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Authors

Liyanage, Marlon
Nikanjam, Mina
McFadyen, Lynn
et al.

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# Maraviroc Population Pharmacokinetics Within the First Six Weeks of Life

**Marlon Liyanage, PharmD**[1], **Mina Nikanjam, MD, PhD**[1], **Lynn McFadyen**[2], **Manoli Vourvahis**[3], **Luise Rogg**[4], **John Moye**[5], **Ellen G. Chadwick**[6], **Patrick Jean-Philippe**[7], **Mark Mirochnick**[8], **Kyle Whitson**[9], **Sarah Bradford**[10], **Edmund V. Capparelli, PharmD**[1,11], **Brookie M. Best, PharmD, MAS**[1,11]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA

[2]Pharmacometrics, Pfizer Global Research and Development, Sandwich, UK.

[3]Clinical Pharmacology, Pfizer Global Research and Development, New York, New York, USA.

[4]ViiV Healthcare, Research Triangle, North Carolina, USA

[5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda.

[6]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois.

[7]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA.

[8]Boston University School of Medicine, Boston, Massachusetts, USA.

[9]Frontier Science Foundation, Amherst, New York, USA

[10]FHI 360, Durham, North Carolina, USA

[11]Pediatrics Department, School of Medicine, University of California San Diego-Rady Children's Hospital San Diego, San Diego, CA

## Abstract

**Background—**Treatment and prophylaxis options for neonatal HIV are limited. This study aimed to develop a population pharmacokinetic model to characterize the disposition of maraviroc in neonates to inform dosing regimens and expand available options.

**Methods—**Using maraviroc concentrations from neonates who received either a single dose or multiple doses of 8 mg/kg of maraviroc in the first 6 weeks of life, a population pharmacokinetic model was developed to determine the effects of age, sex, maternal efavirenz exposure, and concomitant ARV therapy on maraviroc disposition. The final model was used in Monte Carlo simulations to generate expected exposures with recommended dosing regimens.

**Results—**A total of 396 maraviroc concentrations, collected in the first 4 days of life, at 1 week, at 4 weeks, and at 6 weeks, from 44 neonates were included in the analysis. After allometrically scaling for weight, age less than 4 days was associated with a 44% decreased apparent clearance

**Corresponding Author**: Brookie M. Best, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, 9500 Gilman Drive, MC 0719, La Jolla, CA 92093-0719, USA, brookie@ucsd.edu, Phone: (858)822-5550.

compared to participants 7 days to 6 weeks of life. There were no differences identified in apparent clearance or volume of distribution from ages 7 days to 6 weeks, sex, maternal efavirenz exposure, or concomitant nevirapine therapy. Monte Carlo simulations with FDA-approved weight band dosing resulted in the majority of simulated patients (84.3%) achieving an average concentration of ≥ 75ng/mL.

**Conclusions—**While maraviroc apparent clearance is decreased in the first few days of life, the current FDA approved maraviroc weight band dosing provides maraviroc exposures for neonates in the first 6 weeks of life which were consistent with adult maraviroc exposure range. Maraviroc provides another antiretroviral treatment option for very young infants.

### Keywords

Maraviroc; Neonate; HIV; Pharmacokinetics

## Introduction

Perinatal transmission of HIV has significantly decreased in the last two decades with increased usage of antiretroviral therapy during pregnancy and usage in newborns[1,2]. However, neonates remain at risk of transmission across the placenta during pregnancy, during delivery, and after birth via breast milk, especially in resource limited settings.[3] Early antiretroviral therapy for neonates at high risk for or living with HIV is currently recommended and may limit viral seeding of reservoirs in critical areas such as the CNS[4]. Subsequent reservoir size has been correlated with time to first undetectable viral load[5] and early reduction has the potential to improve outcomes in this patient population. Due to lack of adequate neonatal pharmacokinetic and safety data as well as availability of appropriate neonatal formulations for newer antiretrovirals, recommended antiretrovirals for use in neonates are limited to zidovudine, lamivudine, nevirapine and raltegravir.[6] Effective therapies for young infants immediately after birth thus remains an unmet need[7].

