng/mL)	231.60	271.60	287.24	277.65	251.58
C_{avg} (minimum) (ng/mL)	113.6	120.0	102.5	72.0	72.0
C_{avg} (maximum) (ng/mL)	843.6	401.7	613.2	613.0	843.6
C_{max} (geometric mean) (ng/mL)	581.47	546.80	444.37	530.80	527.03
C_{max} (median) (ng/mL)	553.00	570.00	448.00	666.00	588.50
C_{max} (minimum) (ng/mL)	205.0	232.0	176.0	174.0	174.0
C_{max} (maximum) (ng/mL)	1870.0	905.0	995.0	1050.0	1870.0
C_{min} (geometric mean) (ng/mL)	18.97	100.02	115.84	56.17	56.80
C_{min} (median) (ng/mL)	39.50	94.40	124.00	50.50	75.05
C_{min} (minimum) (ng/mL)	0.0	57.4	25.1	5.2	0.0
C_{min} (maximum) (ng/mL)	277.0	157.0	347.0	211.0	347.0

Source: Study 1031 CSR pg 106. Note: The above table includes results from all pediatric subjects regardless of background therapy.

Across stages 1 and 2, 85 subjects with background regimens including CYP3A inhibitors with or without CYP3A inducers had samples included in the PK analysis; the inhibitors were LPV/r (n=68), DRV/r (n=14), ATV or ATV/r (n=2), and FPV/r (n=1). There were ten subjects with neutral background regimens and three subjects on background regimens including CYP3A inducers (without inhibitors).

Comparing cohorts 2 and 3 where subjects aged 6-12 years with LPV/r as an inhibitor were administered either the tablet or solution, there was no apparent difference in PK by formulation (Figure 5, Table 11). Note that only three subjects with neutral background regimens were enrolled in cohorts 2 and 3, thus the effect of formulation on PK was not assessed for subjects with neutral regimens.

Figure 5. Maraviroc concentration-time data by formulation for subjects in cohorts 2 and 3 and who had LPV/r as an inhibitor.



Source: plotted by reviewer. Black = tablet; red = liquid; line = lowess. For subjects with PK after different dose levels, PK was included only for the last (optimized) dose.

Table 11. Demographics and PK of subjects in cohorts 2 and 3 and who had LPV/r as an inhibitor.

Cohort	Formulation	Number of subjects	Age (years)	Weight (kg)	Number of samples	MVC (ng/mL)
2	tablet	24	9 (6, 11)	25 (14, 47)	311	344 (0.625, 1640)
3	liquid	8	10 (7, 11)	24 (17, 36)	136	364 (0.573, 1710)

Source: Prepared by reviewer. Values are N or median (min, max).

The population PK analyses that incorporate stage 1 (intensive PK) and stage 2 (sparse and intensive PK) data and that underlie our assessment of the sponsor's proposed maraviroc pediatric dosing regimens for inclusion in the USPI are discussed in sections 4.2 and 4.3.

Safety

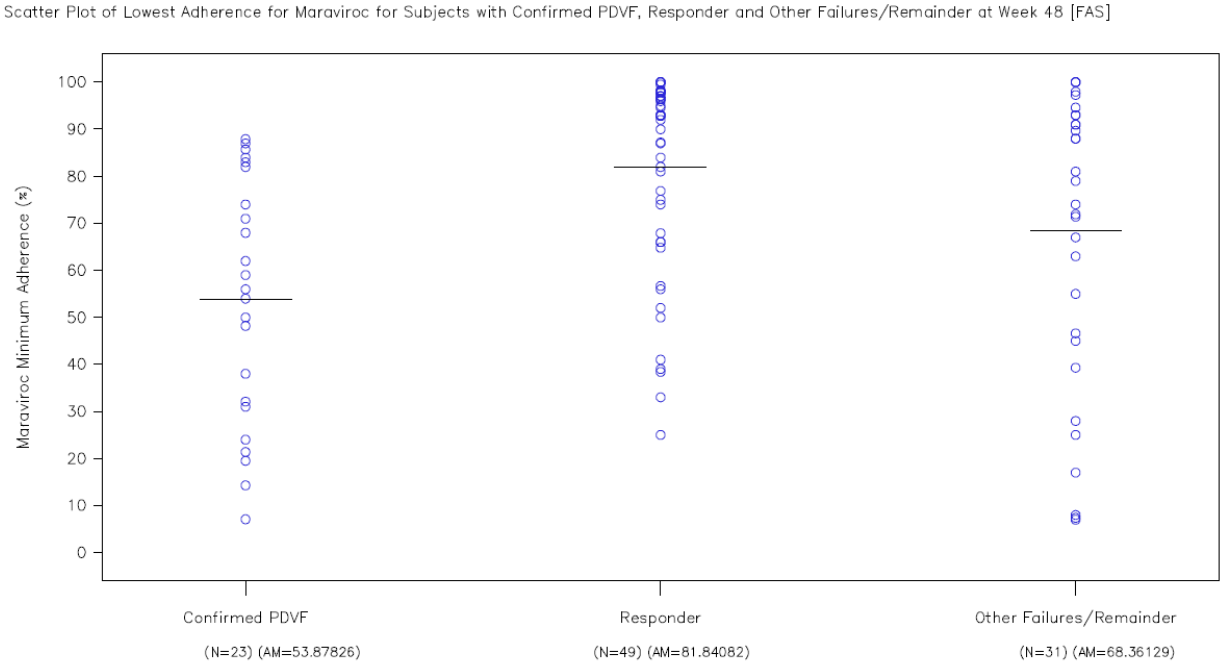
Infections and gastrointestinal disorders were the most common adverse events (AE). Two subjects discontinued the study due to AEs (vomiting [n=1] and pelvic inflammatory disease [n=1]). One death occurred due to pneumonia 489 days after the last maraviroc dose.

Efficacy

The overall proportion of subjects with HIV RNA <400 copies/mL and <48 copies/mL at week 48 was reported to be 65% and 48%, respectively; rates were lower for adolescents (51% and 40%, respectively).

Mean minimum adherence (assessed through pill or volume counts) to maraviroc and background therapy were lower in subjects with virologic failure versus responders (Figure 6, Figure 7).

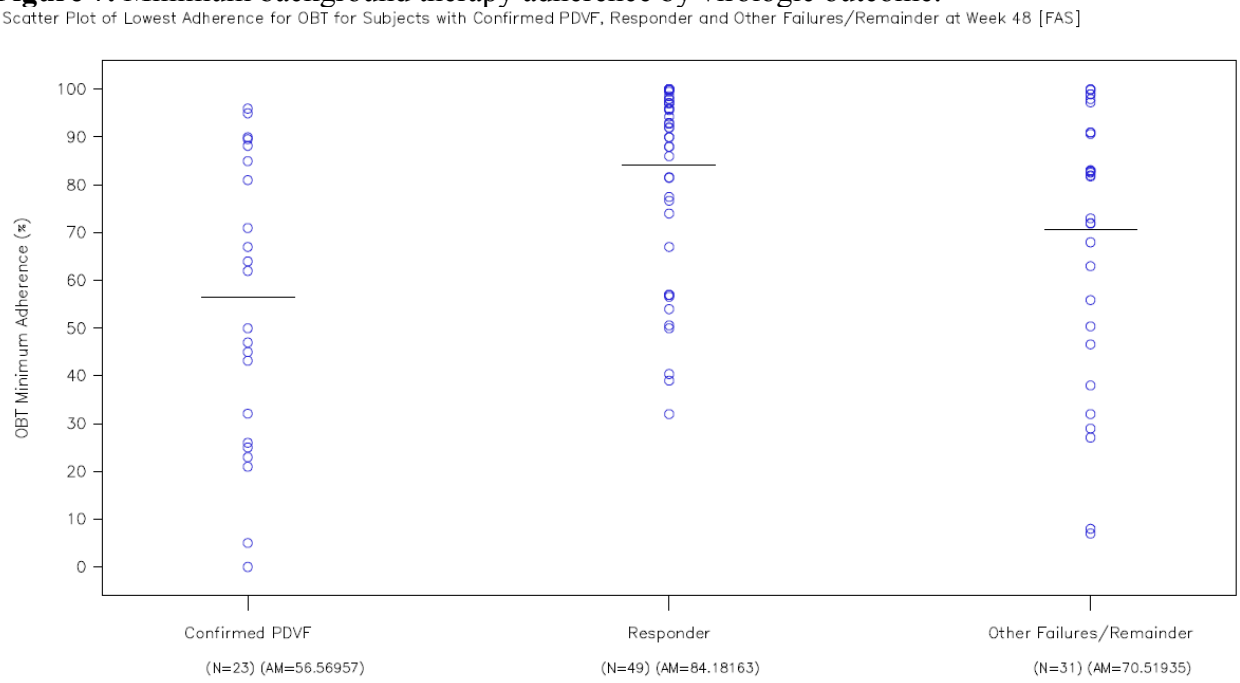
Figure 6. Minimum maraviroc adherence by virologic outcome.



Subject 10291001 is PDVF as well as responder at the point of failure and is grouped under responder.
Response = Week 48 FDA MSDF outcome where HIV-1RNA <= 48.
PDVF : Protocol Defined Virologic Failures.
AM : Arithmetic Mean.

Source: CSR p404.

Figure 7. Minimum background therapy adherence by virologic outcome.



