NDA 208984
sNDA 22128 / SN 017
Clinical Review
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Clinical Review

Date	September 23, 2016
From	Melisse Baylor, M.D.
Subject	Clinical Review
NDA # (oral solution)	208984 (for oral solution)
Supplemental NDA #	22128 / Submission Number 017 (expand indication to pediatrics and new tablet strengths)
Applicant	ViiV Healthcare
Date of Submission	May 6, 2016
PDUFA Goal Date	November 4, 2016
Proprietary Name/ Established (USAN) names	Selzentry / maraviroc (MVC)
Dosage forms / Strength	Oral solution (20 mg/mL) Oral tablets: 25 mg and 75 mg
Proposed indication(s)	Indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic human immunodeficiency virus type 1 (HIV-1) infection in patients 2 years of age and older weighing at least 10 kg
Recommendation	Approval

1. Introduction

This review summarizes the findings from ViiV Heatlhcare's New Drug Application (NDA) and supplemental NDA seeking approval of Selzentry® (maraviroc, MVC) for treatment of only CCR5-tropic HIV-1 infection in patients 2 years of age and older weighing at least 10 kg. Information in the NDA supports use of a new oral solution (20 mg/mL), while the use of two new tablet strengths (25 mg and 75 mg) is supported by information in the sNDA. This review highlights the supporting pharmacokinetic, safety, and efficacy (antiviral activity data). The data support extension of the indication to include the pediatric population of two years of age and older and weighing at least 10 kg. The recommended dose is based on patient weight and on concomitant medications because of maraviroc drug interactions.

The application was granted a priority review for several reasons. The data in the application fulfills a PREA PMR. In addition, the application allows for use of a new class of antiretroviral drugs (CCR5 receptor antagonists) in pediatric patients 2 to <18 years of age who may need additional treatment options. Furthermore, this application provides two pediatric age-appropriate formulations: an oral solution for HIV-infected patients who have difficulty with or are unable to swallow a tablet and two smaller strength tablets (50 and 75 mg).

2. Background

Selzentry (maraviroc), the first CCR5 co-receptor antagonist approved by the Agency, was granted Traditional Approval on November 25, 2008. The approval was based on 48-week data from 2 double-blind, randomized, placebo-controlled studies (Trials A4001027 and A4001028)

in ART treatment-experienced subjects infected with CCR5-tropic HIV-1 and on 96-week data from a double-blind, randomized, placebo controlled study (Trial A4001026) in ART treatment-naïve subjects infected with CCR5-tropic HIV-1. In the 2 trials of treatment-experienced subjects, the percentage of subjects with HIV-1 RNA levels <50 copies/mL at 48 weeks was 46% in subjects who received MVC with an optimized background regimen compared to 17% in subjects who received placebo plus an optimized background regimen. The mean increase in CD4+ lymphocyte cells was 124 cells/mm^3 in the MVC arm and 60 cells/mm^3 in the placebo arm. In Trial A4001026, treatment-naïve subjects were randomized to begin either maraviroc or efavirenz and also started on a background regimen of lamivudine and zidovudine. The percentage of subjects with HIV-1 RNA levels <50 copies/mL at Week 96 was 59% in the MVC arm and 63% in the efavirenz arm. The mean increase in CD4+ lymphocyte cells was 184 cells/mm^3 in the MVC arm and 155 cells/mm^3 in the efavirenz arm. These efficacy data supported an indication for treatment of (b) (4) treatment-experienced (b) (4) patients infected with CCR5-tropic HIV-1. Please refer to the reviews for the original NDA and the supplemental NDA for traditional approval for full details.

According to UNAIDS (2016), the estimated number of people infected with HIV or AIDS worldwide is approximately 36.7 million; 1.8 million of whom are children younger than 15 years of age. Per the Center for Disease Control, transmission of HIV-1 among U.S. adolescents is attributable primarily to sexual exposure and relatively few cases are due to illicit intravenous drug use. In 2014, persons 13 to 24 years of age accounted for an estimated 22% of all new HIV diagnoses in the United States. Therefore, it is important to have effective antiretroviral therapies (ART) for treatment of HIV infection in children and adolescents.

Currently available HIV treatment includes six different antiretroviral drug classes and at least 25 individual antiretroviral drugs, not including fixed drug combinations. The drug classes include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors (INSTI). Most approved ARVs have dosing recommendations in at least one subset of the pediatric age range.

While there are approved ARTs in multiple classes available for the treatment of HIV infection in children, there continues to be challenges. For example, poor adherence, and short and long term toxicities may contribute to the development of drug resistance and failed therapy. As a result, there is a need for continuous development of new ARTs for treatment of HIV infection. In addition, not all ARTs are available as a liquid formulation for children, adolescents, and adults who have difficulty with or who are unable to swallow tablets. Therefore, there is a need for additional liquid formulations for use in the pediatric and adult populations.

Maraviroc was evaluated in a single open-label, uncontrolled, pharmacokinetic (PK), safety, and efficacy trial in 103 pediatric subjects in 24 centers in eight countries. The applicant also conducted a bioavailability trial comparing the maraviroc oral solution to the tablet in adults. Electronic materials submitted included, (1) Clinical Study Report (CSR) for Week 48 data of the pediatric trial, (2) tabular data and safety datasets as SAS transport files for the safety data from 48 to 96 weeks and up to 5 years, (3) the CSR for the bioavailability study, (4) datasets as SAS transport files, and (5) case narratives for all subjects who experienced deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs).

This pediatric supplement fulfills the single outstanding post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA):

PMR #1357-2: Deferred pediatric study under PREA for the treatment of HIV in pediatric subjects from 2 to 18 years of age. This study will determine the maraviroc exposure (pharmacokinetic profile) followed by 48 weeks of dosing, with efficacy based on viral load reduction through 48 weeks of dosing, and safety monitored over 96 weeks for pediatric subjects from 2 to 18 years of age to support maraviroc dose selection, safety, and efficacy.

The applicant submitted the NDA and sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The Division did not consult the Office of Scientific Investigations for inspection of the trial sites.

The applicant also submitted financial information pertinent to the application. The statement specified that the applicant (neither ViiV Healthcare nor the previous company developing maraviroc, Pfizer, Incorporated) had not entered into any financial arrangement with particular clinical investigators whereby the value of compensation to the investigators could be affected by the outcome of the study [as defined in 21 CFR 54.4(a)(3)(i), 54.2(a)].

3. CMC

Data were submitted to NDA 208984 to support the use of a liquid formulation (oral solution) of maraviroc, which will be supplied in a bottle with an adapter and a dosing syringe. Data were submitted to sNDA 22128 to support the use of two new tablet strengths: 25 and 75 mg.

The oral solution is clear, colorless, and strawberry-flavored and contains 20 mg of maraviroc per mL. The oral solution comes pre-mixed and does not require reconstitution. Excipients include (b) (4) citric acid and citrate dehydrate; (b) (4) sodium benzoate; (b) (4) sucralose; and strawberry flavoring. The flavoring contains (b) (4) The excipients, with the exception of the flavoring, are provided in amounts that are consistent with recommendations in the United States Pharmacopeia or the National Formulary.

The bottle is made of high density polyethylene; it is supplied with a press-in bottle adapter and a dosing syringe for ease of use. The dosing syringe holds up to 10 mL and is marked with 0.5 mL gradations. Recommended doses will result in volumes ranging from 2.5 mL to 30 mL administered twice daily. The bottle contains (b) (4) mL; therefore, the fill volume is sufficient from 3.5 to 47 days of dosing. The applicant provided data to demonstrate biocompatibility between the formulation and the bottle, no issues with leachable or extractables, and antimicrobial effectiveness of preservative during storage. These data and other information on the proposed bottle, adapter, and dosing syringe were reviewed by CMC reviewers and by a CDRH consultant and were deemed acceptable. Instructions for use of the bottle, adaptor, and dosing syringe, including drawings, were added to the Patient Package Insert.

The tablet strengths of 25 mg and 75 mg will enable appropriate dosing of the youngest children who are able to swallow a tablet. Children as young as 6 years of age were able to swallow maraviroc tablet formulation in Trial A4001031. No significant changes were made to the maraviroc drug substance.

4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original review of NDA 22128 for details.

5. Clinical Microbiology

Maraviroc inhibits HIV-1 in patients with HIV-1 CCR5-tropic HIV-1 infection by binding to the human chemokine receptor CCR5 on the cell membrane and preventing interaction of HIV-1 gp120 and CCR5 necessary for CCCR5-tropic HIV-1 to enter cells. Maraviroc has no effect on HIV-1 that is CXCR4-tropic or dual tropic.

As part of the trial protocols, viral isolates from adult subjects who participated in Trials A4001026, A4001027, and A4001028 and who experienced virologic failure were examined for ARV resistance and for CCR5 receptor changes from baseline. In the 2 trials of treatment experienced subjects, maraviroc resistance was demonstrated in phenotypic assays in 22 of the 58 isolates (38%) from subjects with virologic failure; in treatment-naïve subjects, maraviroc resistance was detected in 19 of 85 isolates (26%) from subjects with virologic failure. Tropism assays were performed at baseline and at the time of virologic failure in all three studies. A shift from CCR5-tropism to CXCR4- or dual/mixed tropic virus was detected in 55% of isolates from treatment-experienced subjects and in 14% of isolates from treatment-naïve subjects. On re-examination of baseline HIV-1 isolates using clonal analysis, it was determined that the CXCR4-tropic virus was in fact present in low levels at baseline and emerged during treatment with maraviroc.

