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APPLICATION NUMBER:

208984Orig1s000
022128Orig1s017

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 208984 **SDN**: 000 **DATE REVIEWED:** 08/04/2016
Virology Reviewer: Lisa K. Naeger, Ph.D.

NDA: 208984 SDN000
NDA: 22128 SDN663

Reviewer's Name: Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
Viiv Healthcare
50 Pequot Avenue
New London, CT 06320

Important Dates:
Correspondence Date: May 6, 2016
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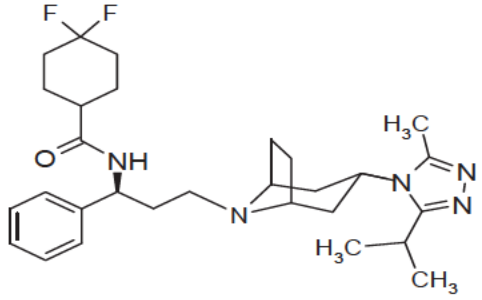
Amendments:
Related/Supporting Documents: NDA-22128.S001

SDN		CDER Stamp Date	Assigned Date
NDA22128	670	06/08/2016	06/09/2016
NDA22128	695	09/16/2016	09/16/2016
NDA208984	019	09/16/2016	09/16/2016

Product Name(s)
Proprietary: Selzentry
Non-Proprietary/USAN: Maraviroc
Code Name/Number: UK-427,857

Chemical Name: 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide
Molecular Formula: $C_{29}H_{41}F_2N_5O$
Structural Formula:



Dosage Form(s): oral solution, 25mg, 75 mg, 150 mg or 300 mg film-coated tablets
Route(s) of Administration: Oral
Indication(s): (b) (4) in combination with other antiretroviral agents; for treatment- (b) (4) CCR5-tropic only HIV-1 (b) (4) (b) (4).

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Dispensed: Rx X OTC_____
Abbreviations:
ARV, antiretroviral; CCR5 or R5, chemokine receptor CCR5; CXCR4, chemokine receptor CXCR4; DM, dual-mixed; EC_{50}, effective concentration at 50%; ENF, enfuvirtide; ESTA, enhanced-sensitivity Trofile assay; GSS, genotypic sensitivity score; HAART, highly active antiretroviral therapy; IC_{50}, inhibitory concentration at 50%; MPI, maximum percentage inhibition; MVC, maraviroc; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor; NR/NP, no replication or non-productive virus; OBT, optimized background therapy; OSS, overall sensitivity score; PBL, peripheral blood lymphocytes; PDTF, protocol-defined treatment failure; PI, protease inhibitor; PR, protease; PSS, phenotypic sensitivity score; RAS, resistance-associated substitutions; RT, reverse transcriptase;

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VIROLOGY REVIEW
NDA: 208984 **SDN**: 000 **DATE REVIEWED:** 08/04/2016
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Executive Summary

In August 2007, maraviroc (MVC) was approved by the Food and Drug Administration (FDA) for the treatment of adults infected with only CCR5-tropic HIV-1 in the United States. [redacted] (b) (4) (b) (4) (b) (4). This NDA supplement has been submitted seeking approval of maraviroc (MVC) combined with OBT in treatment-experienced HIV-1-infected children and adolescents with current ARV therapy failure or with failure of their most recent ARV regimen. The MVC oral and tablet formulations are approvable, from the virology perspective, for children and adolescents 2 to 18 years old.

In the treatment-experienced pediatric Study 1031, the proportion of subjects in all cohorts with HIV-1 RNA <48 copies/mL at Week 24 was 52% (n=53) with a similar response at Week 48 (48% [n=49]). The proportion of subjects with HIV-1 RNA <400 copies/mL at Week 24 was 73% (n=75) and 65% at Week 48 (n=67). The FDA resistance analysis analyzed virologic failures who had a confirmed viral load of >400 copies/mL at rebound or the final timepoint. The FDA analysis determined there were 29 failures in the Week 48 analysis with an additional 9 subjects who failed between Week 48 and 96. The highest proportion of virologic failures was in the oldest age group ≥12 to <18 years (Cohort 4: 57%; n=21) followed by the ≥6 to <12 years age group treated with tablets (Cohort 2: 19%; n=8), the ≥2 to<6 years age group treated with liquid formulation (Cohort 1: 14%; n=5) and ≥6 to <12 years age group treated with the liquid formulation (Cohort 3: 11%; n=4).

The baseline pattern of genotypic resistance from the subjects in Study 1031 showed they were generally infected with virus that showed previous exposure to both NNRTIs and NRTIs. Most subjects did not have major PI resistance-associated substitutions. While numbers were small, there was no indication that more subjects with PDVF had resistance-associated substitutions to drugs from any of these drug classes; i.e., the presence of resistance-associated substitutions at screening was not associated with virologic failure.

Reasons for failure to MVC include tropism change, decreased MVC susceptibility as measured by maximal percentage inhibition (MPI), and/or resistance to a background drug in the regimen. The mechanisms of resistance to MVC observed in this treatment-experienced pediatric population were similar to those observed in adult populations. In the virology Week 48 analysis, there were 5 virologic failure subjects with CXCR4- or dual-mixed (DM)-tropic virus at the failure time point (2 of whom had evidence of DM-tropic virus at baseline), 2 virologic failures with evidence of reduced MVC susceptibility at failure as measured by a decrease in maximal percentage inhibition (MPI), and 4 virologic failures with evidence of emergent resistance-associated substitutions in RT or protease in their virus to a background drug in their regimen.

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NDA: 208984 **SDN**: 000 **DATE REVIEWED:** 08/04/2016
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1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA supplement is approvable, with respect to virology, for dosing in treatment-experienced children and adolescents infected with only CCR5-tropic HIV-1 who have current ARV therapy failure or with failure of their most recent ARV regimen.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are no recommendations for Phase 4 commitments for this NDA submission.