Subject 10291001 is PDVF as well as responder at the point of failure and is grouped under responder.
Response = Week 48 FDA MSDF outcome where HIV−1RNA <= 48.
PDVF : Protocol Defined Virologic Failures.
AM : Arithmetic Mean.

Source: CSR p405.

Mean minimum adherence to maraviroc and background therapy was lowest and the rate of virologic failure was highest in adolescents (Table 12).

Table 12. Mean of minimum adherence values through week 48 by cohort.

Cohort	N	Age (years)	Form	MVC minimum adherence (%)	OBT minimum adherence (%)	Subjects with VF (n, %)	Subjects with BQL (n, %)
1	16	2 - <6	Liquid	76	77	3 (19)	4 (25)
2	31	6 - <12	Tablet	78	77	4 (13)	1 (3)
3	12	6 - <12	Liquid	78	85	3 (25)	0 (0)
4	42	12 - <18	Tablet	63	67	13 (31)	6 (14)

Source: Prepared by reviewer. Minimum adherence %: 1) Adherence based on pill/volume count taken at each visit and 2) Minimum taken for each subject and summarized by cohort. BQL = PK sample whose concentration is below the limit of quantification; MVC = maraviroc; OBT = optimized background therapy; VF = protocol defined virologic failure.

The overall virologic failure rate in the trial was 22%. Six of 11 subjects (55%) with samples below the limit of quantification (BLOQ) of 5 ng/mL (n=20 samples) were virologic failures.

Figure 8. Virologic outcomes for subjects with BLOQ samples.

Cohort	Subject ID	Dosage form	Background therapy	Virologic failure
1	10832004	Solution	LPV/r	
1	10832007	Solution	LPV/r	Yes
1	10881008	Solution	LPV/r	
1	10871004	Solution	Neutral	
2	10651008	Tablet	LPV/r (days 1-145) LPV/r + ATV (days 146-539)	Yes
4	10071002	Tablet	ATV	
4	10322001	Tablet	DRV/r	Yes
4	10571004	Tablet	DRV/r	Yes
4	10451011	Tablet	EFV+LPV/r	Yes
4	10201077	Tablet	LPV/r	Yes
4	10461001	Tablet	LPV/r	

Source: Prepared by reviewer.

Reviewer assessment

Overall, from our perspective, study 1031 is acceptable to support dosing recommendations in labeling (section 2) and for inclusion of pediatric PK data in labeling (section 12.3). The focus of our review of study 1013 was on the adequacy of the study conduct and bioanalysis. It appeared that compliance was highly variable, especially in adolescents (according to pill/volume counts); however, this is likely the case for pediatric studies in general. The maraviroc bioanalytical methods were validated and study samples were analyzed in accordance with FDA guidance.

We did not accept Cavg ≥100 ng/mL target concentration as an indicator of adequate pediatric maraviroc exposures. First, the exposure parameter included in exposure-response analyses in the label is Cmin, not Cavg. Second, predictors of virologic response relationships are multifactorial, and in addition to maraviroc plasma Cmin include baseline viral load, CD4 count, and overall sensitivity score (USPI). Thirdly, the selected metric represents where response rates were predicted to appreciably decline, while the targeted exposures for pediatrics should aim to be on the flat portion of previously identified exposure-response relationships. Finally, the common and accepted approach for pediatric dose selection for HIV is to achieve exposures equal to or at times slightly higher than that observed in adults. As such, our focus was on establishing whether pediatric maraviroc exposures were similar to adults for the proposed pediatric dosing regimen, as discussed in sections 4.2 (coadministration with CYP3A inhibitors) and 4.3 (coadministration with non-interacting concomitant medications).

4.2 PMAR-EQDD-A400b-DP4-195 – PopPK of maraviroc when coadministered with CYP3A inhibitors

Link to study report: \\cdsesub1\evsprod\nda208984\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-a400b-dp4-195\pmar-eqdd-a400b-dp4-195-report.pdf

Background

The sponsor evaluated BSA-based maraviroc dosing in study 1031 and proposed body weight-based maraviroc pediatric dosing for inclusion in the USPI (Table 13). Typically, the proposed doses were equivalent to the doses administered to most subjects in pediatric study 1031; the exception is for subjects ≥40 kg where 125 mg BID was administered whereas 150 mg BID is the proposed dosing (Table 14).

Table 13. Proposed pediatric weight-based maraviroc dosing for subjects with a CYP3A inhibitor-containing background regimen.

Formulation	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
Tablet	50 mg BID	75 mg BID	100 mg BID	**150 mg BID**
Solution	50 mg (2.5 mL) BID	80 mg (4 mL) BID	100 mg (5 mL) BID	**150 mg (7.5 mL) BID**

Source: Proposed maraviroc USPI.

Table 14. Final maraviroc doses for pediatric subjects in study 1031 on a CYP3A inhibitor-containing regimen.

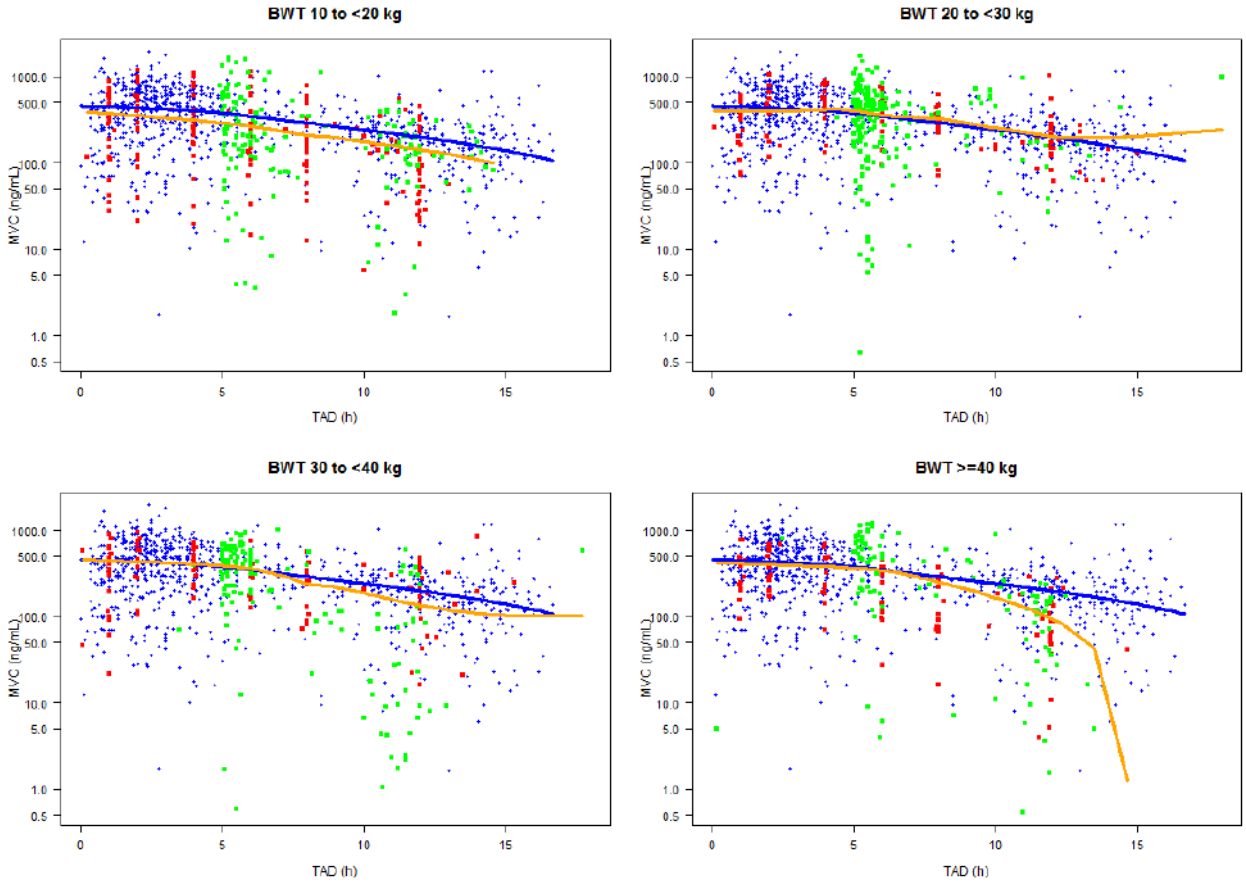
	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
N	20	25	22	18
Median	50 mg BID	75 mg BID	100 mg BID	**125 mg BID**
Min	50 mg BID	75 mg BID	75 mg BID	75 mg BID
Max	75 mg BID	75 mg BID	112.5 mg BID	150 mg BID

Source: Reviewer's analysis.

Graphical comparison of observed pediatric and adult PK

Observed intensive and sparse pediatric concentration-time data were graphically compared to concentration-time data from HIV-infected adults on inhibitor-containing regimens (Figure 9). The sponsor concluded that BSA-based dosing in pediatric study 1031 resulted in similar pediatric exposures compared to adults. In addition, population PK modeling of adult and pediatric PK data was conducted.

Figure 9. Maraviroc pediatric and adult concentration-time data for subjects on inhibitor-containing regimens.



Source: NDA 208984 SDN 10. Weight bands refer to pediatric subjects only. The pediatric data includes subjects not on an optimized dose. Unreliable pediatric data was excluded. Adults = blue; pediatric intensive PK = red; pediatric sparse PK = green. Blue line = adult lowess; orange line = pediatric lowess.