The reasons for virologic failure were also investigated in the pediatric trial of maraviroc (Trial A4001031). Virologic failure was defined as a HIV-1 RNA viral load of 400 copies/mL or greater at Week 48. There were 29 subjects with virologic failure at Week 48. The reasons for virologic failure were defined in 11 subjects. Decreased maraviroc susceptibility was observed in 2 subjects. Tropism change to CXCR-4 or dual/mixed tropic virus was observed in 5 subjects; two of these subjects had evidence of CXCR4- or dual-mixed-tropic virus at baseline. Resistance to other ARVs in the optimized background regimen was reported in 4 subjects. Although the number of isolates available for analysis was small, the virologic mechanisms responsible for failure in subjects receiving maraviroc in this study were similar to the mechanisms of resistance reported in the trials in the adult population.

Please see the original NDA for maraviroc and Dr. Naeger's review of this submission for additional information.

6. Clinical Pharmacology / Biopharmaceutics

Overview

Refer to the USPI and reviews from the original NDA for details of adult pharmacokinetics. Please see Dr. Zheng's and Dr. Sampson's Biopharmaceutics review of this application for additional information.

As stated previously, maraviroc, in combination with other antiretrovirals, is indicated for the treatment of adults infected with only CCR5-tropic HIV-1. Due to drug interactions, the recommended dose of maraviroc is based on what concomitant medications the patient is taking; specifically the maraviroc dose is dependent on whether the patient is also receiving a CYP3A inhibitor, a CYP3A inducer, or drug(s) not affecting CYP3A substrates. Although the administration of maraviroc tablets to adults after a high fat meal resulted in a decrease in C_{max}

and AUC of approximately 33%, the recommended dose does not vary whether taken with or without food.

In *In vitro* and human trials, it has been demonstrated that maraviroc is principally metabolized by the cytochrome P450 (CYP) system. In *in vitro* studies, it was demonstrated that CYP3A4 is the major enzyme responsible for maraviroc metabolism with CYP3A5 having a minor role. Co-administration of maraviroc with medications that inhibit CYP3A may increase maraviroc plasma concentrations, while co-administration with a potent CYP3A inducer may decrease maraviroc serum concentrations and result in decreased efficacy. Therefore, the recommended dose of maraviroc in adults is 150 mg, 300 mg, or 600 mg twice daily, depending on whether subjects are receiving concomitant medications that are CYP3A inhibitors, CYP3A neutral, or CYP3A inducers, respectively.

The initial pediatric doses of maraviroc in Study A4001031 were based on whether or not maraviroc was co-administered with CYP3A inhibitors, inducers, or CYP3A neutral medications and used adult doses scaled to body surface area (BSA) bands. The initial doses were evaluated in Stage 1, the intensive PK phase of the study, with a goal of reaching a target average concentration (C_{avg}) of ≥ 100 ng/mL. The applicant selected this target based on PK modelling that evaluated the effect of exposure and other prognostic factors (such as baseline viral load, race, and baseline tropism) on predictors of response (binary response for viral load <50 copies/mL and for viral load < 400 copies/mL) using data obtained in the adult trials of treatment-experienced subjects. In this model, the probability of failure was reduced to a constant level above a C_{avg} of 100 ng/mL.

During the clinical development of maraviroc in adults, the dose-limiting adverse event was postural hypotension, which was observed in healthy adult volunteers at doses of 600 mg and above and/or C_{max} values greater than 1000 to 1500 ng/mL. However, in Phase 3 trials of HIV-infected adults who received the recommended doses of maraviroc, postural hypotension was reported at a similar rate in subjects who received maraviroc and those who received placebo (0.5%) or an active control. Although postural hypotension was associated with C_{max} levels while C_{avg} levels were targeted in the pediatric studies, the doses used in the pediatric trial were based on the recommended adult dose of maraviroc (300 mg twice daily), which is lower than the doses that were associated with postural hypotension. In addition, the C_{max} levels obtained with the recommended pediatric doses of maraviroc were lower in PK model simulations than the C_{max} levels associated with postural hypotension.

Trial A4001034: Bioavailability Study in Adults
Trial A4001034 was an open-label, randomized, three-way crossover study of the bioavailability of the oral solution compared to the tablet and of the effect of food effect on the pharmacokinetics of the oral solution. The primary objectives were to evaluate the oral bioavailability of the oral solution compared to the tablet and to evaluate to effect of food on the pharmacokinetics of maraviroc administered as an oral solution. In this trial, single doses of the MVC oral solution were compared in fed and fasted subjects to the 75 mg tablet in fasted healthy adult subjects from 21 to 55 years of age. Subjects participated in three treatment period, receiving one dose of MVC in each treatment period (oral solution after a meal, oral solution after fasting, or 75 mg tablet after fasting) with a minimum of a 5 day washout period between doses. The geometric mean ratios of the AUC_{24}, C_{max}, and T_{max} for the three treatment phases were compared.

The ratios of pharmacokinetic parameters are shown in the following table.

Table 1: Pharmacokinetic Results for Trial A4001034

PK Parameter	Maraviroc Solution Fasted / Tablet Fasted	Maraviroc Solution Fed/ Solution Fasted
AUC_{24} (ng.h/mL) Ratio of Means 90% Confidence Intervals	 121.7 99.2, 149.3	 26.8 21.8, 32.8
C_{max} (ng/mL) Ratio of Means 90% Confidence Intervals	 137.3 99.4, 189.6	 9.5 6.9, 13.1
Tmax (ng/mL) Difference between Means 90% Confidence Intervals	 -0.79 -1.62, 0.03	 0.13 -0.70, 0.95

Source: Clinical Study Report A4001034: Table 7, page 31.

As shown in Table 1, the relative bioavailability of the MVC oral solution in the fasted state was slightly higher compared to the 75 mg tablet. However, food reduced the AUC24 and the C_{max} of the solution by 73.2% and 90.5% respectively. There were no significant differences in T_{max} results. This is similar to what has been observed in adult studies in which administration of the tablet Cmax and AUC were reduced 33% after a high-fat meal. However, reviewers of the original maraviroc NDA concluded that protease inhibitors, which are CYP3A and Pgp inhibitors, reduce the dose dependency of maraviroc absorption and are assumed to result in reduced food effects. Therefore, maraviroc dosing in adults, and now in pediatric patients, is not based on food intake. In general the conduct of the clinical trials in adults and pediatric patients was maraviroc dosing without regard to food.

Trial A4001031: Pediatric Trial

Trial A4001031 was an open-label, two-stage, pharmacokinetic, safety, and efficacy study in 103 treatment-experienced children and adolescents 2 to <18 years of age who were infected with CCR5-tropic HIV-1. In order to participate in the study, subjects had to be ARV-experienced for at least 6 months or intolerant to at least 2 ARV classes. They had to be either failing their current antiretroviral therapy with a viral load ≥1,000 copies/mL or off therapy. Maraviroc was administered with investigator-selected background antiretrovirals (3 to 5 commercially available ARVs) that were chosen on the basis of resistance testing, history, safety, and tolerability. Subjects were enrolled in one of four cohorts by age: 2 to < 6 year olds were enrolled in Cohort 1 and received MVC oral solution; subjects 6 to <12 years of age were enrolled in Cohorts 2 and 3, subjects in Cohort 2 received MVC tablet and subjects in Cohort 3 received MVC oral solution; and subjects 12 to <18 years of age were enrolled in Cohort 4 and received MVC tablets.

In Part 1 of the trial, at Week 2, intensive PK sampling was conducted over 12 hours following administration of MVC under fed conditions in order to identify the appropriate dose for Part 2 of the trial. The goal of the pediatric dose selection was to achieve a C_{avg} of 100 ng/mL or higher for each subject. If the C_{avg} was lower than 100 ng/mL at Week 2, the dose was increased, and PK was reassessed at Week 4. After the appropriate dose for an individual subject was identified in Part 1 of the trial, the subject was rolled over into Part 2 of the study, in which subjects were followed for 96 weeks or longer to assess MVC safety and antiviral activity. After Part 1, the overall results were analyzed to identify the optimal dosing for subjects enrolled directly into Part 2 of the trial.

Subjects who participated in both Parts 1 and 2 of the trial had intensive PK sampling repeated at Week 48. Subjects who enrolled directly into Part 2 of the trial had sparse PK sampling done at all study visits (Weeks 4, 8, 12, 16, 20, 24, 32, 40 and 48). Samples were collected from 5 to 12 hours after MVC dosing without regard to whether MVC was administered in a fed or fasted state. Results from Part 1 and from Part 2 were used in PK modelling, along with data from adult trails, to determine the appropriate dosing recommendations for inclusion in the USPI.

A total of 56 subjects were enrolled in Stage 1 of the trial. Fifty of the 56 subjects started maraviroc along with a new optimized background treatment (OBT) regimen at the beginning of Part 1. Of these subjects, only 3 subjects received an OBT that included a CYP3A inducer, 43 subjects received a CYP3A inhibitor as part of their OBT, and 10 subjects received an OBT with CYP3A neutral ARVs.

Of the 50 subjects enrolled in Stage 1 and continuing into Stage 2, 49 subjects met the exposure target of $C_{avg} \geq 100$ ng/mL either on their initial dose or after dose adjustment. One subject in Cohort 4 (12 to <18 year old cohort) did not reach the C_{avg} target but was rolled over into Stage 2 on the recommended adult dose of 300 mg administered twice daily. Overall, dose adjustments were required for 8 subjects: one subject in Cohort 1 receiving a CYP3A inducer, six subjects receiving CYP3A neutral concomitant medications (2 in Cohort 2, 1 in Cohort 3, and 3 in Cohort 4), and one subject in Cohort 3 receiving a CYP3A inhibitor. All dose adjustments were increases in dose, there were no dose reductions.