Maraviroc is a CCR5 co-receptor antagonist that is currently approved for the treatment of HIV-1 in combination with other antiretrovirals.[8] It has been primarily used as second line therapy in adults and adolescents who have failed treatment with an initial regimen.[9] Maraviroc exhibits minimal toxicity in children and adults and is available as an oral solution, making it an attractive therapeutic option for young infants. As a substrate of CYP3A enzymes, maraviroc requires dosage modifications for concomitant administration with CYP3A inducers and inhibitors, thus developmental changes in CYP3A4 could contribute to changes in maraviroc disposition[8]. FDA approval for maraviroc was recently expanded to include all ages starting from birth with a minimum weight requirement of 2 kg. The approved dose was based on the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2007 study which evaluated participants taking maraviroc in the first six weeks of life and formed the basis for infant weight-based dosing.[10]

The current study aimed to develop a population pharmacokinetic model to describe maraviroc disposition in the first six weeks of life. The analysis assessed age and

maturational changes over the first six weeks of life. The final model was used to evaluate current maraviroc dosing recommendations for infants.

## Methods

### Population

IMPAACT 2007 was a Phase 1, multicenter, open-label study of maraviroc safety and pharmacokinetics in full-term, HIV-1-exposed neonates. Participants received maraviroc along with standard ARV prophylaxis against perinatal HIV transmission.[11] Participants were stratified based on potential exposure to maternal efavirenz, as efavirenz has been shown to decrease maraviroc exposure by 50%[12]. Cohort 1 was stratified by in-utero exposure to maternal efavirenz (Stratum 1A: infants without in-utero exposure to maternal efavirenz, Stratum 1B: infants with in-utero exposure to maternal efavirenz). Cohort 2 was stratified by exposure to efavirenz through breastfeeding (Stratum 2A: infants without exposure to maternal efavirenz either in utero or if breastfeeding, while breastfeeding, Stratum 2B: infants with exposure to maternal efavirenz both in utero and during breastfeeding). All required institutional review boards, ethics committees, and applicable regulatory entities at participating sites provided protocol approval. All participants had parental/legal guardian informed consent prior to enrolling in the study.

### Drug Administration and Pharmacokinetic Sampling

Cohort 1 participants received one dose of maraviroc 20 mg/mL oral solution (approximately 8 mg/kg) at study entry (days 0–3 of life, Week 0) and a second dose at Week 1 (days 7–14 of life). Pharmacokinetic samples were collected prior to the dose, and at 1–2, 4–8, 11–13, 20–24, and 48–72 h post dose for the Week 0 visit. Samples were subsequently collected prior to the dose and at 1–2 and 22–26 h post dose for the Week 1 visit. Cohort 2 participants received maraviroc 20 mg/mL oral solution at approximately 8 mg/kg twice daily starting at study entry (days 0–3 of life) until Week 6 (days 35–42 of life). Samples were collected prior to the dose and at 1–2, 3–5, 6–8, and 11–13 h post dose at Weeks 1 and 4, along with a single sample at Week 6 at 0–24 h post dose. Pharmacokinetic samples were analyzed for maraviroc concentrations by HPLC/MS/MS.

### Pharmacokinetic Analysis

Using the computer program NONMEM (version 7.3) with a GNU Fortran G77 compiler, concentration time data were fit using first-order conditional estimation methods (FOCE) with interaction. A one-compartment pharmacokinetic structural model (ADVAN2, TRANS2 subroutine) with first-order absorption was used to describe the data. An exponential-normal distribution error model was used for inter-subject variability.

Pharmacokinetic parameters were scaled by participant size prior to evaluation of other potential covariates using an allometric approach [$WT^{0.75}$ on apparent clearance (CL/F) and $WT^{1.0}$ on apparent volume of distribution (V/F)]. Post-natal age, post-menstrual age, gestational age, sex, cohort, maternal efavirenz exposure, and concomitant ARV therapy were explored as potential covariates for apparent volume of distribution and apparent clearance. Potential covariates were added to the model one at a time as a linear or

categorical function, with covariates that improved the model fitting (decrease in objective function of more than 3.84, $p < 0.05$) being retained in the initial covariate screen. A forward selection approach was utilized for multivariate assessment with a decrease in objective function of 8.0 (p~0.005) used for retaining covariates in the final model.

Empiric Bayesian estimates of the individual pharmacokinetic parameters were generated from the final model using the POSTHOC routine. A 1000 sample bootstrap assessment of the final model was performed using Wings for NONMEM (version 7.4.1).