Maraviroc modeling history

A semi-mechanistic model was previously developed from a dataset consisting of adult and pediatric subjects on maraviroc alone and maraviroc plus CYP3A inhibitor. Due to model complexity and minimization difficulties, EMA and FDA suggested model simplification and modeling subsets of data (report p28).

In this submission, a separate model was developed using maraviroc concentration-time data from pediatric and adult subjects on CYP3A inhibitor-containing regimens. This model was then used to simulate exposures in pediatric subjects administered maraviroc according to the proposed pediatric dosing regimen. Summary statistics of the simulation results were grouped by pediatric body weight category and compared to reference exposures in adults. The simulated pediatric exposures demonstrated similarity to exposures in adults.

Studies included in model building

Adult data were obtained from several drug interaction studies in healthy volunteers in addition to efficacy studies in HIV-infected subjects (Table 15). The dataset contained 85 pediatric subjects and 1116 pediatric samples along with 171 adult subjects and 1489 adult samples (Table 16).

Table 15. Adult studies included in the maraviroc plus CYP3A inhibitor-containing regimen population PK dataset.

Study #	Data used for model building	MVC dosing	Fed / fasted	Population
A4001013	MVC + LPV/r	50 mg or 100 mg BID	Fasted	HV
A4001021	MVC + LPV/r ± EFV	300 mg BID		
A4001025	MVC + ATV/r			
A4001041	MVC + DRV + ETV	150 mg BID		
A4001052	MVC + DRV/r			
A4001027	MVC + LPV/r, ATV, or ATV/r		No restrictions	HIV infected
A4001028	MVC + LPV/r, ATV, or ATV/r			
A4001029	MVC + LPV/r, ATV, or ATV/r			
A4001098	MVC + LPV/r, ATV, ATV/r, DRV/r ± ETR			

Source: popPK report pg 34. HV = healthy volunteers; MVC = maraviroc.

Table 16. Summary of maraviroc plus CYP3A inhibitor-containing regimen population PK dataset.

	Pediatric[a]	Adult Phase 2b/3/4[a]	Adult Phase 1[a]
Number of subjects	85	125	56
Males/females	43/42	112/13	45/11
Weight (kg) : Median (Range)	28.9 (10.2-69.8)	76.7 (50.2-120.0)	71.0 (46.0-92.2)
BSA (m^2) : Median (Range)	1.05 (0.48-1.83)	1.93 (1.50-2.44)[b]	1.87 (1.39-2.19)
Baseline Estimated Creatinine CL (mL/min): Median (Range)	Under 12 years 111 (57-180)[c] 12 years and over 135 (42-189	107 (53-240)	108 (68-172)
Age (years) : Median (Range)	11 (2-17)	45 (28-69)	29.5 (20-55)
Race: White/Black/Asian/Other (N)	13/58/11/3	96/20/4/5	24/5/26/1
OBT:			
PI: ATV alone /ATV/r /FPV/r /LPV/r /DRV/r (N)	0/2/1/68/14	5/33/0/79/8	0/12/0/19/25
NNRTI: None/EFV/NVP/ETR (N)	80/3/1/1	110/11/1/3	46/0/0/10
Integrase Inhibitor: None/Raltegravir (N)	78/7	119/6	56/0
Sampling:			
Subjects/Profiles/Samples (N)	Profiles: 38/67/468[3] Sparse: 84/0/648	Profiles: 0/0/0 Sparse: 125/0/861	Profiles: 56/74/628 Sparse: 0/0/0
Food Status for Samples Fasted/Fed/Not Known (N)	Profiles: 0/460/8[d] Sparse: 0/491/157	Profiles: 0/0/0 Sparse: 152/539/170	Profiles: 628/0/0 Sparse: 0/0/0

[a]All Pediatric subjects, All Adult Phase 1 Subjects and all Phase 4 subjects (A4001098) had baseline demographic values; Adult Phase 2b/3 subjects used earliest available demographic values

[b] 11 Subjects with missing values of BSA

[c]Creatinine Clearance calculated by the modified Schwartz formula and adjusted for BSA for subjects <12 years

[d]Trough samples taken before profile doses have been included; the 8 samples that had unknown food status were pre-dose samples

Source: popPK report 195, page 10.

Excluded data

Forty-two samples from 28 adult subjects were excluded from the analysis (NDA 208984 SDN 23). Reasons for exclusion were not enumerated by sample, but included BLOQ samples, long time after dose (implying missing dose information), no dose information collected prior to sample, and missing concentrations where samples were apparently taken.

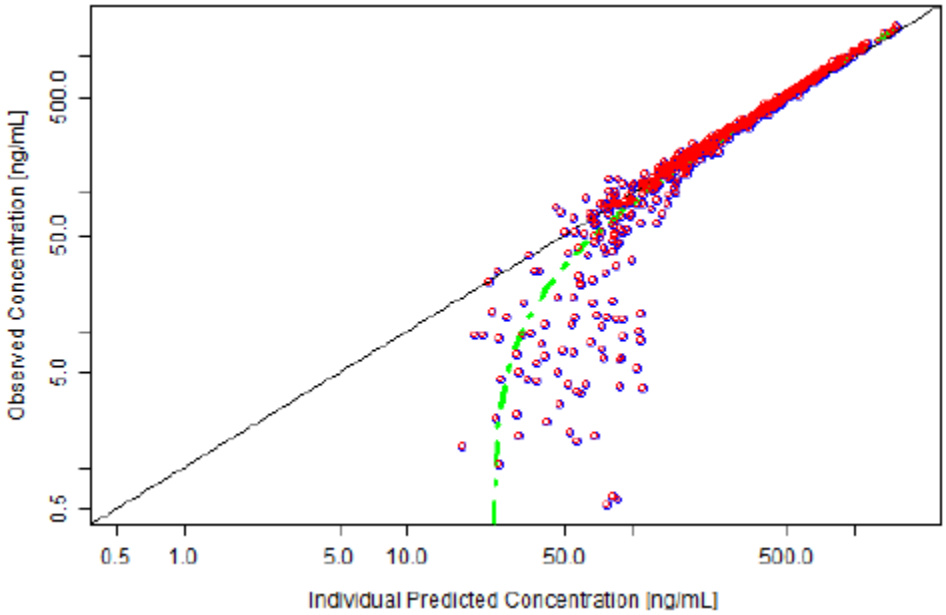
In the pediatric study, 128 samples from 38 subjects were excluded (NDA 208984 SDN 23). These included 70 week 2 intensive PK samples from seven subjects with suspected poor adherence or suspected dosing error. The week 2 PK was subsequently repeated and the final week 2 profile was retained in the analysis dataset.

In addition, 21 samples from 11 pediatric subjects that were BLOQ were excluded. Most of these data were reported to be from subjects with poor compliance and all but one had virologic failure at 48 weeks.

Model development and evaluation

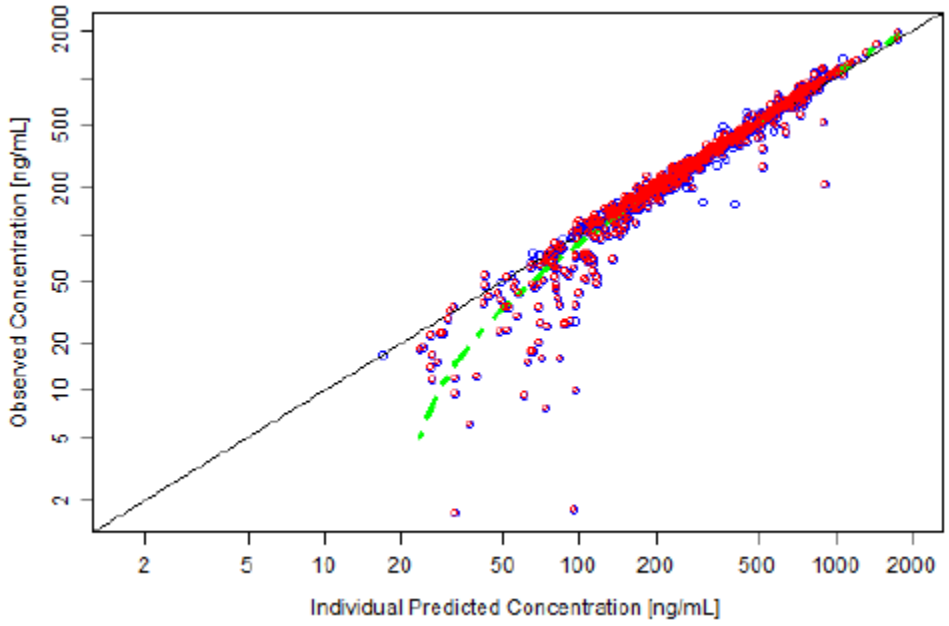
The final 2-compartment model scaled clearance (CL) and volume by body weight, and included covariates for the effect of dose on bioavailability, reduction in CL for other inhibitors relative to LPV/r (reference), increase in CL for presence of inducers versus no inducer (reference), along with the effect of race on central volume. Goodness of fit plots for pediatric and adult intensive PK data were reported to be satisfactory, though a subset of pediatric and adult sparse samples at low concentrations (< 50 ng/mL) were overpredicted (Figure 10, Figure 11). Model parameter estimates (report p81), goodness-of-fit (GOF) plots (report p70-75), and visual predictive checks (VPC, report p77-78) for pediatric and adult data were reported to be satisfactory. Good predictions were obtained for pediatric and adult intensive PK samples (report p70 and p75).

Figure 10. Observed versus individual predicted pediatric maraviroc sparse sample concentrations.