Six additional subjects were not rolled over from Stage 1 to Stage 2. Two subjects were noncompliant with study medication but had PK data available for analysis, one discontinued due to an adverse event (AE) prior to reaching the exposure target, and three withdrew prior to PK sampling (one due to premature discontinuation because of vomiting, one due to withdrawn consent, and one due to poor venous access).

Of the 50 subjects in Part 1 of the Study who continued into Part 2, the median MVC C_{avg} after dose adjustment in Part 1 was 251.58 ng/mL; median MVC C_{avg} was 231.6 ng/mL for subjects in Cohort 1, 271.6 ng/mL in Cohort 2, 287.24 ng/mL in Cohort 3, and 277.65 ng/mL in Cohort 4. The median C_{max} and C_{min} for all four cohorts were 588.50 ng/mL and 75.05 ng/mL respectively. While the results for C_{avg} and C_{max} were similar between the four cohorts, there was more variation for C_{min} with a range of C_{min} from 18.97 ng/mL in Cohort 1 to 115.84 ng/mL in Cohort 3. Although the subjects reached the C_{avg} targets, CDER pharmacology reviewers consider C_{min} a better measure of exposure-response than C_{avg}. Therefore, C_{min} is used in product labeling. In addition to these data, CDER pharmacology reviewers used PK modeling results and use of concomitant medications, as discussed in the next section, to identify pediatric dosing that provided marviroc exposures similar to those observed in adults for the pediatric dosing regimens. Please refer to the Clinical Pharmacology review for further details.

Pharmacokinetic Modeling

PK modelling of clinical data developed from a dataset using intensive and sparse PK sampling in pediatric subjects and adult population PK was used to investigate the effect of food, formulation, unit dose, and co-administered drugs on MVC pharmacokinetics. The model was used to derive weight-based pediatric dosing for the USPI.

While the applicant used C_{avg} in the PK modelling, CDER Clinical Pharmacology reviewers considered the totality of the exposure including C_{min} for each weight band, use of concomitant medications, as well as the results of the PK modelling in order to identify the appropriate doses

of maraviroc for pediatric patients. Please refer to the Clinical Pharmacology review for details regarding the model development and evaluation.

Because only 3 subjects received a CYP3A inducer, there was insufficient data to identify an appropriate dose in this population and dosing recommendations could not be made for individuals receiving a CYP3A inducer. Therefore, the main part of pharmacokinetic evaluation focused on pediatric MVC dosing when coadministered with CYP3A neutral and CYP3A inhibitors agents.

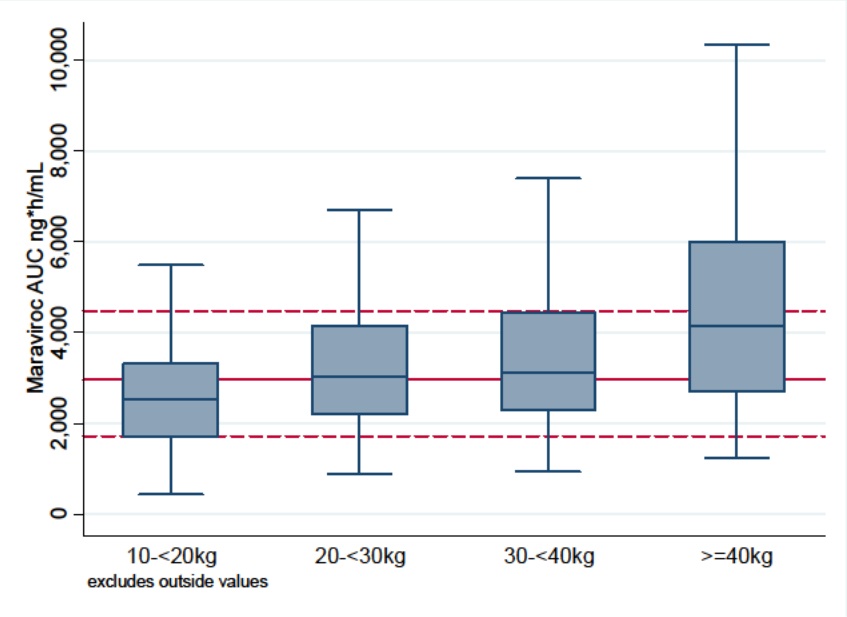
Pediatric maraviroc dosing when coadministered with CYP3A neutral concomitant medications
Overall ten subjects received MVC with a CYP3A neutral regimen. The applicant used different models for analyses of data for use of maraviroc coadminstered with CYP3A neutral concomitant medications and for maraviroc coadministered with CYP3A inhibitors. CDER pharmacology reviewers identified several issues with the CYP3A neutral concomitant medication model. For example, the applicant's model did not study dose as a function of weight and instead and the applicant's model primarily used data from healthy volunteers instead of from HIV-infected adults. However, the main concern was that the applicant's model did not adequately describe the variability observed in the observed PK results for adults and pediatric subjects in MVC trials.

Because the model could not be used to identify a weight based dosing regimen for pediatric subjects, CDER pharmacology reviewers examined the results from intensive PK sampling in subjects in Part 1 of Trial A4001031. Only 10 subjects in Part 1 received maraviroc and CYP3A neutral concomitant medications, and only 2 of the 10 subjects weighed less than 30 kg. Therefore, there were sufficient data from PK sampling to identify appropriate weight-based dosing in the 10 to <20 kg and 20 to <30 kg weight bands. In pediatric subjects who weighed ≥ 30 kg, observed maraviroc exposures at a dose of 150 mg twice daily were similar to adults. As a result, the maraviroc package insert will only include pediatric dosing recommendations for maraviroc when used in subjects on a CYP3A neutral OBT who weigh at least 30 kg. In these patients, the adult dose of 300 mg twice daily is appropriate. No subjects had Cmax values that exceeded the mean value in adults associated with postural hypotension

Pediatric maraviroc dosing when coadministered with CYP3A inhibitor concomitant medications

The population PK model for concomitant use of maraviroc with CYP3A inhibitors used both intensive and sparse PK data from Trial A4001031 as well as an additional 1489 samples from adult studies of maraviroc. Unlike the model used for CYP3A neutral concomitant medications, weight was used as a continuous variable in this model. In addition, the effect of maraviroc bioavailability relative lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DPV/r) use was also assessed in the model. In order to assess the adequacy of the model, results from simulations of the population PK model were compared to actual results from the pediatric and adult studies in subjects who received a CYP3A inhibitor as part of their OBT. In this group of subjects, the population PK model adequately described what has been observed in PK studies. The population PK model was simulated in pediatric subjects using the proposed weight-based dosing regimen for subjects who were receiving CYP3A inhibitors in their OBT. As shown in the figure below, the predicted exposures in these pediatric patients were similar to exposures in treatment-experienced adults supporting the use of dosing based on milligrams per kilograms in patients receiving CYP3A inhibitors.

Figure 1: PK Model Comparison of Maraviroc AUC between Treatment-Experienced Pediatric and Adult Subjects Using Weight-Based Dosing



Source: Figure generated by Biometrics reviewer, Mario Sampson

The solid line in Figure 1 represents the median AUC in 375 treatment-experienced adults receiving MVC. The dashed lines represent the 25th and 75th percentiles. Although the median MVC AUC was lower in pediatric patients weighing 10 to <20 kg, overall, modelling results demonstrated that weight-based dosing provided AUC levels in pediatric patients receiving MVC and a CYP3A inhibitor similar to those observed in HIV-infected adults receiving MVC. These data supported the applicant's proposed dosing for pediatric patients receiving maraviroc and an optimized background regimen containing a CYP3A inhibitor.

In the analyses of concomitant use of maraviroc and CYP3A inhibitors, maraviroc exposures were lower in pediatric subjects receiving DRV/r-containing regimens compared to those receiving LPV/r. In addition, exposures were lower in pediatric subjects 10 - <20 kg on DRV/r compared to adults who received maraviroc and DRV/r. However, CDER reviewers 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 better in that group.

Another point is most subjects in the trial who weighed ≥40 kg received MVC 125 mg BID, whereas the MVC 150 mg BID is recommended for labeling. According to Dr. Sampson's review, for pediatric subjects ≥40 kg receiving MVC 150 mg BID, the exposures are predicted to be 24-45% higher than in treatment-experienced adults on an inhibitor-containing regimen. However, Dr. Sampson assessed the increase is closer to 24% as this is in relation to adults taking the subset of protease inhibitors used in the pediatric study. Another factor that went into recommending MVC 150 mg is because 150 mg is easier to administer. A 150 mg tablet is available while 125 mg (the dose given to most subjects ≥40 kg in the pediatric study) would require administration of the 75 mg and 25 mg tablets. Additionally, Cmax values for all pediatric subjects were lower than the mean adult Cmax associated with postural hypotension.

Please see the labeling section of this review for the specific dosing recommendations.

7. Clinical / Statistical – Efficacy

As stated previously, the NDA and sNDA were submitted to fulfill the outstanding PREA PMR which required efficacy data through Week 48 and safety data through Week 96. The clinical trial report focused on the 48 week safety and efficacy analyses. Therefore, the efficacy section of this review summarizes the Week 48 efficacy results for Trial A4001031. Post Week 48 efficacy analyses were not presented by the applicant in the clinical trial report and were not required for approval or labeling. As a result efficacy data through Week 48 is presented in labeling. In addition post 48 week safety data were submitted to fulfill the PREA PMR. The safety section focuses on the Week 96 safety results. Because the PREA PMR required safety data through Week 96, the review team decided to present the Week 96 data in the label.

Though cross-trial comparisons to the results from the adult trials should be done with caution, the general principal of comparing effectiveness of an ARV drug in children to adults is supported, as further discussed below.