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2. Summary of OND Virology Assessments

The FDA resistance analysis analyzed virologic failures who had a confirmed >400 copies/mL at rebound or final timepoint. The FDA analysis determined there were 29 failures in the Week 48 analysis with an additional 9 subjects who failed between Week 48 and 96. The highest proportion of virologic failures was in the oldest age group ≥12 to <18 years (Cohort 4: 57%; n=21) followed by the ≥6 to <12 years age group treated with tablets (Cohort 2: 19%; n=8), the ≥2 to<6 years age group treated with liquid formulation (Cohort 1: 14%; n=5) and ≥6 to <12 years age group treated with the liquid formulation (Cohort 3: 11%; n=4).

The baseline pattern of genotypic resistance from the subjects in Study 1031 showed they were generally infected with virus that showed previous exposure to both NNRTIs and NRTIs. Most subjects did not have major PI resistance-associated substitutions. While numbers were small, there was no indication that more subjects with PDVF had resistance-associated substitutions to drugs from any of these drug classes; i.e., the presence of resistance-associated substitutions at screening was not associated with virologic failure.

Reasons for failure to MVC include tropism change, decreased MVC susceptibility as measured by maximal percentage inhibition (MPI), or resistance to background drug. Six subjects were found with dual-mixed (DM)-virus at or after the initial failure time point. Three of the 6 subjects with DM virus detected at failure (2 from Cohorts 3 and 1 from Cohort 4) also had detectable DM virus at Baseline. Two virologic failures had evidence of reduced MVC susceptibility as measured by a decrease in maximal percentage inhibition (MPI = 92%) at rebound. There were 5 virologic failure subjects with genotypic evidence of emergence of resistance-associated substitutions in RT or protease in their virus to a drug included in the regimen they received; 4 of these subjects also had emergent detectable phenotypic resistance to a drug in their regimen. Overall, the mechanisms of resistance to MVC observed in this treatment-experienced pediatric population were similar to those observed in adult populations.

3. Administrative

3.1. Reviewer's Signature(s)

_____**Lisa K. Naeger**_____
[Lisa K. Naeger, Ph.D.]
Sr. Clinical Virologist, HFD-530

3.2. Concurrence

HFD-530/Micro TL ____**Julian O'Rear**___Signature _____Date

4. OND Virology Review

4.1 Important Milestones in Product Development

In August 2007, maraviroc (MVC) was approved by the Food and Drug Administration (FDA) for the treatment of adults infected with only CCR5-tropic HIV-1 in the United States. (b) (4)

(b) (4)

(b) (4)

4.2 Methodology

All subjects underwent phenotypic testing for the presence of CCR5-tropic virus exclusively, genotypic and phenotypic testing for resistance to reverse transcriptase inhibitors, PIs, and phenotypic testing for fusion inhibitor susceptibility. Screening tropism as well as genotype and phenotype results were planned to be available approximately 3 to 5 weeks after receipt of samples. Subjects were either on stable ARV regimen for at least 4 weeks prior to screening or on no ARV regimen for at least 4 weeks prior to screening. If a subject was already on ARV therapy, they were required to remain on their existing regimen during the screening period. The proportion of subjects achieving HIV-1 RNA <48 or <400 copies/mL was assessed at 24 and 48 weeks or at the time of discontinuation from the study.

HIV-1 RNA was quantified by Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test.

VIRUS TROPISM
Virus tropism was determined using the Monogram Biosciences Trofile™ viral tropism assay. The current version of the Trofile assay, with enhanced sensitivity, was used throughout the study. The recommended minimum concentration for successful assessment is plasma HIV-1 RNA <1,000 copies/mL. However, in order to maximize data collection, appropriate samples with plasma HIV-1 RNA ≥400 copies/mL were submitted for testing at virologic failure. This Trofile Assay was described in Drug Master File (DMF (b) (4)) submitted June 3, 2008 and reviewed in NDA22128 SE1.

Sensitivity of Trofile™ Assay
At the 1% level of CXCR4-using minor variant, the ES-Trofile assay detected 100% (16/16) of the mixtures. At the 0.3% level of CXCR4-using minor variant, ES-Trofile assay detected 100% (16/16) of the mixtures. At the 0.1% level, the ES-Trofile assay detected 81% (13/16) of the mixtures.

VIRAL SUSCEPTIBILITY TO MVC
The Monogram HIV-1 Entry Assay was used to measure reductions in MVC susceptibility and was reviewed in NDA-22128 SE1.

Overview of the PS Entry Assay (From NDA22128 SE1)
In the PS Entry Assay, an HIV-1 genomic vector (derived from NL4-3) that contains a luciferase indicator gene cassette in the envelope region is cotransfected with a plasmid that expresses HIV-1 envelope. The HIV-1 envelope sequences may be derived from a