Source: popPK report p71.

Figure 11. Observed versus individual predicted adult maraviroc sparse sample concentrations.



Source: report p73.

Simulations

We issued an information request (IR) to the sponsor requesting that they use the model to simulate pediatric exposures using the proposed weight-based dosing regimen in order to facilitate comparisons between pediatric and adult exposures. Using bootstrapping, the sponsor used the pediatric study population (n=85 in the inhibitor dataset) to generate a dataset of 1000 subjects with similar demographic characteristics to the study population for simulation. The simulated pediatric exposures were provided in the sponsor's response (NDA 208984 SDN 10).

Reviewer's analyses

Graphical analysis of observed pediatric and adult concentration-time data

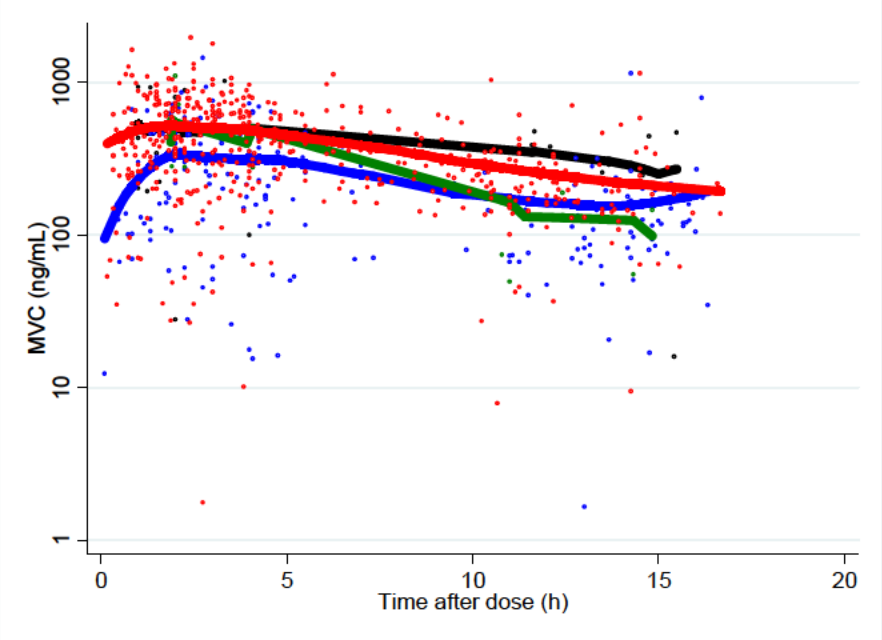
LPV/r was used in the majority of both adult and pediatric subjects; however, 30% of adult subjects used ATV versus 2% in pediatrics (Table 17). Adult maraviroc profiles were not found to differ significantly by inhibitor (Figure 12).

Table 17. Inhibitor use in pediatric and adult subjects included in the graphical analysis.

Regimen	Pediatrics (study 1031) [n=85]	Adults (studies 1027, 1028, 1029, 1098) [n=125]
LPV/r ± inducers	68 (80%)	79 (63%)
ATV or ATV/r ± inducers	2 (2%)	38 (30%)
DRV/r ± inducers	14 (16%)	8 (6%)
FPV/r ± inducers	1 (1%)	0 (0%)

Source: Prepared by reviewer. Values are number (%).

Figure 12. Adult maraviroc concentration-time data stratified by inhibitor.



Source: Prepared by reviewer. Black = ATV; blue = ATV/r; green = DRV/r; red = LPV/r; thick lines = lowess. Subjects with inducers in the background regimen were excluded.

Population PK modeling

We ran the sponsor's final model (run 19) using NONMEM 7.3. This model did not successfully minimize when run by the sponsor or us. When we ran the model repeatedly, identical results were obtained, suggesting the model is stable despite lack of minimization. We attribute the lack of minimization to the complexity of the model and variability in the data. Some parameter estimates differed between the sponsor's final model results (model 19) and our results. Clearance estimates were in close agreement (3% lower in our analysis), but central volume estimates were substantially lower (21% lower). The overall objective function value differed by 1% (Table 18). The sponsor reported problems with the use of bootstrapping to assess precision of parameter estimates; a similar problem occurred when we attempted to bootstrap the model

using PLT Tools. As such, bootstrapping evaluation of the model to obtain confidence intervals around the parameter estimates was not successfully performed.

Table 18. Model 19 results and parameter estimates obtained by the sponsor and by FDA.

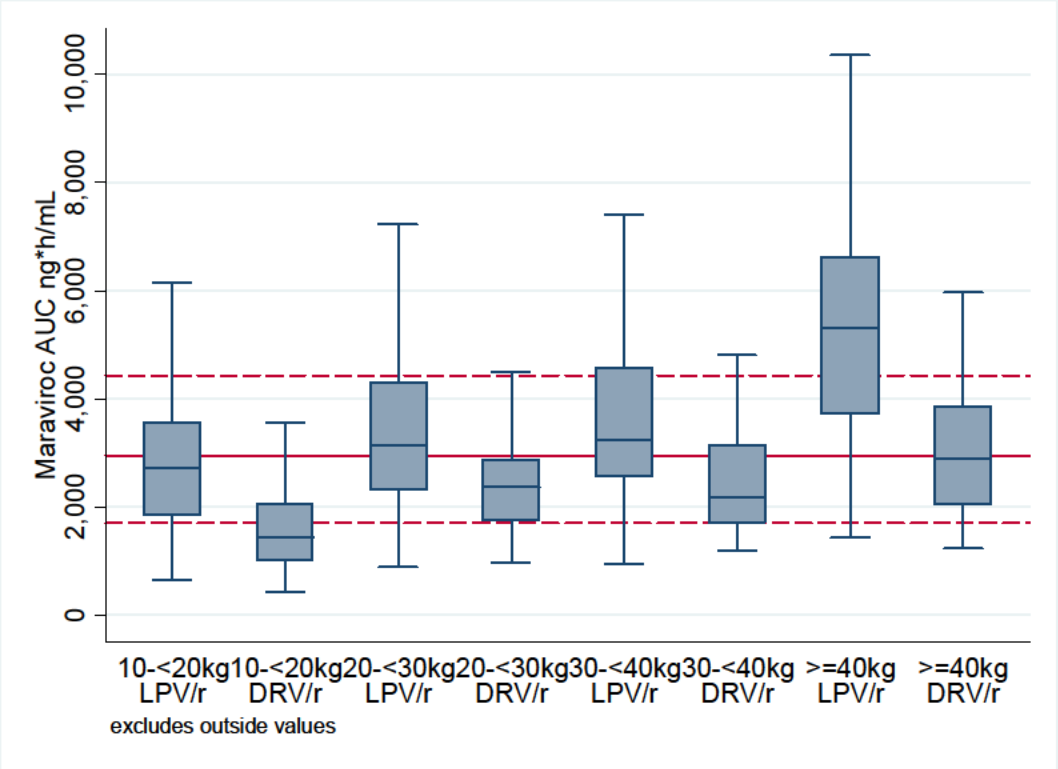
Result	FDA model 19 output	Sponsor's model 19 output		
Nonmem version	7.3.0	7.3.0		
Minimization	Terminated	Terminated		
# function evaluations	809	1136		
SigDigits	UNREPORTABLE	UNREPORTABLE		
Parameter name	FDA model 19 output	Sponsor's model 19 output	Percent difference	Fixed parameter
Objective function	28282.66631	28060.568	1%	
KA	0.384346	0.67	-43%	
V	186.861	237	-21%	
CL	35.3427	36.4	-3%	
Q	25.1208	29.4	-15%	
V3	1840	1840	0%	Y
Lag studies 1013 and 1052	0.864	0.864	0%	
Lag 1021 and 1025 and 1041	0.357	0.357	0%	
Lag 1098	0.631	0.631	0%	
Lag 1027, 1028, 1029, 1031	0.393	0.393	0%	
Allometry V2	1	1	0%	Y
Allometry CL	0.75	0.75	0%	Y
Allometry Q	1.59	1.59	0%	Y
Allometry V3	1.9	1.9	0%	Y
Dose nonlinearity	0.408573	0.546	-25%	
Add error – intensive PK	0	0	0%	Y
Prop error – intensive PK	0.299744	0.267	12%	
Add error - sparse data	43.624	37.9	15%	
Prop error – sparse data	0.165126	0.155	7%	
CL - ATV alone and FPV/r and ATV/r or DRV/r vs LPV/r reference	0.49641	0.463	7%	
V2 - Black increase vs White reference	0.363644	0.329	11%	
V2 - Asian and other increase vs White reference	-0.16963	-0.305	-44%	
CL - EFV, ETR and other 3 A4 inducers increase vs none reference	0.254378	0.267	-5%	
BCrCL - increase in CL over 120 ml/min reference	0.00192038	0.00367	-48%	

Source: Prepared by reviewer.

The CYP3A inhibitors coadministered to most subjects were LPV/r and DRV/r. Predicted maraviroc exposures were lower for subject coadministered DRV/r relative to LPV/r (Figure 13). Exposures were low compared to adults for pediatric subjects 10 - < 20 kg on DRV/r. However,

the rate of virologic failure was numerically higher in the LPV/r versus the DRV/r group (17/68 [25%] versus 2/14 [14%].

Figure 13. Predicted maraviroc AUC for pediatric subjects with LPV/r or DRV/r-containing regimens.