The extrapolation of efficacy for antiretroviral drugs like maraviroc is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects [21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c]. DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease, noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two parameters, HIV RNA viral load and CD4 count. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) are shown to lower HIV RNA, improve CD4 counts (or percentages) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups [see US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, available at http://aidsinfo.nih.gov/guidelines].

Overview of Trial Design

Trial A4001031 was the pivotal pediatric trial evaluating the use of maraviroc. Maraviroc was administered orally as a solution (20 mg/mL) or as a 25, 75, or 100 mg tablet. Fifty-six subjects were enrolled into Part 1 of the trial for intensive PK assessment which allowed for identification of the appropriate dose for maraviroc and the short-term safety and tolerability of maraviroc. Based on the Part 1 intensive pharmacokinetic data and the safety results, enrollment for Part 2 of the study was initiated.

The primary objectives were to determine the PK profile and dosing schedules for MVC in treatment-experienced, HIV-infected children and adolescents and to determine the safety and tolerability of MVC in HIV-infected children and adolescents. The secondary objectives were to describe the efficacy of multiple dose administration of MVC in treatment-experienced children and adolescents infected with CCR5-tropic HIV-1 and to describe tropism changes over time.

See the Clinical Pharmacology section of this review and the Biopharmaceutics review for a discussion of the pharmacokinetic results of the study; see the Clinical Microbiology section of this review and the Clinical Microbiology review for a discussion of the change in tropism over time.

The trial enrolled treatment-experienced children and adolescents from 2 to <18 years of age who were infected with CCR5-tropic HIV-1. Subjects had to be failing their current ARV regimen (defined as a baseline HIV RNA viral load ≥ 1,000 copies/mL) or off antiretroviral therapy. Maraviroc dosing was extrapolated from adult dosing and based on body surface area. Subjects from 2 to <6 years of age received the MVC oral solution, subjects from 6 to <12 years of age received either the oral or the tablet formulation, and subjects from 12 to <18 years of age received the tablet formulation. Fifty subjects from Part 1 were rolled over into Part 2, and 47 additional subjects were enrolled directly into Part 2.

In Part 2 of the study, subjects were followed for safety and tolerability as well as efficacy for a minimum of 48 weeks with an additional planned 4 years-extension period. Efficacy was evaluated at Weeks 24 and 48 by evaluation of immunologic changes and changes in HIV RNA viral load. Resistance information and viral tropism was evaluated in subjects with loss of virologic response.

Trial A4001031 was reviewed for efficacy, safety and tolerability, and pharmacokinetics. Subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results were reviewed using JMP Statistical software.

Disposition

A total of 285 subjects were screened for study participation, and 103 subjects received at least one dose of study drug (MVC). Of the 103 subjects, 74 (72%) were ongoing at the Week 48 analysis cut-off date for the Clinical Study Report. Of the 29 subjects who discontinued treatment before 48 weeks, 23 (28% of all subjects) discontinued due to insufficient clinical response, 3 (2.9%) due to noncompliance, 2 (1.9%) due to withdrawn consent, 2 (1.9%) due to an adverse event, and 1 due to lack of venous access. As shown in Table 2, percentages of subjects who prematurely discontinued the study and the reasons for premature discontinuation differed in adolescent subjects (Cohort 4) compared to other subjects.

Table 2: Subject Discontinuations through 48 Weeks (Full Analysis Set)

	Cohort 1 2-<6 yrs Solution	Cohort 2 6-<12 yrs Tablet	Cohort 3 6-<12 yrs Solution	Cohort 4 12-<18 yrs Tablet	Total
Total No. of Subjects	**16**	**31**	**13**	**43**	**103**
No .(%) of Subjects Discontinuing	**4 (25%)**	**5 (16%)**	**3 (23%)**	**17 (39.5%)**	**29 (28%)**
Reasons for Discontinuation					
Insufficient clinical response	3 (19%)	4 (13%)	2 (23%)	13 (30%)	23 (22%)
Non-compliance with study treatment	1 (6.3%)	0	0	2 (4.7%)	3 (2.9%)
Consent withdrawn	0	1 (3%)	0	1 (2%)	2 (1.9%)
Adverse event	0	0	1 (7.7%)	1 (2.3%)	2 (1.9%)
Other	0	0	0	1 (2.3%)	1 (1.0%)

Source: Clinical Study Report A4001031: Table 5, page 86.

Premature study discontinuation prior to 48 weeks was more commonly observed in adolescent subjects (39.5%) than in other age groups (16 to 25%). This was largely due to a higher percentage of adolescents with insufficient clinical response which was likely due to fewer treatment options since the mean duration since diagnosis varied from 2.7 years to 6.4 years for Cohorts 1, 2, and 3 and was 8.3 years for Cohort 4.

Although there were differences in adverse events (see the safety section on this review) observed with the oral and tablet formulations, there was no difference in the percentages or reasons for premature discontinuations in subjects receiving the oral solution (Cohorts 1 and 3) compared to those receiving the tablet formulation (Cohorts 2 and 4). This may be because most adverse events observed in a higher percentage of subjects receiving the liquid formulation compared to the tablet formulation were Grade 1 and therefore, did not result in an increased number of subjects discontinuing due to withdrawn consent.

Demographics and Baseline Characteristics

The Full Analysis Set included 103 subjects. The majority of subjects were female (52%) and Black/African American (69%). The mean age of subjects was 10.3 years. Almost all subjects (99%) acquired HIV via mother-to-child transmission.

Efficacy Results at Week 48

There was no primary efficacy endpoint, however the proportions of subjects with HIV RNA <400 and <48 copies/mL at Week 48 were used as the primary "analysis." Maraviroc, in combination with other ARVs, demonstrated antiviral activity over the 48 week trial period. The proportion of subjects with plasma viral load <400 copies/mL at Week 48 was 65.0% and the proportion of subjects with viral load <48 copies/mL was 47.6%. These results are consistent with efficacy results in the pivotal trials that enrolled HIV-infected, treatment-experienced adults; in these trials, the percentage of subjects with HIV RNA <400 copies/mL at Week 48 was 56% and the percentage with viral load <50 copies/mL was 46%.

Evidence of antiviral activity was also observed in the analysis of change of CD4+ lymphocyte count from baseline to Week 48. The mean change in absolute CD4 count from baseline was +247.1 cells/mm^3 and the mean change in CD4 percentage was +5.2%. This is consistent with

the results of trials in treatment-experienced adults in which the mean change in CD4+ cell count was +124 cells/mm^3.

With regard to subgroup analysis by age, antiviral activity for subjects in Cohorts 1, 2 and 3 was similar with no substantial differences between the age groups 2 to <6 years (Cohort 1) and 6 to <12 years of age. However, the proportion of subjects with HIV RNA levels <400 and <48 copies/mL was lower in Cohort 4, which enrolled adolescents from 12 to <18 years of age. This is consistent with adolescents having a longer time since diagnosis which likely resulted in fewer ARV treatment options. In addition, poor adherence is often observed during adolescence. The lower virologic response is consistent with other studies of ARVs in the adolescent age group.

Because subjects from 6 to <12 years of age received either the tablet formulation (Cohort 2) or the oral solution (Cohort 3), antiviral activity for the two formulations can be compared in similar populations. However, this analysis is limited due to the small number of subjects (N=13) in Cohort 3. The proportion of subjects with HIV RNA <400 and <48 copies/mL was similar in subjects 6 to <12 years of age who received the oral solution (69.2% and 53.8%, respectively) compared to those who received the tablet (77.4% and 54.8%).

The results for each cohort are shown in the following tables.

Table 3: Proportion of Subjects with HIV-1 RNA <400 copies/mL through Week 48

Cohort Age Formulation	**Cohort 1 2-<6 yrs Solution**	**Cohort 2 6-<12 yrs Tablet**	**Cohort 3 6-<12 yrs Solution**	**Cohort 4 12-<18 yrs Tablet**	**Total**
HIV RNAL <400 copies/mL	12 (75%)	22 (77.4%)	9 (69.2%)	22 (51.2%)	67 (65%)
HIV RNA ≥ 400 copies/mL	4 (25.0%)	6 (19.4%)	3 (23.1%)	18 (41.9%)	31 (30.1%)
No post-baseline data	0	0	1 (7.7%)	1 (2.3%)	2 (1.9%)
No virologic data in 48-week window	0	1 (3.2%)	0	2 (4.7%)	3 (2.9%)
Discontinued treatment due to AE or death	0	0	0	1 (2.3%)	1 (1.0%)
Discontinued treatment for other reasons	0	1 (3.2%)	0	1 (2.3%)	2 (1.9%)
Missing data during window but on study	0	0	0	0	0

Source: Clinical Study Report A4001031: Table 26, page 150.

Table 4: Proportion of Subjects with HIV-1 RNA <48 copies/mL through Week 48

Cohort Age Formulation	**Cohort 1 2-<6 yrs Solution**	**Cohort 2 6-<12 yrs Tablet**	**Cohort 3 6-<12 yrs Solution**	**Cohort 4 12-<18 yrs Tablet**	**Total**
HIV RNAL <48 copies/mL	8 (50%)	17 (54.8%)	7 (53.8%)	17 (39.5%)	49 (47.6%)
HIV RNA ≥ 48 copies/mL	8 (50%)	14 (45.2%)	5 (38.5%)	24 (55.8)	51 (49.5%)
No post-baseline data	0	0	1 (7.7%)	1 (2.3%)	2 (1.9%)
No virologic data in 48-week window	0	0	0	1 (2.3%)	1 (1.0%)
Discontinued treatment due to AE or death	0	0	0	1 (2.3%)	1 (1.0%)
Discontinued treatment for other reasons	0	0	0	0	0
Missing data during window but on study	0	0	0	0	0

Source: Clinical Study Report A4001031: Table 27, page 151.