### Monte Carlo Simulations

Monte Carlo simulations using the final population pharmacokinetic model were performed to assess the current FDA approved dosing for neonates in the first six weeks of life. Concentration profiles were generated for four age groups (0, 1, 4, 6 weeks) with 250 virtual neonates per group. Maraviroc dosing was assumed to start at birth and continue through six weeks of life. Uniform weight distributions for neonates in the simulations were derived from the weight distributions observed in the study. The FDA approved dosing used for the simulations was 30 mg twice daily for participants under 4 kg and 40 mg twice daily for participants 4–6 kg.[8] Simulated patients were evaluated for the proportion reaching a previously determined response target, an average concentration ($C_{avg}$) ≥ 75 ng/mL.[13,14]

## Results

### Participants

A total of 396 pharmacokinetic samples from 44 neonates were used in the population pharmacokinetic modeling. Of these, 15 were enrolled in Cohort 1 and 29 in Cohort 2. In Cohort 1, all 15 infants had pharmacokinetic samples collected following single doses at the Week 0 visit (8 in Stratum 1A, 7 in Stratum 1B), and 13 infants had samples collected following single doses at the Week 1 visit (6 in Stratum 1A, 7 in Stratum 1B). Cohort 2 had 29 participants who had samples collected during steady state while receiving twice daily dosing. All 29 had samples from the Week 1 visit (15 in Stratum 2A, 14 in Stratum 2B), 26 infants had samples from the Week 4 visit (13 in Stratum 2A, 13 in Stratum 2B), and 23 infants had samples from the Week 6 visit (13 in Stratum 2A, and 10 in Stratum 2B). Table 1 summarizes participant demographics and pertinent study design. Median concentration time profiles of maraviroc per visit are shown in Figure 1.

### Population Pharmacokinetic Analysis

A one-compartment structural model described the data well thus more complicated models were not explored. After the addition of allometric scaling for weight, age less than four days was noted to have lower apparent clearance than older ages (see figure, Supplemental Digital Content 1). Age less than four days was found to be a significant covariate on apparent clearance and was retained in the final model. Other continuous age functions (post-natal age, post-menstrual age, gestational age), sex, cohort, maternal efavirenz exposure, and concomitant nevirapine therapy were not found to be significant covariates of apparent volume of distribution and apparent clearance. Additional differences between visits were well accounted for with the addition of inter-occasion variability on

apparent clearance. The model predicted a median apparent clearance of 3.90 L/hr/kg$^{0.75}$ in the first three days of life and 6.96 L/hr/kg$^{0.75}$ from seven days to six weeks of life.

The final model described the data without significant bias for concentrations less than 600 ng/mL, however the model underestimated the peak concentrations in some subjects (see figures, Supplemental Digital Content 2 and 3). Shrinkage estimates for inter-subject variability were low for apparent clearance (9.6%) and apparent volume of distribution (8.1%). Final model parameters and variance estimates are shown in Table 2 along with bootstrap estimation results. Bootstrap evaluation of the final model results in minimization success in 87.1% of runs. Final model estimates were all well within the 95% confidence interval provided by bootstrap analysis, suggesting the final model well represents the population.

### Monte Carlo Simulations

Maraviroc concentration-time profiles for each age group (0, 1, 4, and 6 weeks) from the Monte Carlo simulations are presented in Figure 2a. The majority of simulated patients achieved the $C_{avg}$ goal of ≥ 75 ng/mL (99.2% in Week 0, 81.6% in Week 1, 78.8% in Week 4, and 77.6% in Week 6; Figure 2b and Table 3).