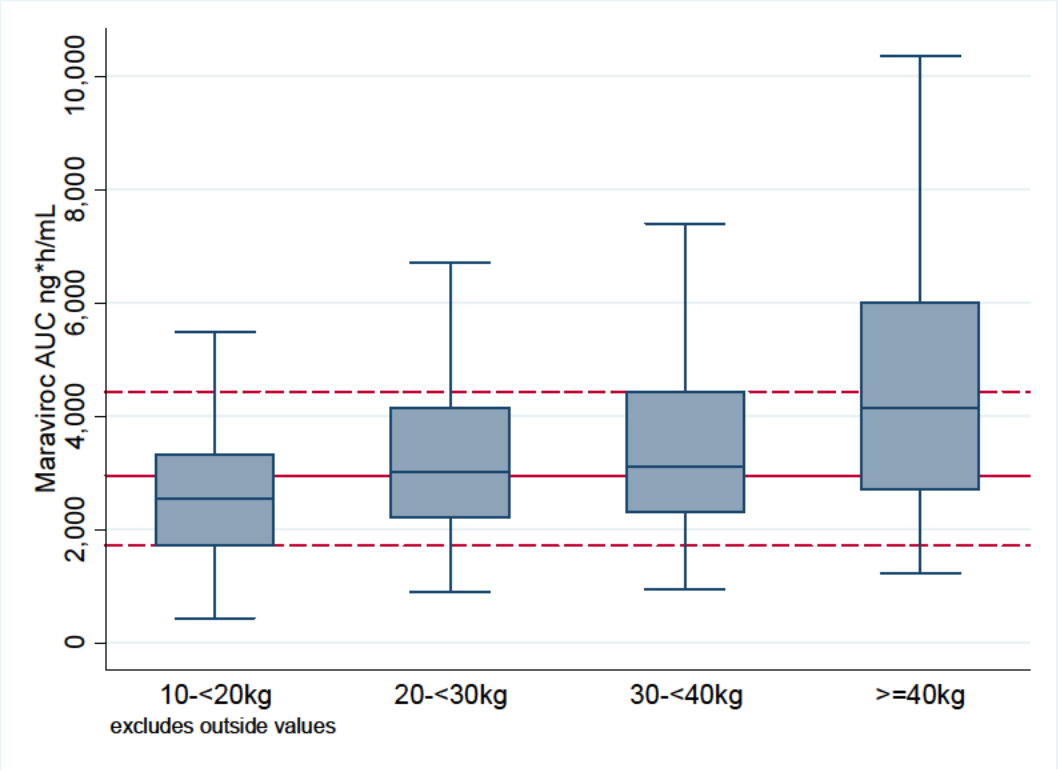


Source: Plotted by reviewer. Solid red line = median from adults on MVC 150 mg BID + background regimen containing a CYP3A inhibitor; Dashed lines = adult 25th and 75th percentiles. Adult reference values were obtained 342 TE adults on inhibitor regimens (NDA 208984 SDN 23); these are the adult maraviroc PK parameters for inhibitor regimens found in the maraviroc USPI.

We compared simulated pediatric exposures for the proposed dosing regimen versus previously reported values for adults to assess whether exposures were similar to adults. Simulated maraviroc pediatric exposures were obtained from the sponsor as described above. The adult reference group was 342 TE adults on inhibitor regimens; these subjects comprise the adult PK parameters in the maraviroc USPI (the label has data from 375 subjects; we excluded 23 on unboosted regimens, three on TPV [classified as noninteracting], and seven with absent protease inhibitor). PK parameters were obtained from a previously developed population PK model. These subjects were on various inhibitors with LPV/r being the most common; DRV/r was not used. A subset of 102 of these 375 TE adult subjects whose inhibitors were ATV/r or LPV/r were included in the current inhibitor model. When AUC values for each subject were compared between the two models, the median (25^{th}, 75^{th} percentile) of the absolute value of the percent differences was 11% (4.8%, 22%). Distributions of pediatric and adult maraviroc AUC generally overlapped with the exception of pediatric subjects ≥40 kg where predicted AUC was ~40%

higher compared to adults (Figure 14). Predicted median (min, max) maraviroc Cmax values in pediatric subjects administered maraviroc at the proposed dosage regimen are 126 ng/mL (4, 970).

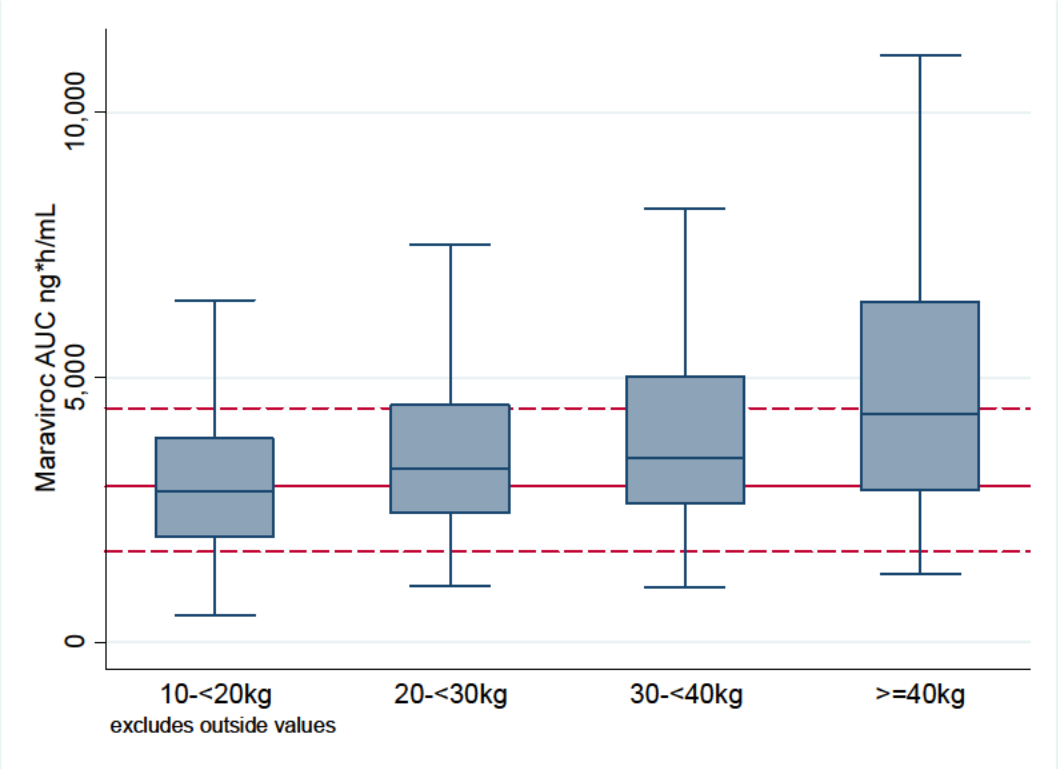
Figure 14. Comparison of maraviroc AUC between HIV-infected TE pediatric and adult subjects using the sponsor's model parameters.



Source: Plotted by reviewer. Pediatric exposures were predicted using model parameters obtained when the model was run by the sponsor. Adult reference values were obtained 342 TE adults on inhibitor regimens (NDA 208984 SDN 23); these are the adult maraviroc PK parameters for inhibitor regimens found in the maraviroc USPI. Solid red line = median AUC in TE adults; dotted red lines = 25th and 75th percentile of AUC in TE adults.

We repeated the simulations using the sponsor's simulation dataset and model parameters obtained from running the model at FDA. AUC values were calculated using STATA and the linear up-log down formula. As was the case using the sponsor's model parameters, the IQR of pediatric exposures was within the adult IQR with the exception of the ≥40 kg group (Figure 15). Simulated pediatric exposures using the FDA model parameters versus sponsor's model parameters were within 13% across weight groups (Table 19).

Figure 15. Comparison of maraviroc AUC between HIV-infected TE pediatric and adult subjects using the FDA's model parameters.



Source: Plotted by reviewer. Pediatric exposures were predicted using model parameters obtained when the model was run by the FDA. Adult reference values were obtained 342 TE adults on inhibitor regimens (NDA 208984 SDN 23); these are the adult maraviroc PK parameters for inhibitor regimens found in the maraviroc USPI. Solid red line = median AUC in TE adults; dotted red lines = 25th and 75th percentile of AUC in TE adults.

Table 19. Comparison of predicted pediatric maraviroc AUC between the model run by the sponsor versus at the FDA.

		Maraviroc AUC		
Weight group (kg)	N	Sponsor's model parameters	FDA's model parameters	Percent difference for median
10-<20	222	2534 (1714, 3322)	2843 (1975, 3856)	12%
20-<30	330	3010 (2203, 4149)	3280 (2431, 4486)	9%
30-<40	241	3103 (2296, 4432)	3493 (2626, 5014)	13%
≥40	207	4130 (2690, 6003)	4304 (2859, 6435)	4%

Source: Prepared by reviewer. AUC values are median (25th percentile, 75th percentile).

Reviewer's assessment

We agree with the proposed maraviroc pediatric dosing regimen for subjects with background therapy containing CYP3A inhibitors.

For the doses used in the pediatric study, similar exposures in each pediatric weight group compared to adults were observed. This graphical analysis is in agreement with the results of the modeling, in which similar pediatric doses to those studied were proposed for labeling.

Overprediction of pediatric and adult sparse samples at the low end of the concentration range was not found to be a significant issue. These were a subset of the sparse samples, and the dataset also contained intensive PK samples which were well predicted across the concentration range. In addition, adequate model performance was observed via VPCs.