Efficacy Summary and Conclusions

The efficacy of twice daily oral maraviroc in the treatment of treatment-experienced pediatric patients from 2 to <18 years of age who are infected with CCR5-tropic HIV-1 was demonstrated in this single arm, uncontrolled trial. At Week 48, maraviroc in combination with other ARVs resulted in virologic response in 65% of subjects; the response rate is consistent with the antiviral response observed in studies of treatment-experienced adults. Virologic response was lower in adolescents compared to children 2 to <12 years of age, but that finding was likely due to adolescents having fewer treatment options and poorer compliance and is consistent with other studies of ARVs in the adolescent patient population. The virologic results also support the antiviral activity of the oral solution; treatment response was similar in subjects who received the oral formulation and those who received tablets.

In summary the exposure data from the intensive PK analyses support weight-based dosing and the efficacy outcomes as measured by HIV RNA and CD4+ cell count, in Trial A4001031 are consistent with results observed during trials of treatment-experienced adults. Therefore, these results support the antiviral activity of maraviroc in treatment experienced, pediatric patients 2 to <18 years of age.

8. Safety

The data submitted support safety and tolerability of maraviroc when administered in combination with other ARVs. The applicant has submitted safety data from 103 pediatric subjects who received at least one dose of maraviroc in Trial A4001031. The duration of follow-up was at least 96 weeks for 63% of subjects enrolled. Maraviroc in combination with other ARV drugs was safe and tolerable when administered to subjects from 2 to <18 years of age. There was an increased incidence of gastrointestinal (GI) adverse events in subjects who received the oral solution; however, the majority of the GI adverse events were mild in intensity and did not result in interruption of treatment with maraviroc or other ARVs. Otherwise, the types of adverse events observed were similar to conditions or illnesses commonly observed during childhood and with the types of AEs observed in HIV-infected, treatment experienced children and adults. The study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings.

Duration of Treatment
Subjects enrolled in Trial A4001031 were to be followed for safety for at least 96 weeks and for up to five years. The Clinical Study Report summarized the safety data for the first 48 weeks. Additional safety information for post-48 weeks follow-up was described in the Clinical Summary (Section 2.7.4.5.10 of the submission) and in tabular form in Section 14.0. In addition, a 60-Day Safety Update was submitted on June 25, 2016. The final safety database cut off for data submitted was March 24, 2016. The duration of treatment for the different time points for safety follow-up are shown in the following table. As shown in Table 5, the majority of subjects have completed 96 weeks of treatment and the percentage of subjects completing Week 96 was only slightly less (-9%) than the percentage who completed Week 48.

Table 5: Number (%) of Subjects with Safety Follow-Up by Duration of Treatment

Cohort **Age** **Formulation**	**Cohort 1** **2-<6 yrs** **Solution**	**Cohort 2** **6-<12 yrs** **Tablet**	**Cohort 3** **6-<12 yrs** **Solution**	**Cohort 4** **12-<18 yrs** **Tablet**	**Total**
Treated	16	31	13	43	103
Completed Week 48	12 (75%)	26 (84%)	9 (70%)	27 (63%)	74 (72%)
Completed Week 96	11 (69%)	23 (74%)	8 (61.5%)	23 (53.5%)	65 (63%)
Completed 5 years	2 (12.5%)	9 (29%)	4 (31%)	5 (12%)	20 (19%)

Source: 60-Day Safety Update: Table 2, page 7.

Deaths and Other SAEs
There were no deaths up to Week 96. One subject who discontinued MVC due to insufficient treatment response died of pneumonia more than one year after discontinuation of maraviroc.

A total of 19 non-fatal serious adverse events were reported in 15 subjects. SAEs reported in subjects from 2 to <6 years of age were oral abscess and vomiting; SAEs in subjects 6 to <12 years of age were bronchopneumonia, pneumonia, gastric fistula, gastritis, rash, osteopenia, extremity pain, tendon disorder, and bipolar disorder; and SAEs reported in adolescents 12 to <18 years of age were pneumonia (N=3), tuberculosis, rifampicin/isoniazid-induced liver injury, influenza, cellulitis, and pelvic inflammatory disease. None of the SAEs were judged as related to maraviroc. All SAEs had resolved at the time the subject discontinued the study except for the SAE of pelvic inflammatory disease. Of these SAEs, 3 were reported within the first 30 days of receiving MVC: one subjects developed a rash on Day 10, which was attributed to efavirenz and one subject was diagnosed with H1N1 influenza on Day 16 and then developed pneumonia on Day 24. Although the subject with the SAE of vomiting was receiving the oral solution of MVC, vomiting did not start until Day 180, resolved without interruption of MVC dosing, and was not attributed by the investigator to MVC. However, the cause of vomiting was not documented in the narrative for this subject.

Discontinuations due to Adverse Events
Two subjects discontinued the study prematurely due to an adverse event during the first 48 weeks of the study. One subject discontinued due to maraviroc-related, Grade 1 vomiting and the other due to pelvic inflammatory disease. An additional subject discontinued all antiretrovirals including maraviroc on Day 624 due to extremity pain.

The subject who discontinued due to vomiting was an 8 year old black male with a history of lipodystrophy who was started on MVC oral solution 150 mg twice daily, Kaletra, zidovudine, and darunavir on Day 1. On Day 2, the mother returned to the study site without the study

subject, returned the bottles of study medication, and told investigators that her son was discontinuing the study due to vomiting.

Adverse Events of Interest
Based on adverse events observed in previous studies of maraviroc, adverse events of interest for further safety evaluation were evaluated regardless of AE causality: the AEs of interest included hepatotoxicity, severe skin and hypersensitivity reactions, and postural hypotension. Because of an increased incidence of gastrointestinal adverse events and ADRs reported in subjects who receive the MVC oral solution in A4001031, GI AEs were also included as an AE of interest.

Hepatoxicity
The maraviroc package insert contains a boxed warning for hepatoxicity. Hepatoxicity with allergic features has been reported in adult trials and in post-marketing reports for maraviroc. Hepatitis along with severe rash, fever, eosinophilia, elevated IgE, and other systemic symptoms has typically been observed within one month of starting maraviroc. As per the USPI recommendations, discontinuation of MVC should be considered in patients who develop hepatotoxicity with allergic features.

Individuals with active hepatitis; cirrhosis of the liver; Grade 3 or higher ALT, AST or bilirubin at screening; change of two or more grades in AST or ALT between screening and baseline visits, or receipt of potentially hepatotoxic agents within 60 days of baseline were excluded from study participation. Potential cases of drug-induced liver injury were to be identified for further evaluation by the biochemical criteria consistent with Hy's Law:

- AST or ALT and total bilirubin values within the normal range that subsequently increase to ≥3 X upper limit of normal (ULN) concurrent with total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available *or*
- Baseline AST or ALT values >ULN with AST or ALT values ≥2 X baseline value and at least ≥3X ULN concurrent with either total bilirubin normal at baseline with increase to above the normal range or total bilirubin increased from baseline by an amount of at least 1 X ULN or ≥3 X ULN (whichever is smaller).

Two subjects in Cohort 4 triggered the biochemical criteria for Hy's Law. One subject who met the criteria had been diagnosed with tuberculosis and increased liver function tests were associated with the start of rifampicin and isoniazid, which are known to be hepatotoxic. The AE was judged as not related to MVC. A second subject had an increase in liver function tests (LFTs) on Day 33 after starting MVC and OBT with an AST of 144 U/L, ALT of 146 U/L, and total bilirubin of 48 Umol/L. Alkaline phosphatase was not measured. All medications were discontinued and LFTs decreased to normal limits within 13 days (AST of 27 U/L, ALT of 16 U/L, and total bilirubin of 11 Umol/L). MVC was restarted 6 days after AST, ALT, and bilirubin values returned to within normal range, and the LFTs remained within normal range at all follow-up visits. No additional testing was done to identify the cause of the increased LFTs, but because the abnormal AST, ALT and bilirubin occurred after 333 days on MVC and did not recur with MVC re-challenge, the hepatic adverse event was not judged as related to MVC.

Increased AST and ALT were reported in three subjects. One subject in Cohort 2 had a Grade 1 elevation in LFTs on Day 48 that resolved by Day 75 with no change in ARV treatment. A second subject in Cohort 3 had a Grade 2 increase in LFTs on Day 70 that was judged as MVC-related. MVC was held for 12 days then restarted. The LFTs remained abnormal but stable, then decreased to Grade 1 at Day 229 and to within normal limits on Day 285 without change in MVC or ARV treatment. The third subject in Cohort 4 had an increase in ALT and AST on Day

333; the reason for hepatoxicity in this subject was unknown. Maraviroc was held temporarily but was restarted and the abnormal liver function tests had resolved 13 days later.

Two subjects in Cohort 4 experienced Grade 1 increases in total bilirubin: one on Day 16 and one on Day 29. Both AEs were considered related to atazanavir, which has been associated with hyperbilirubinemia. MVC was continued in both subjects.

There were no episodes of hepatoxicity associated with allergic reactions or systemic events.

Overall, no new or unexpected findings with regard to hepatoxicity were found, and the hepatic-related findings in Trial 4001031 were consistent with those observed in adult studies of maraviroc.

Severe skin and hypersensitivity reactions
Severe and potentially-life threatening skin and hypersensitivity reactions without hepatic involvement have been reported in adults taking maraviroc.

Skin AEs judged as MVC-related or with no other known cause were reported in five subjects; all five skin AEs were mild in intensity. All events occurred before Week 48. The skin AEs with no known cause were rash (N=2) and allergic dermatitis; all three were reported after the first month of treatment and all resolved without interruption of MVC treatment. Two subjects had skin AEs judged as related to MVC. One AE of Grade 1 rash was reported in a 16 year old female who was also receiving abacavir and raltegravir. The rash resolved without any change in ARV treatment by the investigator; however, unknown to the investigator, the subject was noncompliant and did not take MVC from Day 2 to Day 14. A second subject was diagnosed with allergic dermatitis due to MVC on Day 169. MVC treatment was not interrupted and the Grade 1 rash resolved.