## Discussion

Only six antiretrovirals, zidovudine, lamivudine, nevirapine, raltegravir, lopinavir/ritonavir, and emtricitabine, are commercially available in a formulation suitable for use in neonates and have sufficient neonatal pharmacokinetic and safety data to allow their use in neonates.[6] While the landscape for preventing perinatal HIV transmission has expanded, most currently available therapies have limitations. Zidovudine, the mainstay of perinatal transmission prophylaxis, has a high incidence of anemia in neonates and children.[15–17] Though anemia is reversible post-treatment, it can be severe enough to require transfusion, holding of therapy, or drug discontinuation. Resistance to nevirapine can develop through single point mutations, thereby limiting the usage of this drug. Neonatal drug resistance can result from either maternal exposure to nevirapine[18] or after neonatal administration[18,19]. Preparation of the infant raltegravir formulation is difficult and raltegravir has a complex dosing regimen with multiple changes in dose and frequency within the first two months of life to avoid high exposures and potential toxicity.[6] Lopinavir/ritonavir and dolutegravir have been shown to be safe and efficacious when used in combination regimens in older infants, but reports of neonatal toxicity and/or lack of formulations with adequate neonatal pharmacokinetic and safety data[20] restrict their use to infants over two weeks[21] and four weeks[22] of post-natal age, respectively. There is a crucial gap in prophylaxis and antiretroviral treatment options during the first weeks of life and maraviroc has the potential to improve upon these therapeutic options to provide safe and effective therapy starting at birth.

The current study aimed to develop a population pharmacokinetic model to better characterize maraviroc disposition in the first six weeks of life. The current model was developed from the IMPAACT 2007 study data set and includes exclusively neonatal participants. Age less than four days showed a significantly decreased apparent clearance compared to older neonates from seven days to six weeks of life. We did not find a

significant effect of sex, concomitant nevirapine therapy, or maternal efavirenz exposure on maraviroc apparent clearance or volume of distribution. Simulations with the FDA approved maraviroc weight band doses (2–4 kg: 30 mg, 4–6 kg: 40 mg twice daily) using the final model resulted in the majority of simulated patients (84.3%) maintaining a maraviroc $C_{avg}$ above 75 ng/mL. Neonates reached this target after both the first dose (0–3 days of life) and at steady state, ensuring appropriate coverage is achieved immediately and throughout therapy.

A previous population pharmacokinetic model was developed using maraviroc concentrations in adults and was then updated with data from pediatric and neonatal studies. That final model combined data from 530 adult, 10 pediatric, and 44 neonatal participants.[10] This model relied heavily on adult and older pediatric data which may have limited the ability to accurately describe maraviroc disposition in the first few weeks of life. We have developed a model from data obtained exclusively during the first six weeks of life that can be used in simulations to evaluate alternative dosing strategies in this age group. The typical neonatal maraviroc apparent clearance of 6.96 L/h/kg appears higher than that previously reported for adults (2.3 and 3.3 L/h/kg for fasted and fed maraviroc 300 mg doses, respectively).[23] This increased apparent clearance is consistent with higher doses (on a mg/kg basis) being required in pediatric subjects in order to match adult concentrations.

The recommended maraviroc $C_{avg}$ of ≥ 75 ng/mL target in adults was based on a multivariate analysis of predictors of response from a study of HIV-1 positive treatment-naïve adults receiving maraviroc 300 mg twice daily.[13,14] There is no clear prophylactic target for maraviroc in adults or children. In terms of other antiretrovirals, effective nevirapine prophylaxis against HIV transmission in neonates and breast feeding infants has been demonstrated using doses designed to achieve a target nevirapine $C_{min}$ greater than 0.1 mg/L, which is 30-fold lower than the treatment target of greater than 3.0 mg/L.[24] Thus, with maraviroc, the approximately 15% of simulated patients who did not meet the target treatment goal may still have sufficient maraviroc exposure for prophylaxis of HIV infection.

Maraviroc is a substrate of CYP3A enzymes and has dose modifying recommendations to accommodate inducers and inhibitors.[25,26] In neonates, CYP3A enzymes are expressed differentially with age and consequentially result in altered metabolism during infancy and throughout childhood.[27] Neonatal clearance of midazolam, a commonly used CYP3A4 probe, has been shown to be significantly decreased under three months of age.[28] CYP3A4 expression has been shown to increase dramatically in the first weeks of life and then plateau, which is consistent with our finding that maraviroc has a lower apparent clearance in the first few days of life than at Weeks 1 through 6.[29]

The current study has several limitations. Only a single concentration was collected at the week 6 time point which may have limited the ability to fully characterize maturational changes at this age given the high variability in the data set. While the model overall represented the data well, the peak concentrations may have been underestimated in some subjects. Limited early time point data was available from the study design, thus we had difficulty developing more complicated models to better estimate the peak. While we

had a large data set of 44 neonates with rich data at one and four weeks of age, the considerable variability in the plasma drug concentrations may require a larger sample size to reveal additional covariate effects. Maraviroc plasma concentrations show high intersubject variability in healthy volunteers and HIV-1 infected adults that is attributed to dose dependent absorption and dose dependent (greater at lower doses) food effects.[23,30] Bioavailability when given with a high fat meal is reduced by 24–43% depending on the dose (greater reduction at lower doses) and formulation. It was not possible to standardize feeding in relation to dosing in this infant population which may have contributed to high interindividual and inter-occasion variability in this study.