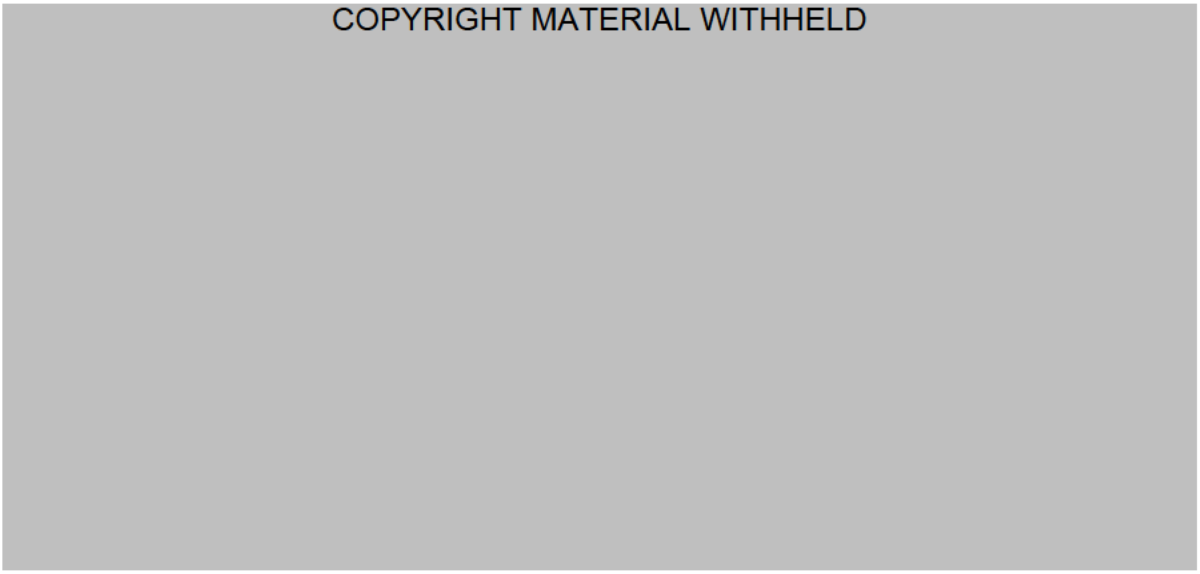
patient HIV-1 sample or from various well-characterized laboratory strains. The patient derived sequences are tested as pools or libraries of sequences that capture the diversity of the viral quasi-species within a patient sample, or alternatively, as molecular clones to further characterize correlations between envelope sequences (genotype) and drug susceptibility (phenotype). Viruses harvested from transfected Human Embryonic Kidney (HEK) 293 cells are used to infect U87 cells that express CD4 and either the CCR5 coreceptor, the CXCR4 coreceptor, or both CCR5 and CXCR4. Infection is performed in the absence of drug and over a wide range of drug concentrations (≥ 4 $\log_{10}$). Inhibition curves are fit to the data using non-linear least squares. Bootstrapping is used to calculate the drug concentrations required to inhibit virus replication by 50% (IC_{50}). Non-competitive entry inhibitors: Susceptibility to non-competitive inhibitors of virus entry, e.g. maraviroc, is measured as the reduction in percent maximum inhibition, i.e. < 100%, at high (saturating) drug concentrations, commonly referred to as the "plateau" phenotype. For these drugs, the IC_{50} fold change is not an appropriate measure of changes in susceptibility (Westby et al., J Virol 2007, Tsibris et al., J Virol 2008, Watson et al., Molec Pharmacol 2005).

Assay Performance Characterization:

Assay Accuracy

Assay accuracy was evaluated by comparing the rank order reductions in maraviroc percent maximum inhibition measured in the PS Entry Assay versus published values using a conventional PBMC infectivity assay. The rank order of maraviroc susceptibility measures of 5 env molecular clones determined using the PS Entry Assay were highly concordant with the published (Westby et al., J Virol 2007) rank order values obtained using a conventional PBMC infectivity assay (Figure 1).

Figure. 1. PS Entry Assay Accuracy: Concordance of PS Entry Assay Results and Conventional PBMC Infectivity Assay (from Westby et al., J Virol 2007).



Assay Precision (intra-assay variation)
Assay precision was assessed by determining the variation of percent maximum inhibition values within a single assay batch or "run" among 10 replicates tests of 9 env clones exhibiting a range of susceptibility to maraviroc. Median maraviroc percent maximum inhibition ranged from 57% to 100% for these 9 envelope clones. Assay precision for 8 of the 9 env clones (samples 2-9) had percent maximum inhibition values varying by ≤ 6 percentage points and coefficients of variation (CV) < 2.8% for 10 replicate tests. The precision of sample 1 was significantly lower with percent maximum inhibition values ranging from 12%-63% and a CV of 31.5%.

Assay Reproducibility (inter-assay variation)
Assay reproducibility was assessed by determining the variation of percent maximum inhibition values in three experiments:

- Experiment A: Nine env clones exhibiting a range of susceptibility to maraviroc were tested in 3 assay batches or "runs" conducted over a 14-day period by multiple operators using 2 different lots of critical reagents
- Experiment B: Paired baseline and on treatment virus samples from 5 patients receiving MVC treatment were tested in 2 separate assay runs
- Experiment C: Forty-four randomly selected maraviroc naïve patient viruses submitted to Monogram for routine coreceptor tropism (Trofile) testing were tested in 2 separate assay runs.

Experiment A: Median maraviroc percent maximum inhibition ranged from 61% to 100% for these 9 envelope clones. Assay reproducibility for 8 of 9 env clones (samples 2-9) had percent maximum inhibition values varying by ≤ 17 percentage points and CVs of ≤ 7.3% over 3 assay runs (batches). The reproducibility of sample 1 was significantly lower with percent maximum inhibition values ranging from 12%-82% and a CV of 30.5%. In this experiment, intra-assay variation was trended higher in batch 1 (precision testing) than batches 2 and 3. Overall, intra-assay variation was less than inter-assay variation for samples exhibiting reductions in maraviroc susceptibility (PMI < 100%).

Experiment B: Assay reproducibility (defined as run 1 minus run 2) averaged 5.2 percentage points (range 3 to 9) for all on-treatment patient samples exhibiting maraviroc percent maximum inhibition values ranging from 55-94%. Assay reproducibility averaged 0.2 percentage points (range -1 to 0) for all pre-treatment (day 1) patient samples exhibiting maraviroc percent maximum inhibition values ranging from 99-100% at treatment baseline.

Experiment C: Assay reproducibility (run 1 minus run 2) differed by ≤1 percentage point for all duplicate test results for 44 maraviroc naïve patient samples submitted to Monogram for routine coreceptor tropism (Trofile™) testing.

Assay Linearity
Assay linearity was assessed by determining the variation of percent maximum inhibition values over a broad (~2 $\log_{10}$) range of infectivity as assessed by the luciferase activity of the virus inoculums. Variation (max/min) in the percent maximum inhibition of virus inoculums that spanned a 2 $\log_{10}$ range of infectivity varied ≤ 1.3 fold (CV ≤ 9.1%) for clones (samples 3, 4) that exhibited reduced maraviroc susceptibility (51% to 76%

inhibition) and ≤1.02 fold (CV≤ 1.65) for clones (samples 7, 8, 59) that were susceptible to maraviroc (100% inhibition).

Assay Sensitivity to Detect Minor Variants
The sensitivity to detect minor variants was assessed by determining the percent maximum inhibition of 10% incremental mixtures of virus preparations that exhibit susceptibility or resistance (reduced susceptibility) to maraviroc. Mixtures were prepared using susceptible and resistant clones that exhibit similar levels of infectivity (luciferase RLU). Susceptible and resistant clones and each mixture were tested in a single assay run. Maraviroc resistant variants with percent maximum inhibitions ranging from 47- 69% were detected when present at 20-30% of the total virus population.