There were no serious or severe skin adverse reactions and no skin reactions, such as angioedema or urticaria, which were consistent with a hypersensitivity reaction.

Postural hypotension
An increased incidence of postural hypotension was observed in healthy adult volunteers who received MVC at doses of 600 mg or higher and / or who had C_{max} values higher than 1000 to 1500 ng/mL. In Phase 3 trials of HIV-infected adults who received the recommended doses of maraviroc, postural hypotension was reported at a similar rate in subjects who received maraviroc and those who received placebo (0.5%).

Standing blood pressure was not obtained in A4001031, so the incidence of postural hypertension may be underestimated in this trial.

There were no AEs of postural hypotension. Dizziness was reported in 1 subject in Cohort 2 and 3 subjects in Cohort 4. The AE of dizziness in the 11 year old in Cohort 2 was associated with vomiting and judged as not related to MVC. All 3 AEs of dizziness in subjects in Cohort 4 were judged as MVC-related. Dizziness occurred on Day 14 in one subject, on Day 5 and Day 192 in one subject, and on Day 6 in one subject. Three of the episodes of dizziness were Grade 1 and one was Grade 2. All resolved without sequelae. The reason for dizziness was not reported, and postural hypotension cannot be ruled out in these 3 adolescents.

This reviewer is unable to determine if there is an increased incidence of postural hypotension in adolescents receiving MVC because standing blood pressure was not obtained. However,

the episodes of dizziness in adolescents were Grade 1 and 2 and resolved without sequelae. Any risks due to postural hypotension in this population are difficult to assess because of the lack of a control group and the background rate of dizziness in adolescents, nevertheless, the risks due to postural hypotension in the pediatric population appear to be minimal.

Gastrointestinal adverse events

In adult maraviroc trials, GI AEs were reported at a similar rate in subjects who received MVC and in those who received placebo or an active control. Overall, 35% of pediatric subjects reported GI AEs in the first 48 weeks of Trial A4001031. The incidence of GI adverse events after Week 48 are not included in this section because subjects were allowed to change formulations after Week 48, and changes in formulation after Week 48 were not included in study datasets. Diarrhea and vomiting were among the most commonly reported adverse events in the trial. When analyzed by cohort, GI AEs were observed in 56.3% of subjects in Cohort 1, 19.4% in Cohort 2, 38.5% in Cohort 3, and 37.2% in Cohort 4. The MVC oral solution was administered to subjects in Cohort 1 and 3. In Cohort 1, more than one-half of subjects reported GI AEs including 6 subjects (37.5%) with diarrhea and 6 with vomiting. One subject in Cohort 1 reported vomiting due to the taste of MVC. Subjects from 6 to <12 years of age were enrolled in either Cohort 2 and received tablets or in Cohort 3 and received the oral solution. The percentage of subjects with GI AEs was higher in Cohort 3 compared to Cohort 2 and was largely driven by the higher percentage of subjects with vomiting in Cohort 3 (23%) compared to Cohort 2 (13%). Adolescents in Cohort 4 received tablets and had a similar percentage of GI AEs as subjects receiving oral solution in Cohort 3. Twenty-one percent of subjects in Cohort 4 experienced diarrhea, 9.3% had nausea, and 9.3% had vomiting. This might have been related to more advanced HIV disease in Cohort 4 because the mean baseline CD4+ cell count was lower in Cohort 4 at 419.3 cells/mm^3) than in Cohort 3: 592.1 cells/mm^3).

The overall percentage of subjects with GI AEs that were judged as related to maraviroc and that occurred in the first 48 weeks of the study was 17.5%: 25% in Cohort 1, 9.7% in Cohort 2, 15.4% in Cohort 3, and 20.9% in Cohort 4. As with GI AEs of any causality, the majority of GI ADRs were vomiting and diarrhea. On comparison of subjects in the 6 to <12 year old age group, the percentage of subjects with GI ADRs was higher in subjects who received the oral solution compared to the tablet. However, the percentage of adolescents with GI ADRs was higher than for the subjects 6 to <12 year olds who received the oral solution.

In summary, GI AEs were the most commonly reported AEs in Trial A4001031; vomiting and diarrhea were the most commonly reported individual AEs. The percentage of subjects with GI AEs, all cause and MVC-related were highest in Cohort 1; in this cohort subjects 2 to <6 years of age received the MVC oral solution. On comparison of subjects in the same age range (subjects 6 to <12 years of age enrolled in Cohorts 2 and 3), the incidence of subjects with GI AEs and ADRs was higher in subjects who received the oral solution compared to the tablet. Therefore, this reviewer concludes that gastrointestinal adverse events are more common in subjects who received the oral solution compared to the tablet formulation. Language will be added to the maraviroc package insert to reflect the increased rate of GI ADRs in subjects who received the oral solution.

Adverse Events with Severe or Life-threatening Intensity

Most AEs were Grade 1 or 2 in severity. Grade 3 and 4 adverse events (regardless of causality) were reported in 10 (9.7%) subjects through Week 96. Two Grade 4 adverse events were reported in 2 subjects: a 5 year old subject with a history of lipodystrophy experienced a Grade 4 increase in lipase that resolved without interruption of MVC and a 16 year old male with tuberculosis had a Grade 4 liver injury related to rifampicin and isoniazid therapy for TB. None

of the Grade 4 AEs was considered related to maraviroc. Ten Grade 3 AEs were reported in 8 subjects and included vomiting, pneumonia, otitis media, increased LFTs, extremity pain, bipolar disorder, H1N1 influenza and pneumonia in the same subject, and gastritis and vomiting in the same subject.. One of the Grade 3 AEs, vomiting, was considered related to maraviroc. Vomiting was reported in an 8 year old subject in Cohort 2 on Day 501. The subject was also diagnosed with gastritis, which was attributed to underlying HIV disease. Maraviroc was temporarily discontinued but was restarted without further vomiting. One subject had all antiretrovirals discontinued due to extremity pain; the individual antiretroviral thought to be causing the extremity pain was not identified..

Common Adverse Events

A total of 41 adverse drug reactions (ADRs), e.g., adverse events considered maraviroc-related, as assessed by the investigator, were reported in 29 (28.1%) subjects through 96 weeks of the study. The most commonly reported ADRs were in the gastrointestinal system organ class (19 subjects or 18.4%), and the most commonly reported ADR was vomiting. ADRs reported in at least 2 subjects are shown in the following table.

Table 6: Adverse Drug Reactions Reported in at Least 2 Subjects through Week 96

	Cohort 1 2-<6 yrs Solution	**Cohort 2 6-<12 yrs Tablet**	**Cohort 3 6-<12 yrs Solution**	**Cohort 4 12-<18 yrs Tablet**	**Total**
Number of Subjects	16	31	13	43	103
Vomiting	4	4	1	3	12 (12%)
Diarrhea	0	0	1	3	4 (4%)
Abdominal pain	0	0	0	3	3 (3%)
Dizziness	0	0	0	3	3 (3%)
Nausea	0	0	0	3	3 (3%)
Headache	0	0	0	2	2 (2%)
Hyperbilirubinemia	0	0	0	2	2 (2%)

Source: Clinical Study Report A4001031: Adverse Events dataset.

The ADRs reported were all Grade 1 or 2 in intensity; there were no Grade 3 or 4 AEs or SAEs that were judged as maraviroc –related.

With the exception of vomiting and diarrhea, the other ADRs were consistent with those reported in trials enrolling treatment-experienced adults. While vomiting and diarrhea were the most commonly reported ADRs in Trial A4001031, the incidence of adult subjects with vomiting and diarrhea was not higher in the MVC arm than in the placebo arm.

Adverse events of any causality

Most subjects (79/103; 77%) experienced at least one adverse event through Week 96. The most common AEs (by preferred term, all grades, regardless of causality) with incidence reported in at least 10% of subjects were upper respiratory tract infection (26%), diarrhea (20%), vomiting (19%)and bronchitis (9.7%).

The following table summarizes adverse events through week 48, by SOC and by cohort, reported in at least 2 subjects. The percentage of subjects with AEs was higher in Cohort 4

than in the other cohorts for most system organ classes. This may be related to more advance disease in Cohort 4. Mean duration since HIV diagnose was 8.3 years for subjects in Cohort 4 compared to 2.7 to 6.4 years in the other cohorts. Baseline CD4+ count was 419.3 cells/mm^3 for subjects in Cohort 4 compared to a mean baseline CD4+ cell count between 503-966 cells/mm^3 in the other cohorts. Alternatively, the increased incidence may have been related to the increased ability of adolescents to verbalize their complaints compared to younger children.