One limitation to the modeling was that the model did not converge. Convergence is a desired but not essential feature, and failure to do so may be due to the complexity of the model.

There were differences in parameter estimates when the model was run by the sponsor and FDA. As we both used NONMEM 7.3, we are unsure what is the source of the parameter differences; one possibility is that the sponsor used a different compiler. The parameter differences did not have a significant impact on prediction of pediatric exposures.

Another potential limitation to the modeling was that the dataset likely precluded estimation of the effect of food status as a covariate. This is because there was no data for the fasted state in pediatrics. However, it is thought that protease inhibitors, which are CYP3A and P-gp inhibitors, reduce the dose dependency of maraviroc absorption and are assumed to result in reduced food effects (NDA 208984 SDN 10). This would explain why food effect was not detected in this model while food effect was a significant covariate in modeling of maraviroc with neutral concomitant medications.

Maraviroc exposures were lower in pediatric subjects on DRV/r-containing regimens versus LPV/r. Exposures were lower than adults for pediatric subjects 10 - <20 kg on DRV/r. However, we concluded that dosing need not depend on the inhibitor present because despite lower maraviroc exposures in the DRV/r-containing group, virologic response rates were numerically higher.

In pediatric subjects ≥40 kg given maraviroc 150 mg BID, exposures are predicted to be 40% higher than in TE adults on an inhibitor-containing regimen. Despite this increased exposure compared to adults, we recommend 150 mg BID rather than the 125 mg BID given to this weight group in the pediatric study. One reason is because 150 mg is easier to administer because there is a 150 mg tablet, while 125 mg would require administration of the 75 mg and 25 mg tablets. Also, based on allometric scaling, it is expected that giving the adult dose of 150 mg BID to adolescents would result in somewhat higher exposures.

Maraviroc Cmax is associated with postural hypotension at doses of ≥600 mg (maraviroc label). Mean day 7 Cmax in healthy adults at a dose of 600 mg daily is 1351 ng/mL (NDA 22128 Clinical Pharmacology review dated 6/19/2007, pg 6). Based on the pediatric simulations of the proposed dosage regimen, no subjects are expected to exceed this threshold.

4.3 PMAR-EQDD-A400b-DP4-196 - PopPK of maraviroc when coadministered with non-interacting concomitant medications

Link to popPK report: \\cdsesub1\evsprod\nda208984\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-a400b-dp4-196\pmar-eqdd-a400b-dp4-196-report.pdf

Background

(b) (4) Six of the eight subjects requiring stage 1 dose adjustments had neutral concomitant regimens. Based on a preliminary evaluation of stage 1 PK, protocol doses were increased for subjects on neutral regimens. Seven of 10 subjects had a final dose that was equivalent to the proposed dose (Table 21).

Table 20. Proposed pediatric weight-based maraviroc dosing for subjects with a noninteracting background regimen.

Formulation	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
Tablet	(b) (4)		300 mg BID	300 mg BID
Solution			300 mg (15 mL) BID	300 mg (15 mL) BID

Source: Proposed maraviroc USPI.

Table 21. Final maraviroc doses for pediatric subjects in study 1031 on a noninteracting background regimen.

	10 kg - <20 kg	20 kg - <30 kg	30 kg - <40 kg	≥40 kg
N	2	2	5	1
Median	200 mg BID	375 mg BID	300 mg BID	600 mg BID
Min	200 mg BID	300 mg BID	300 mg BID	600 mg BID
Max	200 mg BID	450 mg BID	300 mg BID	600 mg BID

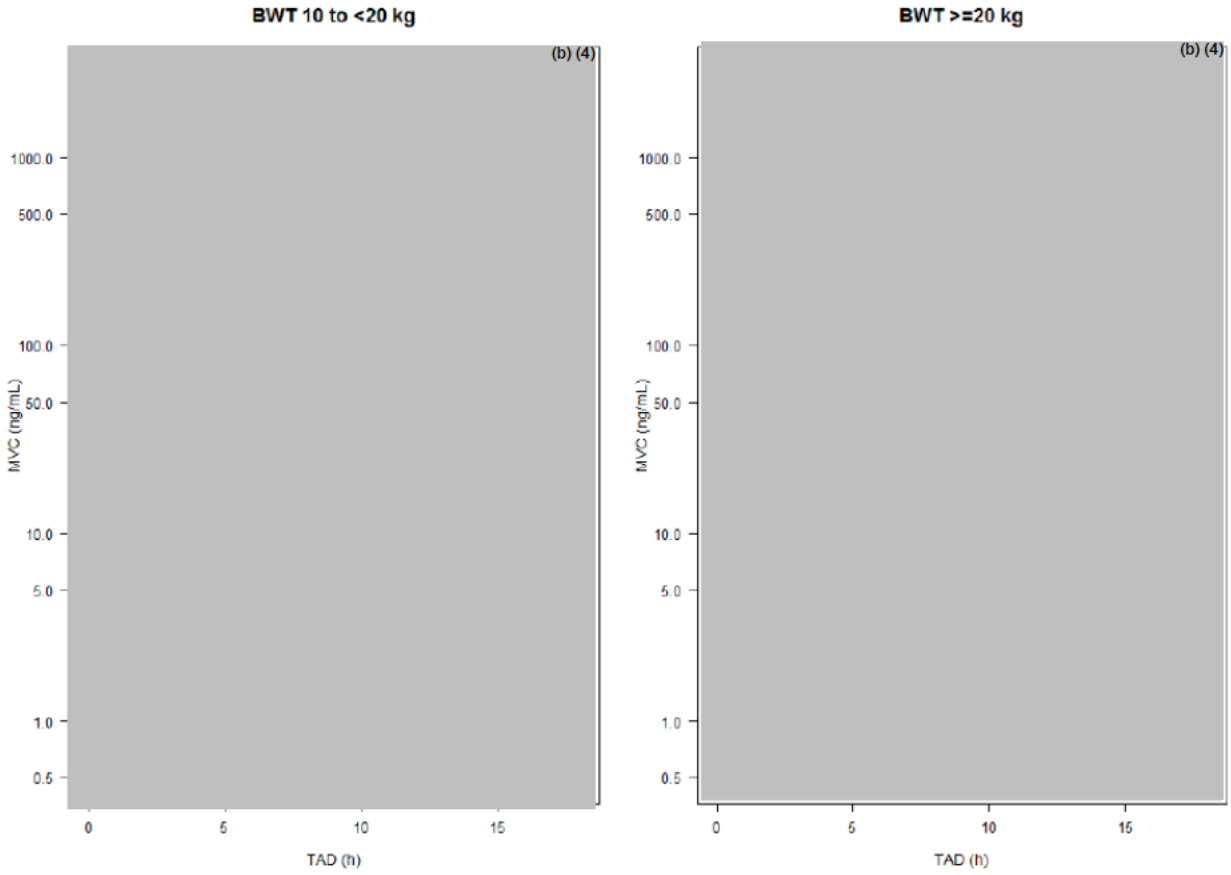
Source: Reviewer's analysis.

The sponsor developed a model of dose-normalized noncompartmental PK parameters (Cmax and AUC) as a function of dose using adult and pediatric intensive PK parameters. (b) (4)

Graphical comparison of observed pediatric and adult PK

Observed intensive and sparse pediatric concentration-time data was graphically compared to concentration-time data from HIV-infected adults on neutral regimens (Figure 16). The sponsor then developed a population PK model using the adult and pediatric PK data.

Figure 16. Maraviroc pediatric and adult concentration-time data for subjects on neutral regimens.



Source: NDA 208984 SDN 10. Weight bands refer to pediatric subjects only. The pediatric data includes subjects not on an optimized dose (6 of 10 had dose increases). Adults = blue; pediatric intensive PK = red; pediatric sparse PK = green. Blue line = adult lowess; orange line = pediatric lowess.

Studies included in model building

Intensive PK parameters from fourteen adult studies were included in the dataset; all but two of these adult studies were in healthy volunteers. The dataset contained 297 adults who contributed 416 PK parameters at maraviroc doses of 50-900 mg; 10 pediatric subjects contributed 26 intensive PK parameters at maraviroc doses of 150-450 mg.

Excluded data

The amount of excluded data from the adult studies was not reported. No pediatric data was excluded.

Model development and evaluation

Separate models were developed for dose-normalized AUC versus dose and for dose-normalized Cmax versus dose. An Emax model was used in both cases. Body weight was only included in

the AUC model. Body weight was significant as a binary covariate for weight <20 kg versus ≥20 kg as well as when weight was modeled as a continuous variable using a power function; the binary covariate was selected in the final model. Food effect was a significant covariate for both models. Goodness-of-fit plots and VPCs were provided but these were not stratified by pediatric versus adult population (popPK report 196, pg 95).

Simulations

Simulations were provided but are not discussed here because the model was not accepted (see Reviewer's assessment).