The current study developed a population pharmacokinetic model for maraviroc therapy in neonates over the first six weeks of life. Although a lower apparent clearance was observed in the first week of life leading to higher drug levels, increased toxicity was not seen early on and no dose adjustments were warranted. The model supports the approved weight band dosing for this age group and provides a straightforward description of maraviroc disposition in this population which can be used to assess alternate dosing strategies. This study helps support further development of maraviroc to improve therapeutic options for young infants.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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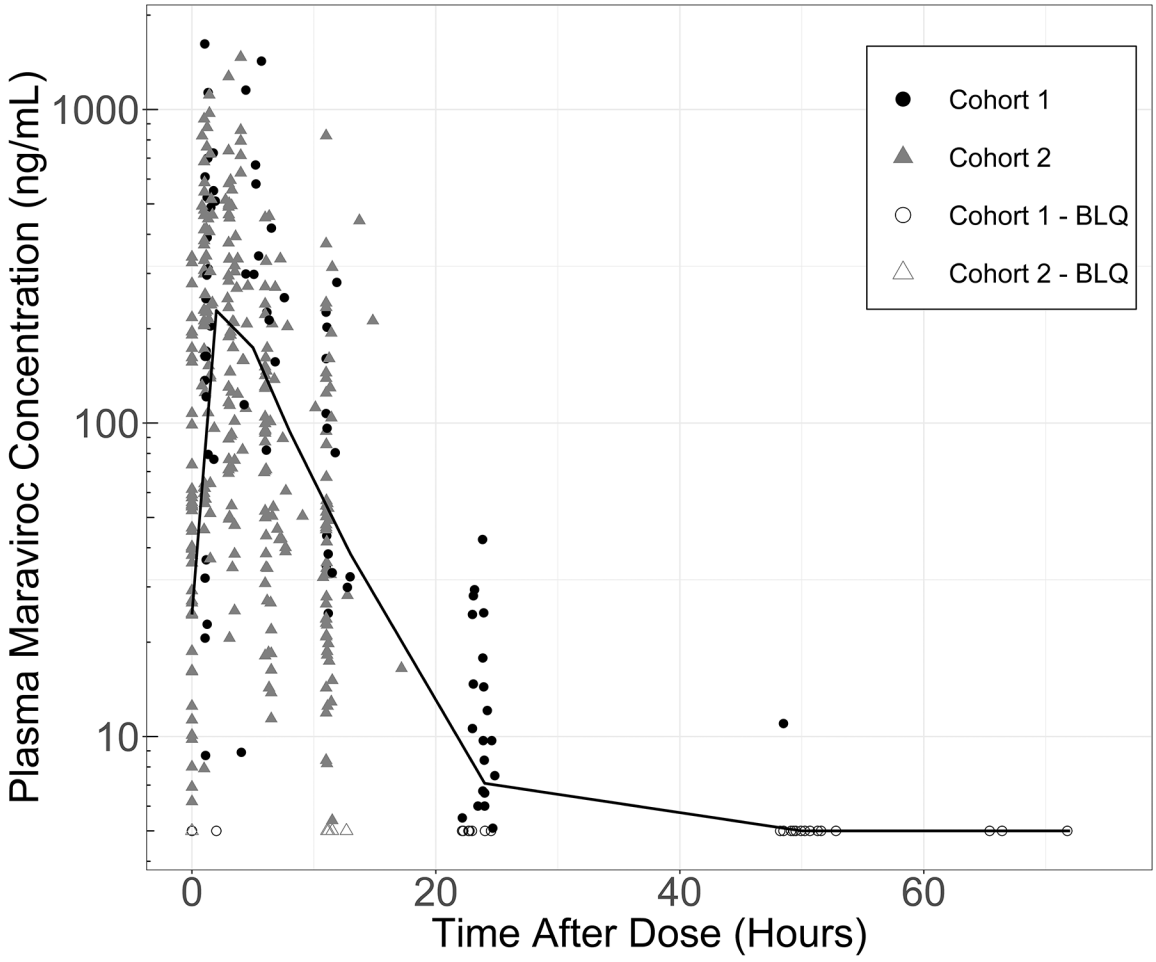
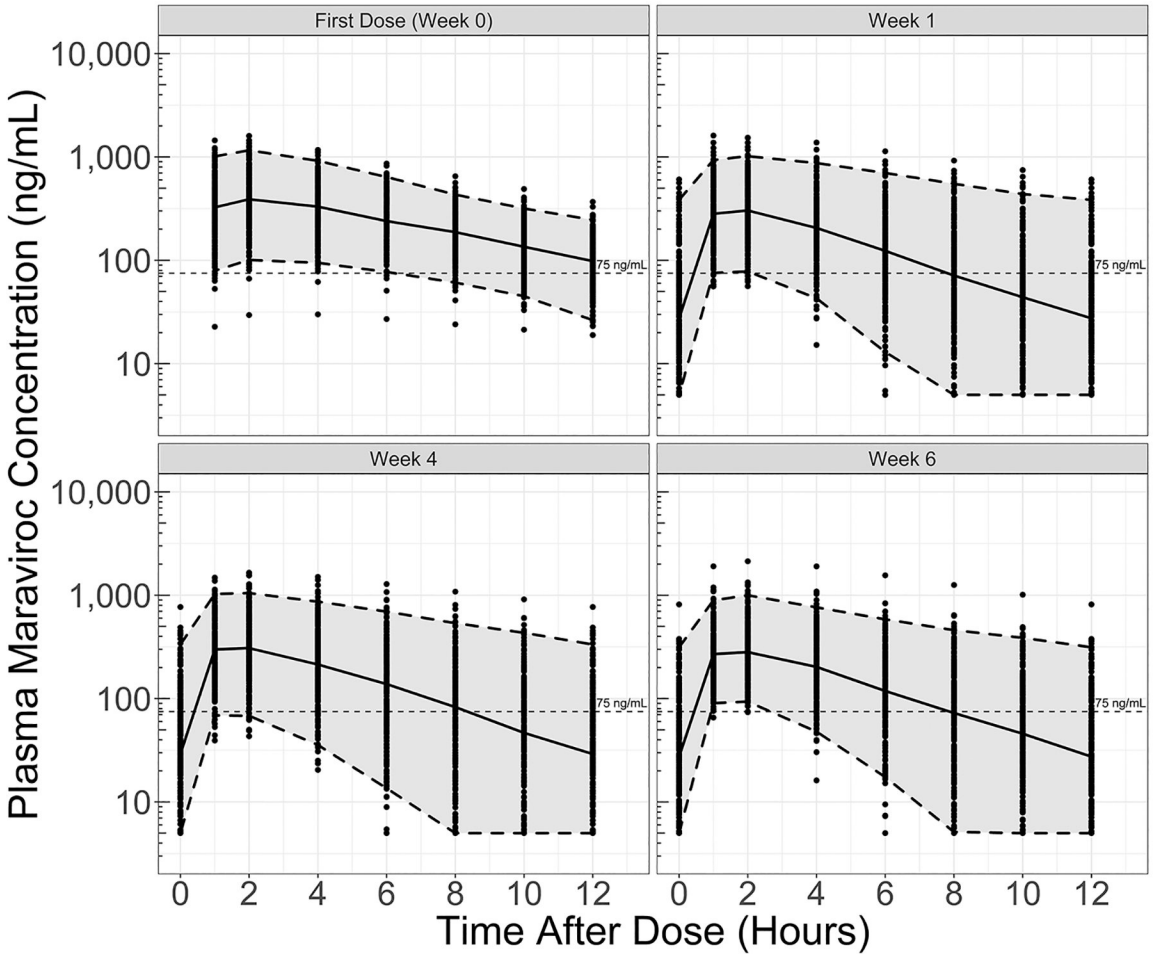