Table 7: Common Adverse Events by System Organ Class (Adverse Events Reported in at Least 2 Subjects through Week 96)

	Cohort 1 2-<6 yrs Solution	**Cohort 2 6-<12 yrs Tablet**	**Cohort 3 6-<12 yrs Solution**	**Cohort 4 12-<18 yrs Tablet**	**Total**
Number of subjects	16	31	13	43	103
Any adverse events	11 (69%)	23 (74%)	10 (77%)	35 (81%)	79 (77%)
Infections and infestations	11 (69%)	15 (48%)	6 (46%)	26 (60%)	58 (56%)
Gastrointestinal disorders	9 (56%)	11 (35%)	6 (46%)	17 (39.5%)	43 (42%)
Respiratory, thoracic, and mediastinal disorders	3 (19%)	8 (26%)	1 (7.7%)	6 (14%)	18 (17%)
Skin and subcutaneous tissue disorders	4 (25%)	3 (10%)	4 (31%)	5 (12%)	16 (15.5%)
Nervous system disorders	0	2 (6.5%)	3 (23%)	10 (23%)	15 (14.5%)
General disorders and administration site conditions	2 (12.5%)	2 (6.5%)	1 (7.7%)	5 (12%)	10 (9.7%)
Injury, poisoning, and procedural complications	1 (6.3%)	3 (9.7%)	1 (7.7%)	4 (9.3%)	9 (8.7%)
Musculoskeletal and connective tissue disorders	0	3 (9.7%)	2 (15%)	4 (9.3%)	9 (8.7%)
Investigations	1 (6.3%)	2 (6.5%)	2 (15%)	3 (7.0%)	8 (7.8%)
Blood and lymphatic s stem disorders	2 (12.5%)	0	0	5 (12%)	7 (6.8%)
Psychiatric disorders	0	1 (3.2%)	2 (15%)	2 (4.6%)	5 (4.8%)
Reproductive disorders	0	0	0	3 (6.9%)	4 (3.9%)
Hepatobiliary disorders	0	0	0	4 (9.3%)	4 (3.9%)
Metabolic and nutrition disorders	1 (6.3%)	0	0	1 (2.3%)	2 (1.9%)
Eye disorders	0	1 (3.2%)	0	1 (2.3%)	2 (1.9%)
Neoplasms	0	1 (3.2%)	0	1 (2.3%)	2 (1.9%)

Source: Clinical Study Report A4001031: Adverse Events Dataset.

Laboratory Abnormalities
Sixteen Grade 3 and 4 laboratory toxicities were reported in 14 subjects through Week 96. The majority of laboratory abnormalities were Grade 3. Grade 4 laboratory abnormalities were increased lipase in a subject with a history of lipoatrophy and increased total ALT and AST in a subject receiving rifampicin and isoniazid. Neither of the Grade 4 abnormalities was judged as MVC-related. Overall, the most commonly reported laboratory abnormality was decreased absolute neutrophil count; which was reported in 8 subjects; all were Grade 3 in intensity and all resolved. The timing of the episodes of neutropenia varied, and onset varied from Day 15 to Day 280. None of the subjects was prematurely discontinued due to neutropenia. In addition, the study used the 2004 DAIDS grading criteria; if the 2014 DAIDS criteria had been used, all of the AEs of neutropenia in A4001031 would have been classified as Grade 2 instead of Grade 3. Other Grade 3 laboratory abnormalities were observed in one subject each and were increased ALT, increased bilirubin, increased fasting cholesterol, decreased sodium, and decreased serum bicarbonate. Aside from neutropenia, the types of Grade 3 and 4 laboratory abnormalities were varied and are consistent with the trial population of treatment-experienced subjects.

Safety Summary
In summary, no new safety signal or changes in the frequency of previously described AEs were identified for maraviroc tablets. Overall, the findings in this pediatric clinical trial are consistent with previously described adverse events observed with the use of maraviroc in treatment-experienced adults. The Clinical Adverse Events (Section 6) will be updated to include ADRs as identified by the applicant. As described previously in this review, results related to increased rate of gastrointestinal adverse events in subjects who were administered the oral solution compared to those who were administered tablets will also be included in the USPI.

9. Advisory Committee Meeting
Not applicable.

10. Pediatrics
This application contains pediatric data for subjects from 2 to <18 years of age. The pediatric trial design, clinical outcome, and proposed labeling for pediatric patients from 2 to <18 years of age was presented to the PeRC. The PeRC agreed with the Division's proposed plans for labeling.

The submission of the Clinical Study Report for A4001031 fulfills the PREA PMR for the study of maraviroc in patients 2 to <18 years of age. The requirement to study maraviroc in subjects <2 years of age was waived in 2015.

Data included in this submission represents a partial response to the Pediatric Written Request for maraviroc. Additional data to satisfy the outstanding elements of the Written Request must be submitted by January 15, 2021.

11. Other Relevant Regulatory Issues
No additional regulatory issues have been identified.

12. Labeling
The labeling has been updated to reflect changes in the indication, extending the population to treatment-experienced children 2 years of age and older infected with CCR5-tropic HIV weighing at least 10 kg. In addition, the Dosage and Administration section has been updated to include recommendations on dosing in pediatric patients by weight and by concomitant

medications. An Instruction for Use section has been added to the Patient Package Insert to demonstrate how to use the bottle, adapter, and oral dosing syringe supplied with the oral solution. The changes with this efficacy supplement primarily affected the following sections. Note, while most of the labeling sections have been agreed upon, the addition of wording related to gastrointestinal adverse events with the MVC oral solution is currently being negotiated with the applicant. In addition, the safety information in Section 6.1, Clinical Trials Experience, will be revised to reflect safety data through 96 weeks.

In addition to labeling changes based on the submitted pediatric data, Sections 8.1 Pregnancy and 8.2 Lactation, were updated by consultants from the Division of Pediatric and Maternal Health.

1 INDICATIONS AND USAGE

Selzentry is indicated in combination with other antiretroviral agents for the treatment of only CCR-5 tropic human immunodeficiency virus type 1 (HIV-1) infection in patients 2 years of age and older and weighing at least 10 kg.

2.4 Recommended Dosage in Pediatric Patients

The recommended dosage of SELZENTRY should be based on body weight (kg) and should not exceed the recommended adult dose. The recommended dosage also differs based on concomitant medications due to drug interactions (Table 2 and Table 3) *[see Drug Interactions (7.1), Use in Specific Populations (8.4)]*.

Before prescribing SELZENTRY tablets, assess children for the ability to swallow tablets. If a child is unable to reliably swallow SELZENTRY tablets, the oral solution formulation should be prescribed. Administer the oral solution using the included press-in bottle adapter and oral dosing syringe.

Table 2. Recommended Dosage in Pediatric Patients Aged 2 Years and Older Weighing at Least 10 kg (Tablets)

	Dosage of SELZENTRY Based on Weight			
Concomitant Medications	**10 kg to <20 kg**	**20 kg to <30 kg**	**30 kg to <40 kg**	**≥40 kg**
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: protease inhibitors (except tipranavir/ritonavir) delavirdine elvitegravir/ritonavir ketoconazole, itraconazole, c arithromycin other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) boceprevir	50 mg twice daily	75 mg twice daily	100 mg twice daily	150 mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide	Not recommended	Not recommended	300 mg twice daily	300 mg twice daily
Potent CYP3A inducers	Not recommended			

(without a potent CYP3A inhibitor) including: efavirenz rifampin etravirine carbamazepine, phenobarbital, and phenytoin	

Table 3. Recommended Dosage in Pediatric Patients Aged 2 Years and Older Weighing at Least 10 kg (Oral Solution)

	Dosage (Volume of Solution) of SELZENTRY Based on Weight			
Concomitant Medications	**10 kg <20 kg**	**20 kg <30 kg**	**30 kg <40 kg**	**≥40 kg**
Potent CYP3A inhibitors (with or without a CYP3A inducer) including: protease inhibitors (except **tipranavir**/ritonavir) delavirdine elvitegravir/ritonavir ketoconazole, itraconazole, c arithromycin other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) boceprevir	50 mg (2.5 mL) twice daily	80 mg (4 mL) twice daily	100 mg (5 mL) twice daily	150 mg (7.5 mL) twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide	Not recommended	Not recommended	300 mg (15 mL) twice daily	300 mg (15 mL) twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: efavirenz rifampin etravirine carbamazepine, phenobarbital, and phenytoin	Not recommended			

3 DOSAGE FORMS AND STRENGTHS

Tablets:
25-mg blue, oval, film-coated tablets debossed with “MVC 25” on one side and plain on the other.
75-mg blue, oval, film-coated tablets debossed with “MVC 75” on one side and plain on the other.
150-mg blue, oval, film-coated tablets debossed with “MVC 150” on one side and plain on the other.
300-mg blue, oval, film-coated tablets debossed with “MVC 300” on one side and plain on the other.

Oral Solution:
20 mg per mL clear, colorless, strawberry-flavored oral solution.

6.1 Clinical Trials Experience

Clinical Trials Experience in Pediatric Subjects

Trial A4001031 is an open-label trial in which 103 treatment-experienced, CCR5-tropic, HIV-1–infected pediatric subjects aged 2 to less than 18 years weighing at least 10 kg received SELZENTRY twice daily in combination with OBT. The dose of SELZENTRY was based on body surface area (BSA) and on whether the subject was receiving potent CYP3A inhibito and/or inducers. The median duration of therapy with SELZENTRY was 131 weeks with 7 (b) (4) of subjects receiving study treatment for greater than 48 weeks.

In these 103 children and adolescents, the safety profile through 96 weeks was similar to that for adults. Most of the adverse events reported were mild to moderate; severe (Grade 3 and 4) adverse events occurred in (b) (4)% of (b) (4) The most common adverse drug reaction (all grade (b) (4) reported with twice-daily therapy with SELZE(b) TRY, (b) (4) were vomiting (12%), diarrhea (4%), abdominal pain ((4)%), dizziness (3%) and nausea (b) (4)%).. Maraviroc-related gastrointestinal adverse events (nau ea, vomiting, diarrhea, and abdominal pain/cramps) were observed more commonly in subjects who received the SELZENTRY oral solution ((b) (4)%) compared to those who received SELZENTRY tablets ((b) (4)%).

(b) (4).

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SELZENTRY during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

The following statement was added to the Risk Summary section of the **Pregnancy** section:
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The subheadings of Data and Animal Data were also added to the **Pregnancy** section of the USPI.