Reviewer's analysis

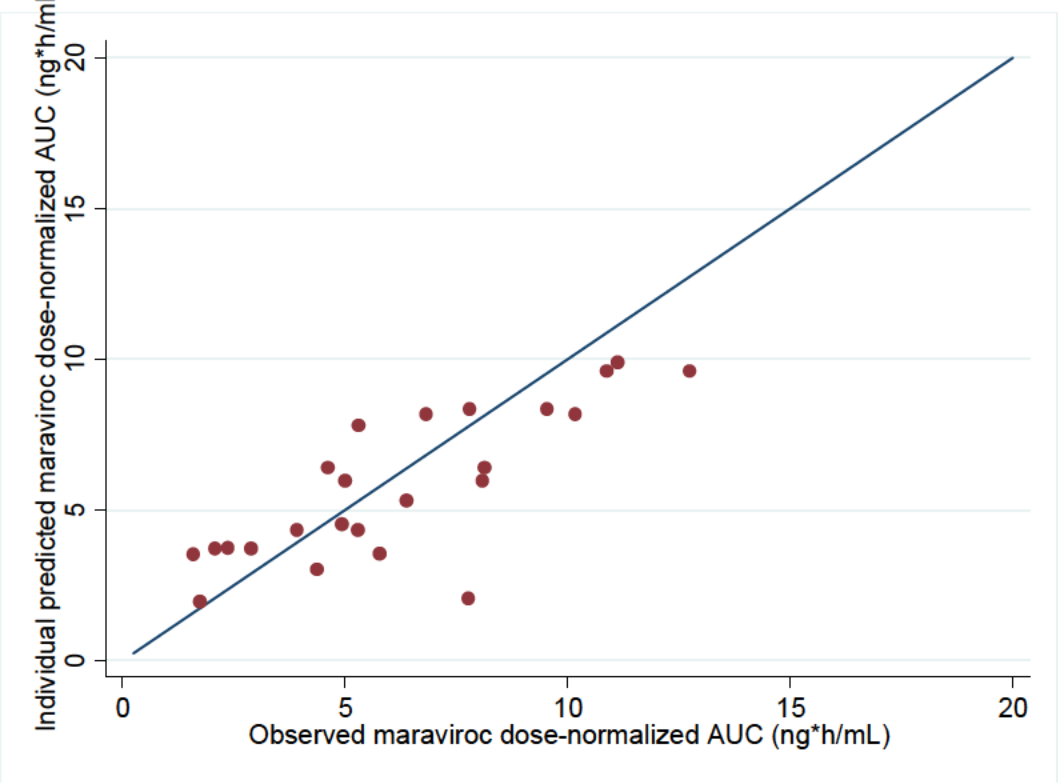
Graphical analysis

There was no apparent difference between pediatric and sparse sample concentrations despite different food recommendations between intensive (maraviroc recommended to be taken with food) and sparse PK (no food restrictions) visits (Figure 16). Of the neutral agents used in the study, didanosine (to be taken fasted) and tenofovir disoproxil fumarate (TDF) oral powder (to be taken with food) have food restrictions. Only one subject used didanosine. One subject was reported to have used TDF solution..

Population PK analysis

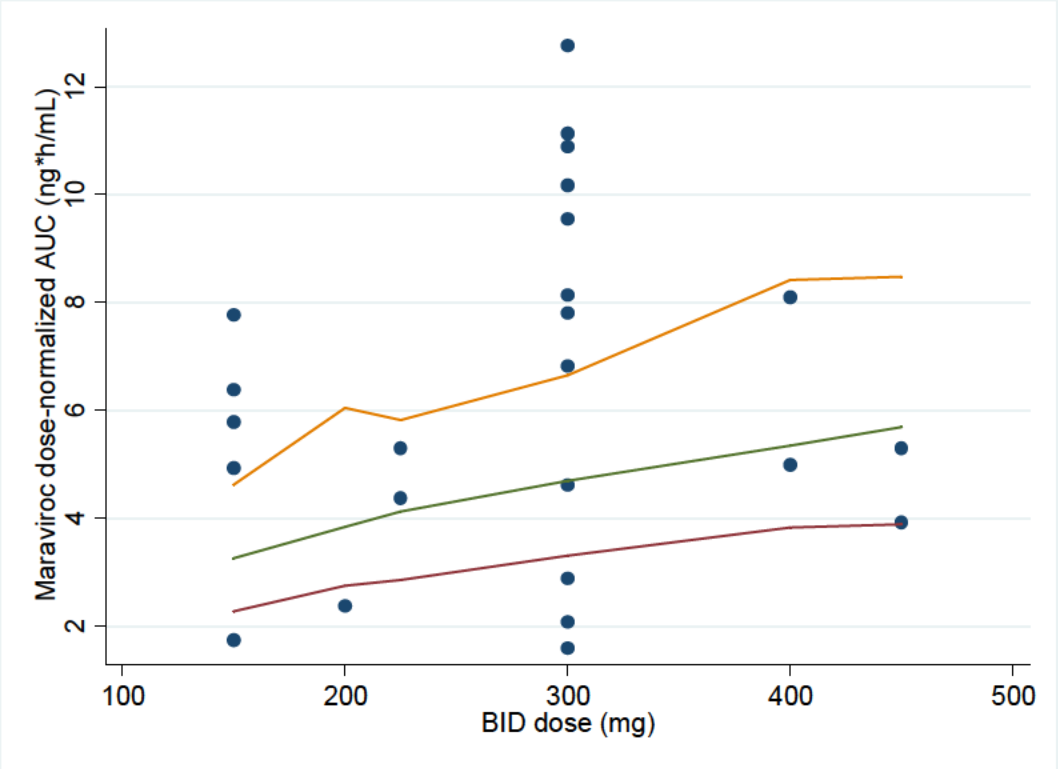
We ran the sponsor's model using NONMEM 7.3. The model converges, and we obtained an identical objective function value and identical parameter estimates. We generated goodness-of-fit plots and VPCs that were stratified by pediatric versus adult data. There was good agreement between observed and individual predicted values, however, variability was underpredicted in the pediatric and adult VPCs (Figure 17, Figure 18).

Figure 17. Observed versus individual predicted pediatric maraviroc dose-normalized AUC values.



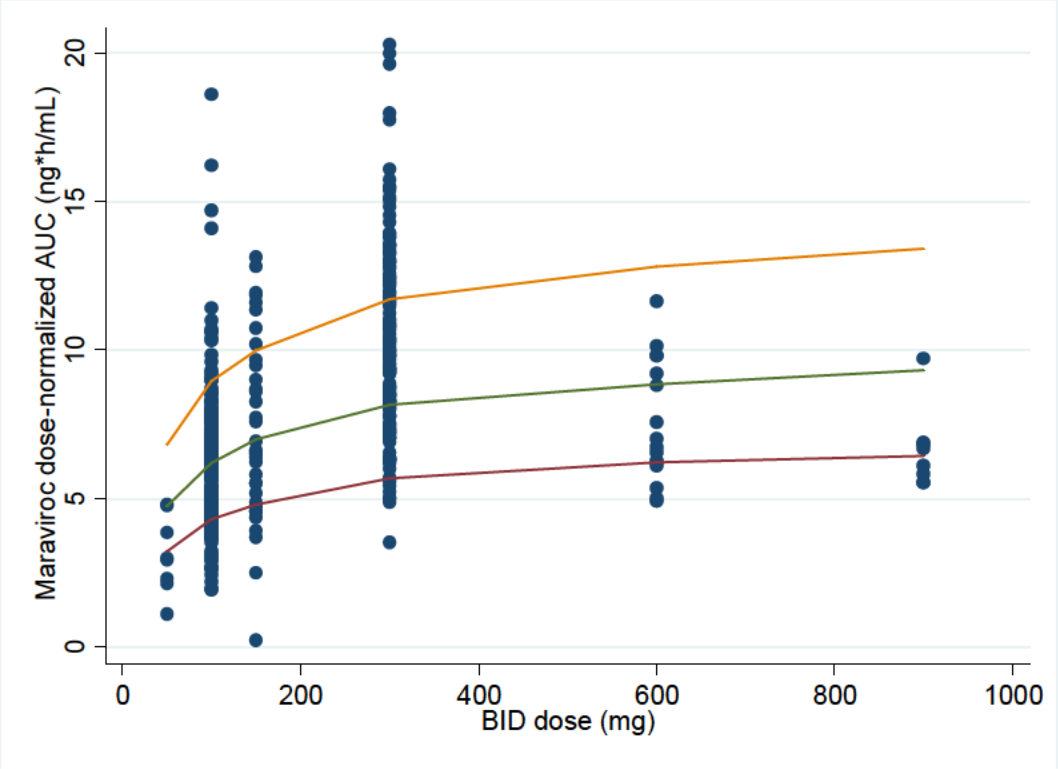
Source: Prepared by reviewer.

Figure 18. Visual predictive check for pediatric subjects.



Source: Prepared by reviewer. All data was obtained in the fed state. Circles = observed data; lines = 5th, 50th, and 95th percentiles of 1000 model simulations of the subjects contributing observed data.

Figure 19. Visual predictive check for adult subjects where maraviroc was administered in the fasted state.