VIRUS SUSCEPTIBILITY TO OBT REGIMEN
Phenotypic and genotypic susceptibility to reverse transcriptase and PIs was evaluated at screening using the Monogram Biosciences PhenoSense™ Genotype (PSGT) assay; fusion inhibitor susceptibility was assessed using the PhenoSense Entry assay. PSGT output included a viral subtype assessment. Samples from a confirmatory PDVF visit or early termination of MVC were planned to be analyzed if the plasma HIV-1 RNA was ≥400 copies/mL. Samples from subjects experiencing PDVF who received an integrase strand-transfer inhibitor (INSTI) also had a PhenoSense Integrase analysis performed both pre- and on-treatment.

PROTOCOL DEFINED VIROLOGIC FAILURE (PDVF)
The occurrence of any one of the following criteria constituted protocol-defined virologic failure (PDVF):

- Decrease from baseline plasma HIV-1 RNA <1 $\log_{10}$ and plasma HIV-1 RNA >400 copies/mL starting at Week 12 and confirmed at Week 16;
- Decrease from baseline plasma HIV-1 RNA <2.0 $\log_{10}$ and plasma HIV-1 RNA >400 copies/mL at Week 24 OR plasma HIV-1 RNA >10,000 copies/mL at Week 24, and confirmed 14–21 days later;
- Increase from nadir plasma HIV-1 RNA of ≥1 $\log_{10}$ (≥1,000 copies/mL if nadir plasma HIV-1 RNA <48 copies/mL) at any time, and confirmed 14–21 days later.

4.3 Major virological issues that arose during product development

At the preNDA meeting, the Division requested that the sponsor submit genotypic and phenotypic resistance data (for MVC and DRV), tropism data and viral load data for all virologic failures in the MVC+DRV/r arm from the pediatric study, A4001031, in accordance with the HIV resistance template format.

4.4 State of antiretrovirals used for the indication (s) sought*:*

An estimated 33 million people including 2.5 million children less than 15 years worldwide were infected with HIV-1 in 2007. Pediatric HIV infection is a leading cause of morbidity and mortality worldwide. Of 2.1 million deaths due to HIV/AIDS that occurred in 2007, approximately 330,000 were among children. Approximately 90% of these

children were infected through perinatal transmission. Of these, approximately 15-20% were infected during pregnancy, 50% during labor and delivery, and the remaining 33% while breastfeeding. Since HAART regimens have been introduced, the number of AIDS cases and deaths from HIV has decreased dramatically. HAART does not clear HIV-1 from subjects and even though the number of HIV-1 RNA copies is reduced to undetectable levels, HIV-1 re-emerges quickly after discontinuation of HAART. Therefore, with the currently available regimens, it is likely that most HIV-infected subjects will require antiretroviral therapy throughout their lives.

There are currently 27 FDA-approved anti-HIV drugs including INSTIs (dolutegravir, elvitegravir, and raltegravir), NNRTIs (delavirdine, efavirenz, etravirine, nevirapine, rilpivirine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine), PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir), the fusion inhibitor enfuvirtide, and the CCR5 coreceptor antagonist maraviroc with numerous fixed-dose combinations available among these. Maraviroc inhibits the interaction between the viral envelope glycoprotein gp120 and the human CCR5 receptor membrane protein and inhibits entry of the virus into the cell. Enfuvirtide is a gp41 fusion inhibitor preventing the fusion of the viral and cellular membranes necessary for virus entry. NRTIs mimic nucleosides and target HIV-1 RT by competing with natural deoxynucleoside triphosphates for binding to RT and by incorporating into newly synthesized viral DNA resulting in chain-termination. NNRTIs inhibit HIV-1 RT by binding near the catalytic site of RT and acting as noncompetitive inhibitors. INSTIs inhibit the viral encoded integrase which catalyzes the integration of linear viral DNA into host cell DNA forming the provirus. PIs work at a late stage of viral replication to prevent virus production from infected cells. They block the HIV-1 protease enzyme, which is necessary for the production of mature virions, resulting in defective particles which are unable to infect new cells.

Unfortunately, HIV-1 develops resistance to antiretroviral drugs over time usually from the accumulation of multiple mutations. HAART regimens are also associated with acute toxicities such as diarrhea, kidney stones, rash, CNS toxicities and hepatotoxicity. Long-term toxicities from antiretroviral therapies include mitochondrial toxicities associated with NRTIs (lactic acidosis, myopathy, neuropathy, pancreatitis), and disorders of lipid metabolism (dyslipidemia) and glucose metabolism (lipodystophy, hypercholesterolemia, hypertriglyceridemia) associated with PIs. These tolerability issues make compliance to therapy more challenging. Compliance is an important determinant of successful virologic suppression for subjects on HAART. Regimens that are well-tolerated and easy to administer with a few pills once daily are likely to aid in subject compliance and improve clinical outcomes. There is a need for new anti-HIV drugs that are well-tolerated and easy to use with new modes of action and low likelihood of viral resistance development, especially for children and adolescents. Additionally, drugs that are effective against viruses resistant to all currently approved drugs are needed for the heavily treatment-experienced adult and pediatric population.

4.5 Clinical Studies

STUDY A4001031
An Open-Label, Multicenter, Multiple-Dose Pharmacokinetic, Safety and Efficacy Trial of Maraviroc in Combination with Optimized Background Therapy for the Treatment of Antiretroviral-Experienced CCR5-Tropic HIV-1 Infected Children 2 - <18 Years of Age

STUDY A4001031 is an open-label, 2-stage, age-stratified, non-comparative, multi-center study to evaluate the safety, efficacy, tolerability, and PK/dosing of multiple doses of MVC combined with OBT in ARV treatment-experienced children and adolescents who were failing current ARV therapy or had failed their most recent ARV regimen, defined by plasma HIV-1 RNA ≥1,000 copies/mL, were infected with only CCR5 (R5) HIV-1, and had ARV experience ≥6 months, or intolerance to at least 2 ARV drug classes.