The title of Section **8.2** was changed from Nursing Mothers to **Lactation**
The following sentences were revised:
Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving SELZENTRY.

8.4 Pediatric Use

The safety, pharmacokinetic (PK) profile, and antiviral activity of SELZENTRY were evaluated in treatment-experienced, CCR5-tropic, HIV-1-infected pediatric subjects aged 2 to less than 18 years weighing at least 10 kg in an open-label, multicenter clinical trial, A4001031 *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*. Pharmacokinetic data evaluated from intensive and sparse PK sampling in 44 pediatric subjects were similar to those observed in adults receiving recommended doses of SELZENTRY with concomitant medications *[see Clinical Pharmacology (12.3)]*. Sparse PK only was evaluated in additional subjects receiving potent CYP3A inhibitors

(n=47). See *Dosage and Administration (2.4, 2.5)* for dosing recommendations for pediatric patients aged 2 years and older and weighing at least 10 kg.

8.6 Renal Impairment

Maraviroc has not been studied in pediatric patients with renal impairment. There are no data to recommend specific doses of SELZENTRY in pediatric patients with mild to moderate renal impairment *[see Use in Specific Populations (8.4)]*. SELZENTRY is contraindicated in pediatric patients with severe renal impairment or ESRD on regular hemodialysis who are receiving potent CYP3A inhibitors *[see Contraindications (4)]*.

11 Description

SELZENTRY oral solution contains 20 mg per mL of maraviroc and the following inactive ingredients: citric acid (anhydrous), purified water, sodium benzoate, sodium citrate dihydrate, strawberry flavoring (501440T), and sucralose.

12.3 Pharmacokinetics

Effect of Food on Oral Absorption

Coadministration of a 300-mg tablet with a high-fat breakfast reduced maraviroc C_{max} and AUC by 33% and coadministration of 75 mg of oral solution with a high-fat breakfast reduced maraviroc AUC by 73% in healthy adult volunteers. Studies with the tablet formulation demonstrated a reduced food effect at higher doses.

There were no food restrictions in the adult trials (using the tablet formulation) or in the pediatric trial (using both tablet and oral solution formulations) that demonstrated the efficacy/antiviral activity and safety of maraviroc *[see Clinical Studies (14.1, 14.2)]*.

Special Populations, *Pediatric Patients*

The pharmacokinetics of maraviroc in CCR5-tropic, HIV-1–infected, treatment-experienced children aged 2 to less than 18 years (b) (4). In the dose-finding stage of Trial A4001031, doses were administered with food on intensive PK evaluation days and optimized to achieve an average concentration over the dosing interval (C_{avg}) of greater than 100 ng per mL; (b) (4) maraviroc was taken with or without food. The initial dose of maraviroc was (b) (4)

(b) (4)

(b) (4)

Table 13. Maraviroc Pharmacokinetic Parameters in Treatment-Experienced Pediatric Patients Receiving SELZENTRY with Potent CYP3A Inhibitors (without a Potent CYP3A Inducer)

Weight	Dose of SELZENTRY	Maraviroc Pharmacokinetic Parameter Geometric Mean			
		AUC_{12} (ng.h/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
10 kg to <20 kg	50 mg twice daily	(b) (4)			
20 kg to <30 kg	75 mg twice daily				
30 kg to <40 kg	100 mg twice daily				
≥40 kg	150 mg twice daily				

12.4 Microbiology

Antiretroviral Treatment-Experienced Pediatric Subjects (Trial A4001031): In the Week 48 analysis of Trial A4001031 (n = 103), the mechanisms of resistance to maraviroc observed in the treatment-experienced pediatric population were similar to those observed in adult populations: reasons for virologic failure included failing with CXCR4- or dual/mixed-tropic virus, evidence of reduced maraviroc susceptibility as measured by a decrease in maximal percentage inhibition (MPI), and emergence of resistance to background drug in the regimen.

14.2 Clinical Studies in Pediatric Subjects

Trial in CCR5-Tropic, Treatment-Experienced Subjects

Trial A4001031 is an open-label, multicenter trial in pediatric subjects aged 2 to less than 18 years infected with only CCR5-tropic HIV-1. Subjects were required to have HIV-1 RNA greater than 1,000 copies per mL at screening. All subjects (n=103) received SELZENTRY twice daily and OBT. Dosing of SELZENTRY was based on BSA and doses were adjusted based on whether the subject was receiving potent CYP3A inhibitors and/or inducers.

The population was 52% female and 69% black, with mean age of 10 years (range: 2 to 17 years). At baseline, mean plasma HIV-1 RNA was 4.4 $\log_{10}$ copies per mL (range: 2.4 to 6.2 $\log_{10}$ copies per mL), mean CD4+ cell count was 551 cells per mm^3 (range: 1 to 1,654 cells per mm^3), and mean CD4+ percent was 21% (range: 0% to 42%).

At 48 weeks, 48% of subjects treated with SELZENTRY and OBT achieved plasma HIV-1 RNA less than 48 copies per mL and 65% of subjects achieved plasma HIV-1 RNA less than 400 copies per mL. The mean CD4+ cell count (percent) increase from baseline to Week 48 was 247 cells per mm^3 (5%) *[see Clinical Pharmacology (12.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

SELZENTRY film-coated tablets are available as follows:

25- mg, 75- mg, 150- mg, and 300-mg tablets are blue, biconvex, oval, film-coated tablets debossed with “MVC 25”, “MVC 75”, “MVC 150”, or “MVC 300”, respectively, on one side and plain on the other.

25-mg tablets: Bottle of 120 tablets (NDC 49702-233-08).

75-mg tablets: Bottle of 120 tablets (NDC 49702-235-08).

SELZENTRY oral solution is a clear, colorless, strawberry-flavored liquid. Each mL of the solution contains 20 mg of maraviroc. It is packaged in plastic bottles as follows:

Bottle of 230 mL (NDC 49702-237-55). Each bottle is packaged with one press-in bottle adapter and one 10–mL oral dosing syringe with 0.5–mL gradations. The press-in bottle adapter and oral dosing syringe are not made with natural rubber latex. This product does not require reconstitution.

13. Outstanding Issues

None. However labeling negotiations are currently ongoing.

14. Recommendations / Risk Benefit Assessment

NDA 208984 and supplemental NDA 22128 (supporting document 017) containing 48-week data from the pediatric clinical trial A4001031, from a bioavailability study comparing the oral solution to the tablet, and from PK modelling support dosing recommendations for Selzentry® (maraviroc) in combination with other antiretroviral drugs for the treatment of CCR5-tropic HIV-1 infection in treatment-experienced pediatric patients 2 years of age and older weighing at least 10 kg. This reviewer recommends the approval of this NDA and supplemental NDA.

Through the review of this NDA and sNDA, no deficiencies that would preclude the approval of the NDA and sNDA were identified. Maraviroc was studied in a multicenter Phase 1 /2, open-label, non-comparative trial in which 103 pediatric subjects were enrolled and followed for at least 48 weeks. The trial design comprised two stages: Stage 1 was a dose-finding stage and Stage 2 evaluated the safety and efficacy of the maraviroc.

Similar to other pediatric trials which evaluate the safety and effectiveness of ARVs, this trial was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe findings.

Doses used in Stage 1 of Trial A4001031 were based on body surface area and were adjusted for concomitant medications. The appropriate doses to achieve an average exposure of 100 ng/mL or higher for each subject were identified prior to that subject enrolling in Stage 2 of the study. Pharmacokinetic results from Stage 1 and population PK modelling using adult and pediatric data were used to identify appropriate dosing of maraviroc using weight based dosing. The PK results support weight based dosing for patients who weigh at least 10 kg and who are also receiving a CYP3A inhibitor. The results also support use of the adult dose in patients who weigh at least 30 kg and are receiving concomitant medications that are CYP3A neutral. There were insufficient data to make recommendations for dosing for patients who are receiving CYP3A neutral concomitant medications and weigh less than 30 kg and to make recommendations for any patient receiving CYP3A inducers.

After establishing the PK primary endpoint in Part 1 of A4001031 and completion of Part 2 of the trial, partial extrapolation of the antiviral activity of maraviroc in pediatric subjects 2 to <18 years of age was made. The efficacy outcome, as measured by HIV RNA <48 copies/mL, for the overall study population was 47.6% and increased to 65% when measured by HIV RNA <400 copies/mL. The efficacy outcome was similar to that observed in treatment-experienced adults.

The applicant demonstrated an acceptable safety profile for maraviroc in combination with other antiretroviral drugs. Maraviroc was generally safe and well tolerated in pediatric subjects enrolled in this trial. No deaths were reported and serious adverse events were uncommon. Two subjects discontinued the trial prematurely: one due to Grade 1, maraviroc-related vomiting and the other due to pelvic inflammatory disease. Gastrointestinal adverse events were reported more often in subjects who received the oral solution compared to the tablet, but GI adverse events were mild in intensity and resulted in temporary or permanent discontinuation of

study drugs in only 1% of subjects. Adverse events of special interest that have been reported in adults receiving maraviroc occurred in few pediatric subjects, were mild in intensity, and resolved without treatment interruption. No new safety concerns were identified. The observed risks of maraviroc use have been described previously, and the rate and nature of adverse events were similar to those in treatment-experienced adults.

Of note, the size of the safety database in pediatric patients is limited and this trial has continued to follow subjects beyond the Week 48 cutoff.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
The current submission partially fulfills the Pediatric Written Request, and no additional pediatric post-marketing study commitments will be sought. The current submission also fulfills the only Post-Marketing Requirement under Pediatric Research Equity Act (PREA) (see Section 2.5).

Recommendation for Other Postmarketing Requirements and Commitments
None. The applicant will continue to submit PAERS and annual reports (DSURs) for review.

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/s/

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10/07/2016

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