**Figure 1. Maraviroc Concentration Versus Time**

Maraviroc concentrations in neonates following an 8 mg/kg dose. The solid line represents median concentrations for neonates in the study. Open shapes represent concentrations below the limit of quantification (BLQ) of 5 ng/mL and were thus set to 5 ng/mL for this figure. There were no significant differences in concentrations over time between Cohorts 1 and 2.



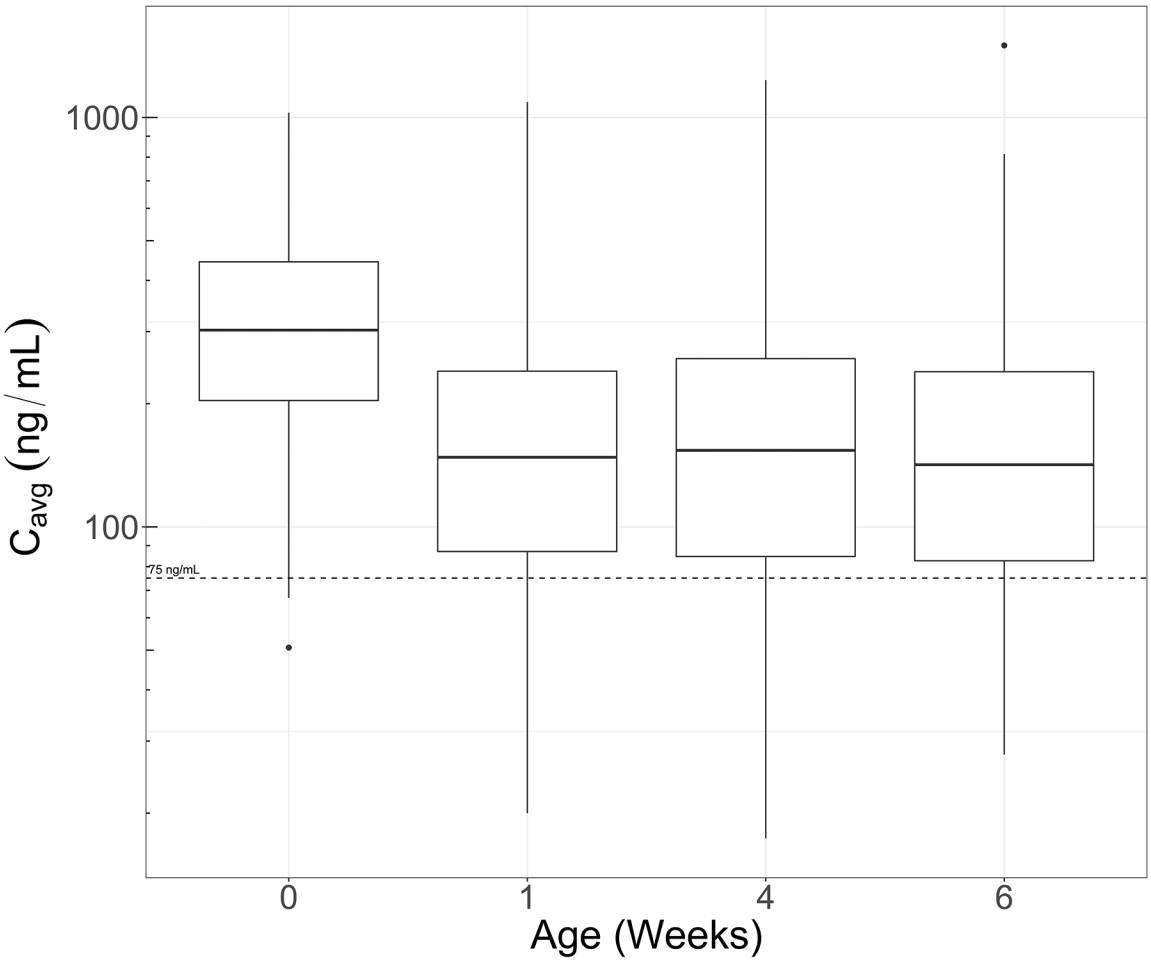



**Figure 2. Monte Carlo Simulations of Maraviroc in Neonates**

Monte Carlo simulations of maraviroc in neonates at 0 and 6 weeks of life using FDA approved dosing. Week 0 represents concentrations following first dose. Week 6 represents concentrations at steady state after 6 weeks of twice daily dosing. (**a)** Concentration vs. time profile for each age group. Solid represents median and dashed lines represent the 2.5 to 97.5 percentile. **(b)** $C_{avg}$ for simulated patients by age group. The horizontal dashed line represents the $C_{avg}$ goal of ≥ 75 ng/mL.