Subjects were stratified by age at Day 1 and MVC formulation into one of the following cohorts:

- Cohort 1: ≥2 - <6 years of age, MVC liquid formulation;
- Cohort 2: ≥6 - <12 years of age, MVC tablet formulation;
- Cohort 3: ≥6 - <12 years of age, MVC liquid formulation, and
- Cohort 4: ≥12 - <18 years of age, MVC tablet formulation.

The study was conducted in 2 stages. The target for Stage 1 was to enroll a minimum of 42 subjects, 12 in Cohort 1 and 10 each in Cohorts 2 to 4. The target for Stage 2 was to enroll a minimum of 58 additional subjects, with a minimum of an additional 10 subjects in each cohort for evaluation of safety after finding the appropriate dose. Approximately 125 total subjects were planned to be enrolled to yield 100 subjects with 24-week safety data.

The primary analysis was the proportion of subjects reaching <400 and <48 copies/mL at Week 24 and 48 endpoints using the FDA snapshot algorithm. The proportion of subjects with HIV-1 RNA <400 copies/mL at Week 24 was 73% (75 subjects) and 65% at Week 48 (67 subjects) (Table 1). At Week 24, the proportion of subjects with HIV-1 RNA <400 copies/mL for all 4 cohorts ranged from 63% to 90% and at Week 48 ranged from 51% to 77% with the lowest efficacy observed in the adolescent group, Cohort 4.

The proportion of subjects with HIV-1 RNA <48 copies/mL at Week 24 was 52% (n=53) and a similar response was maintained at Week 48 (48%; n=49) (Table 2). At Week 24, the proportion of subjects with HIV-1 RNA <48 copies/mL for all 4 cohorts ranged from 25% to 65% and at Week 48 ranged from 39.5% to 55% (Table 2).

Table 1. Proportion of Subjects with HIV-1 RNA <400 copies/mL through Week 48
(page 150 Clinical Study Report)

	Cohort 1 (N=16) n (%)	Cohort 2 (N=31) n (%)	Cohort 3 (N=13) n (%)	Cohort 4 (N=43) n (%)	Total (N=103) n (%)
HIV-1 RNA <400 copies/mL	12 (75.0)	24 (77.4)	9 (69.2)	22 (51.2)	67 (65.0)
HIV-1 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: Section 14.2, Table 14.2.1.6.2.
Abbreviations: AE=adverse event; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; ISOD=in-study, off-drug; MSDF=missing, switch, discontinuation = failure; N=number of subjects in cohort; n=number of subjects with observations; RNA=ribonucleic acid.
[#]Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects who are equal to or above 400 copies/mL in the 48 week window. Note: One death event occurred at post-Week 48 in an ISOD subject, see Section 11.5.3.1.
* Includes subjects who discontinued study drug or study due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on-treatment during the specified window.
** Other includes: withdrew consent, loss to follow-up, moved, etc.
FDA's Snapshot (MSDF) algorithm approach is used for determining visit windows around study day. Study day is calculated as event - start dose date of final selected dose+1. Stage 1 subject's final dose is defined as the first day of the selected dose for Stage 2. Stage 2 subjects are assumed to start on their selected dose.
[a]MSDF analysis was used.

Table 2. Proportion of Subjects with HIV-1 RNA <48 copies/mL through Week 48
(page 151 Clinical Study Report)

	Cohort 1 (N=16) n (%)	Cohort 2 (N=31) n (%)	Cohort 3 (N=13) n (%)	Cohort 4 (N=43) n (%)	Total (N=103) n (%)
HIV-1 RNA <48 copies/mL	8 (50.0)	17 (54.8)	7 (53.8)	17 (39.5)	49 (47.6)
HIV-1 RNA ≥48 copies/mL[#]	8 (50.0)	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: Section 14.2, Table 14.2.1.6.2.
Abbreviations: AE=adverse event; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; ISOD=in-study, off-drug; MSDF=missing, switch, discontinuation = failure; N=number of subjects in cohort; n=number of subjects with observations; RNA=ribonucleic acid.
[#]Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects who are equal to or above 48 copies/mL in the 48 week window.
* Includes subjects who discontinued study drug or study due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on-treatment during the specified window. Note: One death event occurred at post-Week 48 in an ISOD subject, see Section 11.5.3.1.
** Other includes: withdrew consent, loss to follow-up, moved, etc.
FDA's Snapshot (MSDF) algorithm approach is used for determining visit windows around study day. Study day is calculated as event - start dose date of final selected dose+1. Stage 1 subject's final dose is defined as the first day of the selected dose for Stage 2. Stage 2 subjects are assumed to start on their selected dose.
[a]MSDF analysis was used.

4.6 Clinical Virology

Analysis of Protocol Defined Virologic Failure through Week 48

PDVFs were identified during the course of the Week 48 study period and subjects were discontinued due to insufficient clinical response. This group was assessed for virus susceptibility (genotype and phenotype) at screening and at the time of failure, virus tropism at screening and time of failure, and the association between screening susceptibility and virologic response through Week 48.

The sponsor states that 22% (n = 23) of subjects experienced PDVF through Week 48 (Table 3). The FDA resistance analysis analyzed virologic failures who had a confirmed viral load >400 copies/mL at rebound or final timepoint. The FDA analysis determined there were 29 failures in the Week 48 analysis with an additional 9 subjects who failed between Week 48 and 96 (Table 4). The highest proportion was in the oldest age group ≥12 to <18 years (Cohort 4: 57%; n=21) followed by the ≥6 to <12 years age group treated with tablets (Cohort 2: 19%; n=8), the ≥2 to<6 years age group treated with liquid formulation (Cohort 1: 14%; n=5) and ≥6 to <12 years age group treated with the liquid formulation (Cohort 3: 11%; n=4).