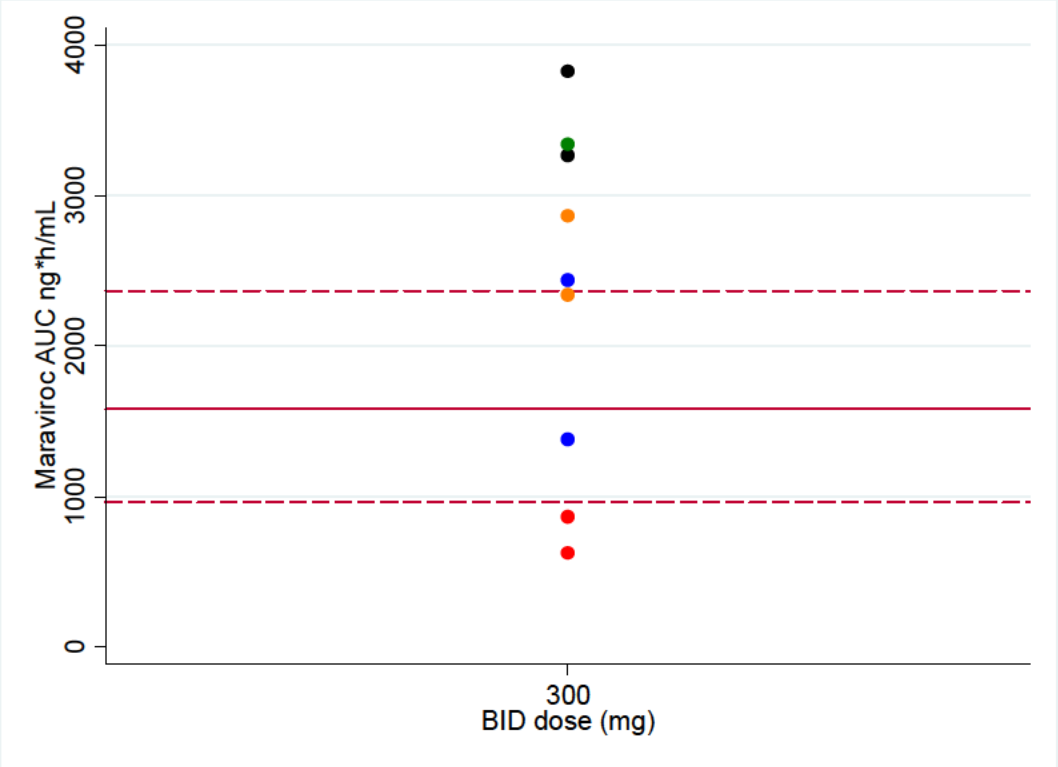


Source: Prepared by reviewer. Circles = observed data; lines = 5th, 50th, and 95th percentiles of 1000 model simulations of the subjects contributing observed data.

Comparison of observed intensive PK for pediatric subjects ≥30 kg versus adults

When the 30-40 kg and ≥40 kg weight groups are combined, there are five pediatric subjects ≥30 kg with a total of nine intensive PK assessments at a dose of 300 mg BID. Four of five subjects had maraviroc AUC values that were within or above the adult interquartile range (Figure 20). Pediatric Cmax and Cmin values are also within the adult distribution. Median (min, max) maraviroc Cmax values observed in pediatric subjects weighing ≥30 kg and administered a dose of 300 mg BID were 459 ng/mL (174, 721).

Figure 20. Maraviroc AUC in pediatric subjects ≥30 kg and adults with noninteracting background regimens.



Source: Plotted by reviewer. References lines are adult median (solid line), 25th, and 75th percentiles (dashed lines).

Reviewer's assessment

We agree with the proposed dosage regimen for pediatric subjects weighing ≥30 kg, (b) (4) .

There was no apparent difference between pediatric and sparse sample concentrations despite different food recommendations between intensive (maraviroc to be taken with food) and sparse PK (no food restrictions) visits. We investigated whether this was because the background agents required administration with food and no subjects were confirmed to have such a regimen. One subject was reported to have used TDF solution, which is not approved in the United States, and we do not know if this dosage form requires administration with food. Thus, the lack of difference between intensive and sparse concentrations is not likely due to the presence of neutral agents that require administration with food.

The sponsor submitted an unusual model to support pediatric maraviroc dosing with neutral regimens. Typically, drug concentrations are modeled as a function of time whereas in this case AUC and Cmax were modeled as a function of dose. One limitation to this approach is that hundreds of adult and pediatric sparse samples were not included in the analysis. Another limitation is that the adult dataset consisted mostly of HIV-uninfected subjects because most of the intensive PK profiles were obtained in phase 1 studies.

Body weight was modeled in a binary fashion as opposed to the typical continuous approach. [redacted] The inability to model the effect of weight may be due to the presence of only ten pediatric subjects versus 297 adults. In addition, the dose-dependent effect of food on absorption may mask the effect of body weight (NDA 208984 SDN 10). [redacted] the model was that it underpredicted variability in both adults and pediatric subjects.

[redacted] we sought to identify any weight bands where a sufficient number of pediatric subjects were administered the proposed dose. This was the case only when considering the subset of pediatric subjects weighing ≥30 kg. In these pediatric subjects, observed exposures at a dose of 300 mg BID were sufficiently similar to adults; no subjects had Cmax values that exceeded the value associated with postural hypotension. Due to only two subjects enrolled in the 10-20 kg and 20-30 kg groups, we do not recommend maraviroc for patients in these weight groups.

4.4 A4001034 – Relative bioavailability study of the tablet and solution formulations and food effect assessment for the solution formulation

A4001034: An Open, Randomized, 3-Way Crossover Study to Investigate the Relative Bioavailability and Effect of Food on the Pharmacokinetics of a Proposed Pediatric Solution Formulation of Maraviroc

Objectives:

- To investigate the relative oral bioavailability of the pediatric oral solution versus the research tablet (75 mg).
- To investigate the effect of food on the pharmacokinetics of maraviroc given as a pediatric oral solution (75 mg).

Study Design: This was an open, randomized, 3-way crossover study of maraviroc oral solution (20 mg/mL) 75 mg single dose fasted, maraviroc oral solution (20 mg/mL) 75 mg single dose fed and maraviroc tablet (75 mg) 75 mg single dose fasted, in 12 healthy subjects (21- 55 years of age). For fed period, subjects received a standard high fat meal.

Formulation: The following table shows the lot and formulation identification (FID) numbers.

	Potency	Formulation	Lot Number	FID Number
Maraviroc	75 mg	Research tablet	10082-125A	S10404AA
Maraviroc	20 mg/mL	Oral solution	11644-055	D0602438

PK Sampling: Intensive PK samples were collected on Day 1 predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose.

Analytical Methods: Maraviroc concentrations in plasma samples were determined using a validated liquid chromatography/mass spectroscopy/ mass spectroscopy (LC-MS/MS) bioanalytical method. All samples were analyzed in the timeframe supported by frozen stability storage data. The assay was performed and validated by (b) (4)

The standard curve and QC data indicated that the plasma assay method for maraviroc was precise and accurate.

Pharmacokinetic Results: Table 22 summarizes the maraviroc pharmacokinetic data.

Table 22. Maraviroc Pharmacokinetic Data.

	Maraviroc solution fasted (20 mg/mL)	Maraviroc solution fed (20 mg/mL)	Maraviroc tablet fasted (75 mg)
AUC_{24} (ng.h/mL)			
Unadjusted geometric mean	567.7	152.0	466.4
C_{max} (ng/mL)			
Unadjusted geometric mean	174.8	16.6	127.4
T_{max} (h)			
Arithmetic mean	2.21	2.33	3.00

Table 23 summarizes the analysis for maraviroc solution (fasted) versus maraviroc tablet (fasted) and the comparison of maraviroc oral solution (fed versus fasted). The geometric mean ratios for AUC24 and Cmax were 121.7% and 137.3% respectively for maraviroc solution versus maraviroc tablets in the fasted state. Food reduced the AUC24 and Cmax of the solution by 73.2% and 90.5% respectively following administration of 75 mg single dose.

Table 23. Statistical Analysis of Treatment Comparisons

	Maraviroc solution fasted (20 mg/mL) /tablet (75 mg) fasted	Maraviroc solution fed/solution fasted (20 mg/mL)
AUC_{24} (ng.h/mL)		
Ratio of means	121.7	26.8
90% confidence interval	99.2, 149.3	21.8, 32.8
C_{max} (ng/mL)		
Ratio of means	137.3	9.5
90% confidence interval	99.4, 189.6	6.9, 13.1
T_{max}		
Difference between means	-0.79	0.13
90% confidence interval	-1.62, 0.03	-0.70, 0.95

Reviewer's Comment: As indicated in the Clinical Pharmacology review for original NDA 22128, there is a dose dependent and time dependent effect of food when maraviroc is administered with a high fat meal, and the effect seems to be without regard to formulation (Table 24). The food effect observed in this study is as expected.

Table 24. Summary of food effect studies.

Study	Maraviroc Dose	Formulation	Timing of Food	Change of Cmax with food	Change of AUC_{inf} with food
1001	100 mg	Solution	With food	↓88%	↓63%
1004	100 mg	Research Tablet	1h before food	↑3%	↓20%
1004	100 mg	Research Tablet	With food	↓68%	↓52%
1004	100 mg	Research Tablet	1h after food	↓70%	↓49%
1004	100 mg	Research Tablet	2h after food	↓67%	↓42%
1004	100 mg	Research Tablet	4h after food	↓13%	↓21%
1043	300 mg	Commercial Tablet	With food	↓33%	↓33%
1003	600 mg	Research Tablet (4 x 150 tablets)	With food	↓36%	↓33%

Conclusion:

- The relative bioavailability (AUC_{24}) of the maraviroc pediatric oral solution (20 mg/mL) in the fasted state was 122% compared to the tablet (75 mg).
- Food reduced the AUC24 and Cmax of the solution by 73.2% and 90.5% respectively following administration of 75 mg single dose.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIO SAMPSON
10/07/2016

SHIRLEY K SEO on behalf of HUIMIN ZHENG
10/07/2016

JEFFRY FLORIAN
10/07/2016

SHIRLEY K SEO
10/07/2016