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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:** Selzentry™ / Celsentri® / Maraviroc

**PROTOCOL NO.:** A4001078

**PROTOCOL TITLE**: Pilot Study of Novel Combination of Maraviroc + Atazanavir/Ritonavir vs Atazanavir/Ritonavir + Emtricitabine/Tenofovir for the Treatment of Treatment Naive HIV-Infected Patients With R5 HIV-1

**Study Centers:** A total of 33 centers took part in the study and randomized subjects; 22 centers in the United States (US), 6 centers in Spain, and 5 centers in Germany.

**Study Initiation Date and Final Completion Date:** 03 March 2009 to 21 July 2011

**Phase of Development**: Phase 2b

**Study Objectives:**

Primary:

- To examine if the combination of maraviroc and atazanavir/ritonavir was effective for the treatment of treatment-naïve human immunodeficiency virus Type 1(HIV-1) infected subjects as measured by the percentage of subjects with HIV-1 ribonucleic acid (RNA) below the limits of assay detection (<50 copies of HIV-1 RNA per milliliter of plasma) at 48 weeks.

Secondary:

- Safety and tolerability.
- To assess the viral kinetics within the first 2 weeks in the first 15 subjects in each treatment arms (US sites only).
- To evaluate the pharmacokinetics (PK) of maraviroc in a subset of subjects (n=15) enrolled in the maraviroc treatment arm (US sites only).
- To assess virological response over time.
- To assess immunological response (cluster of differentiation [CD4] and CD8 counts) over time.

- To examine the evolution of viral resistance and/or tropism in treatment failure subjects only.

## METHODS

**Study Design:** This was an open-label, randomized, 2 arm, international Phase 2b study of maraviroc in combination with atazanavir/ritonavir versus atazanavir/ritonavir in combination with emtricitabine/tenofovir, in treatment-naive subjects infected with C-C chemokine receptor Type 5 (CCR5) co-receptor using HIV-1. It was originally planned to enroll a total of 88 subjects (40/treatment group + 10% over-enrollment) for 48 weeks, although the study was extended to 96 weeks. After signing the informed consent at screening, subjects underwent resistance testing (using GenoSeq® and/or PhenoSenseGT®) for resistance to protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), and a tropism assay (enhanced sensitivity Trofile ES™ assay with a sensitivity to detect 100% of spiked samples with 0.3% dual/mixed tropic HIV) for the presence of R5 virus. Subjects who met all inclusion/exclusion criteria received either:

- Maraviroc (150 mg once daily [QD]) with atazanavir/ritonavir (300/100 mg) QD or
- Emtricitabine/tenofovir (200/245 mg) (truvada) QD in combination with atazanavir/ritonavir (300/100 mg) QD.

Both formulations of tenofovir used in this study (tenofovir disoproxil 245 mg and tenofovir disoproxil fumarate (TDF) 300 mg) are equivalent. Both tablets provide 245 mg tenofovir.

Detailed assessments and procedures are described in the schedule of events Table 1.