Table 3. Subject Outcomes at Week 48 (page 155 Clinical Study Report)

	Cohort 1 N=16	Cohort 2 N=31	Cohort 3 N=13	Cohort 4 N=43	Total N=103
Response n (%)	8 (50.0)	17 (54.8)[a]	7 (53.8)	17 (39.5)	49 (47.6)
PDVF[b] n (%)	3 (18.8)	4 (12.9)[a]	3 (23.1)	13 (30.2)	23 (22.3)
Other Failure (Remainder) n (%)	5 (31.3)	10 (32.3)	3 (23.1)	13 (30.2)	31 (30.1)

Source: Derived from Section 14.2, Table 14.2.4.3.1.
Abbreviations: HIV=human immunodeficiency virus; N, n=number of subjects; PDVF=protocol-defined virologic failure; RNA=ribonucleic acid.
[a] One subject (Subject 10291001) met PDVF criteria, but on discontinuation at Week 48, showed full virologic suppression (plasma HIV-1 RNA <48 copies/mL) and was included here in the response category.
[b] PDVF was flagged using insufficient clinical response outcomes.

Table 4. FDA Analysis: Virologic Failures in Study 1031 (n=38)

SUBJID	Group	Regimen	NONRECAT (Failure visit)	Baseline RT and PR Substitutions	Emerging RAS	Phenotype at Failure (bold if emerged)	Tropism at Failure (MPI)
10071002	4	ABC LAM ATV RAL	Non compliance (8 weeks)	T69T/A K103N PR: A71T	K66K/R		R5 (99.6%)
10201004	2	ABC D4T LPV/R	Rebound (Week 16)	K101P/Q K103N/S M184V		LAM-R	R5 (96%)
10201008	3	LAM D4T LPV/R	Rebound (Week 20)	PR: M46L	K103N **M184V**	**LAM-R**	X4/DM (DM at BL)
10201018	4	D4T AZT LPV/R	Never Suppressed (Week 96)				R5 (100%)
10201033	3	ABC D4T	Rebound	K103N			R5

		LPV/R	(Week 16)	M184V G196E			(96%)
10201041	4	LAM D4T LPV/R	Rebound (Week 40)	K103N	G196G/E PR:L89L/I/ M		R5 (99%)
10201043	4	ABC LAM LPV/R	Rebound (Week 40)	D67N K70R K101K/E V106M V179V/I M184V K219E PR: V82I	K64K/R H221H/Y	ABC-R LAM-R	DM
10201057	4	LAM D4T LPV/R	Rebound (Week 96)	M184I/V			R5 (99%)
10201069	4	LAM D4T LPV/R	Rebound (Week 12)	K103N V106M Y188Y/C G196K	**D67G**		R5 (99%)
10201076	4	ABC LAM LPV/r	Rebound (Week 16)				R5 (99%)
10201077	4	ABC LAM LPV/r	Nonresponse (Week 16)	K103N M184V		LAM-R	R5 (98%)
10201087	4	AZT LAM LPV/r	Rebound (Week 40)	K103N V108I M184V	PR: V77V/I	LAM-R	R5 (97%)
10201090	4	DDI AZT LPV/R	Nonresponse (Week 12)	K103N M184V K219Q			R5 (99%)
10201096	4	ABC LAM LPV/r	Rebound (Week 20)	K103N V106M G196D			R5 (99%)
10201097	1	LAM AZT LPV/R	Rebound (Week 24)	E138A			R5 (99%)
10201103	2	LAM AZT LPV/R	Rebound (Week 48) resuppressed	M184V		LAM-R	R5 (92%)
10201104	1	LAM AZT LPV/R	Rebound (Week 72)	L74V M184V	**M41M/L** PR: P53F/L	LAM-R	NR
10201109	1	LAM AZT LPV/R	Nonresponse (Week 12)	A98A/G M184V PR: V82V/I		LAM-R	R5 (99%)
10201113	2	LAM AZT LPV/R	Rebound (Week 40)	M184V G190A	K103K/N	LAM-R	R5 (99%)
10221003	2	TDF AZT LPV/R	Rebound (Week 48)				R5 (99%)
10291001	2	ABC LAM LPV/r	Rebound (Week 40)				R5 (99%)
10291014	4	TDF FTC ATV/r	Non Compliance		T69T/A		R5 (99%)

			(Week 96)				
10322001	4	TDF FTC DRV/r	Rebound (Week 16)	S68S/G L74V V106I Y115F Y181C M184V		FTC-R (BL)	DM (DM at BL)
10371003	4	LAM RAL TPV/r	Rebound/ Nonresponse (Week 96)	K65R S68G K70R V75I Y115F Q151M G190A L210F K219E PR: D30N L33F M36L I50I/V F53F/L I54I/V V82A N88D	**M41L** V189I PR: M36I R57R/K **I84V**	LAM-R **TPV-R**	NR
10451011	4	LAM EFV LPV/r	Rebound (Week 24)	M41L D67N K101Q V118I M184V L210C/W T215C/D/G/Y PR: V82A		LAM-R	R5 (99%)
10461001	4	LAM TDF LPV/R	Non Compliance (Week 12)	D67N T69D A98G K101E G190A L210S		LAM-R	R5 (99%)
10571004	4	TDF FTC DRV/R	Nonresponse/ Rebound (Week 16)	M41M/L A98S E138E/Q V179V/I Y181Y/C T215D PR: A71A/T V77V/I	NR	NR	NR
10651002	4	ABC TDF NVP	Rebound (Week 16)	M41L D67N V118I M184V G196E L210E T215Y H221Y PR: V32I L33F M36I M46I I47V I54M A71V G73G/C/D/Y I84V L90M	**K103N** T165A	ABC-R **TDF-R NVP-R**	R5 (96%)
10651008	2	AZT LAM LPV/R	Rebound (Week 20)	K103N Y181C M184V H221C/Y		LAM-R	R5 (99%)
10651010	4	ABC AZT LPV/R	Rebound (Week 96)	S68G M184V PR: V77I	PR: K43K/R R57R/K		R5 (100%)
10651026	2	ABC AZT LPV/R	Rebound (Week 20)	A98G K103N M184V P225H	K101K/Q		DM
10831007	3	ABC AZT	Nonresponse	PR: V82I	PR:		DM