**Table 1.**

Demographics and Study Design

| | Cohort 1 Week 0 | Cohort 1 Week 1 | Cohort 2 Week 1 | Cohort 2 Week 4 | Cohort 2 Week 6 |
|---|---|---|---|---|---|
| Sex (N = F\|M) | 9\|6 | 8\|5 | 12\|17 | 11\|15 | 9\|13 |
| PK Sampling (Hours after dose) | 1–2, 4–8, 11–13, 20–24, 48–72 | 1–2, 22–26 | 1–2, 3–5, 6–8, 11–13 | 1–2, 3–5, 6–8, 11–13 | 0–24 |
| Length (cm) * | 50 (35,53) | 50.5 (48,52.5) | 49.2 (45,54.9) | 52 (46.8,55.5) | 53.75 (46.8,56.6) |
| Weight (kg) * | 3.3 (2.04,3.97) | 3.54 (2.72,4) | 3.08 (2.44,3.94) | 3.72 (2.37,4.54) | 4.23 (2.76,5.24) |
| PNA (days) * | 1 (0,3) | 9 (7,14) | 8 (5,12) | 24.5 (19,32) | 38.5 (34,42) |
| PMA (weeks) * | 39.1 (37.1,40.4) | 40 (38,41.4) | 40.4 (37.7,43.7) | 43 (39.7,45.7) | 44.9 (41.9,47.9) |
| Twice Daily Dose (mg/kg) | 8.72 (7.81,10.08) | 8.62 (7.89,10.13) | 8.06 (6.76,9.26) | 7.40 (6.13,8.89) | 7.70 (5.90,9.76) |

* Median (min,max)

PK, pharmacokinetic; PNA, post-natal age; PMA, post-menstrual age

**Table 2.**

Final Population Pharmacokinetic Model Parameters and Bootstrap Estimates

| | Final parameter estimates | Standard error of estimates | Bootstrap estimates[a] Median (95% CI) |
|---|---|---|---|
| $\Theta_1$ (V/F; L/kg)[b] | 20.0 | 2.80 | 19.9 (15.0–26.1) |
| $\Theta_2$ (CL/F; L/h/kg$^{0.75}$)[c] | 6.96 | 0.918 | 6.90 (5.39–8.99) |
| $\Theta_3$ (KA; h$^{-1}$) | 1.03 | 0.253 | 1.02 (0.782–2.42) |
| $\Theta_4$ (Age less than 4 days on CL) | 0.56 | 0.0761 | 0.56 (0.409–0.710) |
| **Variability (η)** | | | |
| Between-subject (V) | 67.8% | 0.0861 | 66.6% (50.4%–85.3%) |
| Between-subject (CL) | 57.4% | 0.0655 | 56.9% (40.9%–71.0%) |
| Inter-occasion variability on CL between visits | 54.2% | 0.0646 | 54.8% (41.5%–69.6%) |
| **Correlation** | | | |
| Interaction Between CL and V | 0.866 | 0.0684 | 0.876 (0.686%–0.994%) |
| **Error (ε)** | | | |
| Proportional | 56.9% | 0.0410 | 56.1% (48.7%–65.1%) |
| Additive (μg/mL) | 0.1 FIXED | - | - |

CI, confidence interval; CL/F, apparent clearance; KA, first-order absorption rate constant; V/F, apparent volume of distribution.

[a] Bootstrap successfully converged 87.1% of the time.

[b] $V/F = 20.0 \times WT^{1.0}$

[c] $CL/F = 6.96 \times WT^{0.75} \times$ (0.56 if age less than 4 days)

**Table 3.**

Simulated Patients Meeting Goal $C_{avg}$ of ≥ 75 ng/mL

| Age (Weeks) | $C_{avg}$ ≥ 75ng/mL [n (%)] | |
|---|---|---|
| | 30 mg Twice Daily (2 kg to 4 kg)[a] | 40 mg Twice Daily (4 kg to 6 kg)[a] |
| 0 | 248/250 (99.2%) | - |
| 1 | 204/250 (81.6%) | - |
| 4 | 142/172 (82.6%) | 55/78 (70.5%) |
| 6 | 81/112 (72.3%) | 113/138 (81.9%) |

[a]FDA approved dosing by recommended weight band