## Table 1. Schedule of Events

| Protocol Activity | Screening[a] | Randomization[a] | Baseline[b] (Day 1)[a] | Days 4, 7, 10[c] | Week 2[a] | Weeks 4, 8, 12, 16, 20, 32, 40, 60, 72, 84[a] | Weeks 24, 48, 96[a] or Early Termination | Follow-Up Contact[d] |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | |
| Review inclusion/exclusion criteria | X | | X | | | | | |
| Medical history | X | | X | | | | | |
| Adverse event assessment | | | X | X[c] | X | X | X | X |
| Complete physical examination | X | | | | | | X[e] | |
| Targeted/symptom directed physical examination | | | X | X[c] | X | X | X | |
| Perform and document vital signs[f] | X | | X | | X | X | X | |
| Concomitant medications | X | | X | | X | X | X | X |
| Non-drug treatment and procedures | X | | X | | X | X | X | |
| Laboratory | | | | | | | | |
| Serum hematology | | X | X | | X | X | X | |
| Serum chemistry | | X | X | | X | X | X | |
| Fasting metabolic assessment and Framingham score[g] | | | X | | | | X | |
| Pregnancy test – serum[h] | | X | | | | | | |
| Pregnancy test – urine[h] | | | X | | | X | X | |
| Plasma HIV-1 RNA | X | X | X | X[c] | X | X | X | |
| PK sampling | | | | | X[i] | X[i] | X[i] | |
| CD4, CD8 counts | X | | X | | X | X | X | |
| Trofile assay with enhanced sensitivity | X | | | | | X[j] | X[j] | |
| Hepatitis B and C serology[k] | X | | | | | | | |
| Hepatitis B and C viral load[l] | | | | | | | | |
| Immune activation markers[m] | | | X[m] | | X[m] | X[m] | X[m] | |
| Viral resistance (phenotype/genotype) | X | | | | | X[j] | X[j] | |
| Maraviroc resistance testing | | | | | | X[j] | X[j] | |

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|---|---|---|---|---|---|---|---|---|
| Collect blood sample for archive | | | | | | | | |
| Possible repeat Trofile assay with enhanced sensitivity | X | | X | | X | X | X | |
| Possible maraviroc resistance testing | X | | | | X[n] | X[n] | X[n] | |
| Possible viral resistance testing (phenotype/genotype) | | | | | X | X | X | |
| Possible alternate co-receptor tropism assay | X | | X | | X | X | X | |
| Possible testing for bone mineral density markers | | | | | | | X[o] | |
| 12-lead ECG | | | X | | | | X[o] | |
| Assess dosing compliance | | | | | X | X | X | |
| Dispense study medications | | | X | | | X | X[p] | |
| Subject summary | | | | | | | X[e] | |

CD = cluster of differentiation; ECG = electrocardiogram; HDL = high density lipoprotein; HIV 1 = human immunodeficiency virus Type 1; LDL = low density lipoprotein; PK = pharmacokinetic; RNA = ribonucleic acid; US = United States.

a. Visit windows: The Screening Visit occurred within 42 days prior to the Baseline Visit. The Randomization Visit was recommended to occur within 28 days of the Screening Visit and within 14 days of the Baseline/Day 1 Visit. Weeks 2, 4, and 8 had a window of +/-4 days. Week 12 through Week 24, and follow-up phone contact had a window of +/-7 days. Note: The first 15 subjects per treatment group did not have a window for the Week 2 (Day 14) Visit.
b. Day 1, prior to dosing.
c. Only for first 15 subjects enrolled per treatment group (US sites only).
d. Follow-up contact could have been a phone call unless the visit was required by Investigator's discretion. The follow-up should have been 28 days after the last dose of study treatment (±7 days).
e. Only at early termination.
f. Vital signs included; blood pressure including orthostatic blood pressure monitoring, pulse, temperature, and weight.
g. Fasting metabolic assessment included total cholesterol, HDL/LDL, triglycerides, glucose, and glycosylated hemoglobin. This was not needed for an Early Termination Visit.
h. For women of childbearing potential: Serum pregnancy at randomization and urine tests at Day 1 Baseline Visit, Week 4, and all scheduled study visits after Week 4. A positive urine test was confirmed with a serum test.

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| Protocol Activity | Screening[a] | Randomization[a] | Baseline[b] (Day 1)[a] | Days 4, 7, 10[c] | Week 2[a] | Weeks 4, 8, 12, 16, 20, 32, 40, 60, 72, 84[a] | Weeks 24, 48, 96[a] or Early Termination | Follow-Up Contact[d] |
|---|---|---|---|---|---|---|---|---|