		LPV/R	(Week 20)		K20K/R		
10831008	4	LAM TDF LPV/R	Rebound (Week 72)	K103K/N M184V PR: V77I		LAM-R	R5 (100%)
10832002	2	ABC LAM LPV/R	Rebound (Week 72)	K67N S68S/G K70R A98G K103N V179V/I G190A T215F K219Q	NR	NR	NR
10832007	1	ABC LAM LPV/R	Nonresponse (Week 32)	M41L D67N T69T/A L74I A98S K103N M184V T215Y K219K/Q PR: V82I		ABC-R LAM-R	NR
10871006	1	DDI AZT RAL	Rebound (Week 16)		PR: I47I/M M36M/I		R5 (99%)
10881002	4	TDF AZT ATV/R	Rebound (Week 16)	K103S M184V G190A L210L/I			R5 (99%)
10881004	3	ABC AZT LPV/R	Rebound (Week 72)	K103N M184V P225H PR: V77I			DM (DM at BL)

Italicized Subject ID's numbers were failures outside the Week 48 window.
NR: non-reportable
BL: present at Baseline

Viral Susceptibility and Response

The baseline pattern of genotypic resistance indicates that subjects were generally infected with virus that showed previous exposure to both NNRTIs and NRTIs. Virus from 23 subjects did not have detectable NNRTI resistance-associated substitutions present, while 14 had ≥3 NNRTI resistance-associated substitutions (Table 5). There were relatively few subjects without any NRTI resistance-associated substitutions (18/103; Table 5) and >3 NRTI resistance-associated substitutions was observed in virus from 23 subjects. Most subjects (81/103) did not have major PI resistance-associated substitutions. While numbers were small, there was no indication that more subjects with PDVF had resistance-associated substitutions to drugs from any of these drug classes.

The sponsor states that the subjects with PDVF appear generally to have lower compliance to both the MVC and OBT elements of their regimens.

Table 5. Screening RTI and PI RAMs by Outcome
(page 161 Clinical Study Report)

Screening Resistance-associated mutations:	Response (n=49)	PDVF (n=23)	Other Failure (n=31)
NRTI			
None	8 (16.3)	5 (21.7)	5 (16.1)
Any	41 (83.7)	18 (78.3)	26 (83.9)
Of which >3 RAMs	14 (28.6)	5 (21.7)	4 (12.9)
NNRTI			
None	10 (20.4)	3 (13.0)	10 (32.3)
Any	39 (79.6)	20 (87.0)	21 (67.7)
Of which >3 RAMs	8 (16.3)	2 (8.7)	4 (12.9)
Major PI			
None	34 (69.4)	20 (87.0)	27 (87.1)
Any	15 (30.6)	3 (13.0)	4 (12.9)
Of which >3 RAMs	5 (10.2)	1 (4.3)	1 (3.2)

Source data: Section 14.2, Table 14.2.4.4.1.
Abbreviations: IAS=international antiviral society; n=number of subjects with observations; NNRTI=non-nucleoside reverse-transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PDVF= protocol-defined virologic failure; PI=protease inhibitor; RAM=resistance-associated mutation; RTI=reverse transcriptase inhibitor; USA=United States of America.
[1] Wensing et al., 2014.[16]

Tropism On-treatment of Virologic Failures

Of the 37 virologic failure subjects with on-treatment tropism determination, 29 subjects were virologic failures in the Week 48 analysis. Six subjects (10201008, 10201043, 10322001, 10651026, 10831007, 10881004) were found with dual-mixed (DM)-virus at or after the initial failure time point (Table 6). Three of the 6 subjects with DM virus detected at failure (2 from Cohorts 3 and 1 from Cohort 4) also had detectable DM virus at Baseline (Table 6). The other subjects with only R5 virus detected at baseline had virus that showed maximal percent inhibition [MPI] of 99.9% at baseline to MVC (1 did not have MVC susceptibility determined).

Table 6. Virologic Failures with Tropism Changes

SUBJID	Group	Regimen	NONRECAT (Failure visit)	Baseline RT and PR Substitutions	Emerging RAS	Phenotype at Failure (bold if emerged)	Tropism at Failure (MPI)
10201008	3	LAM D4T LPV/R	Rebound (Week 20)	PR: M46L	K103N **M184V**	**LAM-R**	X4/DM (DM at BL)
10201043	4	ABC LAM LPV/R	Rebound (Week 40)	D67N K70R K101K/E V106M V179V/I M184V K219E PR: V82I	K64K/R H221H/Y	ABC-R LAM-R	DM
10322001	4	TDF FTC	Rebound	S68S/G L74V		FTC-R (BL)	DM

		DRV/r	(Week 16)	V106I Y115F Y181C M184V			(DM at BL)
10651026	2	ABC AZT LPV/R	Rebound (Week 20)	A98G K103N M184V P225H	K101K/Q		DM
10831007	3	ABC AZT LPV/R	Nonresponse (Week 20)	PR: V82I	PR: K20K/R		DM
10881004	3	ABC AZT LPV/R	Rebound (Week 72)	K103N M184V P225H PR: V77I			DM (DM at BL)

BL: present at Baseline

All 5 subjects with DM virus on-treatment were treated with 2 NRTIs and a boosted PI. In 3 of the 5 subjects, full susceptibility of these drugs was demonstrated pre-treatment, while the other 2 received background regimens with one drug for which their virus had reduced susceptibility (Table 6). However, according to the sponsor, whenever the weighted scoring was considered, all 5 subjects were considered to have received a regimen with reduced antiviral activity due in part to the re-use of drugs from the failing regimen immediately prior to starting study treatment. On-treatment, 2 subjects showed further susceptibility reduction to their background regimens (Subject 10201008 and Subject 10201043).

Viral Susceptibility to MVC of Virologic Failures with CCR5-Tropic Virus

Three virologic failures had evidence of reduced MVC susceptibility as measured by a decrease in maximal percentage inhibition (MPI) (Table 7). Subject 10201033 in Cohort 3 had a MPI of 92% at Week 16 on confirmation; however, an increase (MPI 96%) was subsequently observed at the next visit, at the time when the subject discontinued treatment. Subject 10201103 in Cohort 2 had a MPI of 92% at Week 48. Another failure subject, Subject 10201004 in Cohort 2 had reduced susceptibility to MVC pre-treatment with a 89% MPI, but a MPI of 96% during treatment.

Table 7. R5-Tropic Virologic Failures with Evidence of Reduced MVC Susceptibility

SUBJID	Group	Regimen	NONRECAT (Failure visit)	MVC (MPI) at Screening	MVC (MPI) at Failure
10201033	3	ABC D4T LPV/R	Rebound (Week 16)	SC: 98%	WK16: 92% EOT: 96%
10201004	2	ABC D4T LPV/R	Rebound (Week 16)	SC: 89%	EOT: 96%
10201103	2	LAM AZT LPV/R	Rebound (Week 48) resuppressed	SC: 97%	WK 48: 92%

Emergence of Resistance-Associated Substitutions for Other ARVs during Therapy

There were 5 virologic failure subjects with evidence of emergence of resistance-associated substitutions in RT or protease in their virus to a drug included in the regimen they received; 4 of these subjects also had emergent detectable phenotypic resistance to a drug in their regimen (Table 8).

- Subject 10201008 had emergent M184V and resistance to lamivudine at rebound (Week 20). The sponsor stated that this subject had previously received lamivudine for approximately 6 years. This subject also had evidence of X4/DM-tropic virus at rebound and baseline.
- Subject 10201069 had emergent NRTI resistance-associated substitution, D67G at rebound (Week 12).
- Subject10201104 had emergent NRTI resistance-associated substitution, M41M/L at rebound (Week 72).
- Subject10371003 had the emergent NRTI resistance-associated substitution, M41M/L, and the protease resistance-associated substitution, I84V, with associated phenotypic resistance to TPV at rebound (Week 96).
- Subject 10651002 had emergent NNRTI resistance-associated substitution, K103N, at rebound (Week 16) which conferred resistance to nevirapine. The sponsor states that this subject had few treatment options with multiple NRTI and major PI resistance-associated substitutions at screening and prior treatment with multiple NRTIs and PIs, efavirenz, nevirapine and raltegravir. The only active background drug in their ARV regimen prior to study treatment, as assessed using the weighted OBT susceptibility score, was nevirapine.

Subject 10201104 and Subject 10371003 were virologic failures after Week 48.

Table 8. Subjects with PDVF and Emergent Resistance-Associated Substitutions On-treatment

SUBJID	Group	Regimen	NONRECAT (Failure visit)	Baseline RT and PR Substitutions	Emerging RAS	Phenotype at Failure (bold if emerged)	Tropism at Failure (MPI)
10201008	3	LAM D4T LPV/R	Rebound (Week 20)	PR: M46L	K103N **M184V**	**LAM-R**	X4/DM (DM at BL)
10201069	4	LAM D4T LPV/R	Rebound (Week 12)	K103N V106M Y188Y/C G196K	**D67G**		R5 (99%)
10201104	1	LAM AZT LPV/R	Rebound (Week 72)	L74V M184V	**M41M/L** PR: P53F/L	LAM-R	NR
10371003	*4*	*LAM RAL TPV/r*	*Rebound/ Nonresponse (Week 96)*	*K65R S68G K70R V75I Y115F Q151M G190A L210F K219E*	***M41L*** *V189I PR: M36I R57R/K* ***I84V***	*LAM-R* ***TPV-R***	*NR*

				PR: D30N L33F M36L I50I/V F53F/L I54I/V V82A N88D			
10651002	4	ABC TDF NVP	Rebound (Week 16)	M41L D67N V118I M184V G196E L210E T215Y H221Y PR: V32I L33F M36I M46I I47V I54M A71V G73G/C/D/Y I84V L90M	**K103N** T165A	ABC-R **TDF-R NVP-R**	R5 (96%)

Italicized subject is outside Week 48 window.

5. CONCLUSION

In the treatment-experienced pediatric study 1031, the proportion of subjects in all cohorts with HIV-1 RNA <48 copies/mL at Week 24 was 52% (n=53) with a similar response at Week 48 (48%; n=49). The proportion of subjects with HIV-1 RNA <400 copies/mL at Week 24 was 73% (n=75) and 65% at Week 48 (n=67).

The mechanisms of resistance to MVC observed in this treatment-experienced pediatric population were similar to those observed in adult populations. In the virology analysis out to 96 weeks, there were 6 virologic failure subjects with CXCR4- or dual-mixed (DM)-tropic virus at failure time point out to Week 96 (3 of whom had evidence of DM-tropic virus at baseline), 2 virologic failures with evidence of reduced MVC susceptibility at failure as measured by a decrease in maximal percentage inhibition (MPI), and 5 virologic failure subjects with evidence of emergence of resistance-associated substitutions in RT or protease in their virus to a drug included in the regimen they received. In the Week 48 analysis (reflected in the drug package insert), there were 5 virologic failure subjects with CXCR4- or dual-mixed (DM)-tropic virus at the failure time point (2 of which had evidence of DM-tropic virus at baseline), 2 virologic failures with evidence of reduced MVC susceptibility at failure as measured by a decrease in maximal percentage inhibition (MPI), and 4 virologic failures with evidence of emergent resistance-associated substitutions in RT or protease in their virus to a background drug in their regimen.

Overall, the presence of resistance-associated substitutions at screening was not associated with virologic failure. The sponsor states that poor compliance with study regimens may have contributed to failure.

6. SPONSOR-PROPOSED PACKAGE INSERT

Antiretroviral Treatment-Experienced Pediatric Subjects (Trial A4001031): In the Week 48 analysis of Trial A4001031 (n = 103), [redacted] the mechanisms of resistance to maraviroc observed in [redacted] treatment-experienced pediatric population were similar to those observed in adult populations.

7. FDA-NEGOTIATED PACKAGE INSERT

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 [redacted]-tropic virus [redacted] evidence of reduced maraviroc susceptibility as measured by a decrease in maximal percentage inhibition (MPI), and emergence of resistance to a background drug in the regimen.

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/s/

LISA K NAEGER
09/22/2016

JULIAN J O REAR
09/23/2016