i. PK samples were collected.
j. Samples were collected for real time assay at the time of protocol-defined treatment failure. The time points for real time assay and for archiving were outlined. Maraviroc resistance testing was only applicable to subjects randomized to the maraviroc treatment group (except for the screening sample).
k. Hepatitis B and C serology was conducted at baseline and as needed for subjects with acute Grade 3 or 4 elevations of transaminase values and no obvious cause.
l. Only if hepatitis surface antigen or Hepatitis C antibody was positive at Screening Visit.
m. Immune marker samples (frozen) were collected for all subjects at the Baseline Visit, Weeks 2, 4, 8, 12, 24, and at the time of protocol-defined treatment failure. Also, subjects in the US had additional immune marker samples drawn that were to be shipped immediately as fresh blood samples.
n. Maraviroc treatment group subjects only.
o. Excluded Week 24.
p. Weeks 24 and 48 only.

**Number of Subjects (Planned and Analyzed):** It was anticipated that approximately 80 subjects with a 10% over-enrollment, to account for the drop-outs, would provide adequate data to calculate the point estimate and its 95% confidence interval (CI) for each treated arm with a reasonable precision for 48 weeks, although the study was extended to 96 weeks. A total of 129 subjects were randomized, of which 121 subjects were treated, 60 in the maraviroc + atazanavir/ritonavir treatment group and 61 in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group.

**Diagnosis and Main Criteria for Inclusion:** Subjects with HIV-1 RNA viral load of ≥1,000 copies/mL and CD4 count ≥100 cells/$mm^3$ measured at the Screening Visit. Subjects who have had only R5 HIV-1 at Screening as verified by the Monogram Bioscience Trofile® assay with enhanced sensitivity.

Exclusion Criteria: Subjects on prior treatment with any other HIV antiretroviral therapy for more than 14 days at any time or any evidence of resistance to atazanavir, tenofovir, and emtricitabine. Subjects with X4-or dual/mixed-tropic virus by enhanced Trofile assay or repeated assay failure or not reportable results.

**Study Treatment:** Subjects were randomized to 1 of 2 treatment groups to initially receive treatment for 48 weeks. The duration of the study was extended to 96 weeks:

- Treatment Group A: Maraviroc 150 mg QD + atazanavir/ritonavir 300/100 mg QD (labeled 'maraviroc + atazanavir/ritonavir' in the results sections of this synopsis).

- Treatment Group B: Atazanavir/ritonavir 300/100 mg QD + emtricitabine/tenofovir 200/245 mg QD (labeled 'atazanavir/ritonavir + emtricitabine/tenofovir' in the results sections of this synopsis).

All the study treatments were tablets or capsules and were taken orally. Food enhances the PK of atazanavir/ritonavir. Therefore, the maraviroc QD with atazanavir/ritonavir combination was taken with food to optimize the possibility of the boosting effect on maraviroc. Where a subject missed a planned dose, he/she could take a replacement dose only if it was not within 6 hours of the planned next dose. Other drugs, atazanavir, ritonavir, and emtricitabine/tenofovir, (or darunavir or lopinavir/ritonavir in the case that the Investigator replaced atazanavir) were taken according to the Investigator's instructions and the package inserts.

**Efficacy and Pharmacokinetic Endpoints:**

Primary Endpoint:

- The percentage of subjects with plasma HIV-1 RNA <50 copies/mL in each treatment arm at Week 48.

Secondary Endpoints:

- Safety and tolerability of the treatment with novel combinations of maraviroc with atazanavir/ritonavir; and another combination regimen (atazanavir and emtricitabine/tenofovir) in antiretroviral-naïve HIV-1 infected subjects.

- Plasma HIV RNA of the first 15 subjects enrolled in two treatment arms at Days 4, 7, 10, and 14 (US sites only).

- PK of maraviroc of the subjects enrolled in maraviroc arm.

- Virological Response:

    - Reduction of plasma $\log_{10}$ viral load from Baseline through Weeks 16, 24, 48, and 96 in each treatment arm.

    - Percentage of subjects who achieve <50 copies/mL and <400 copies/mL over time in each treatment arm.

    - Time to loss of virological response (TLOVR) through Weeks 96 in each treatment arm.

    - Time-Averaged Difference (TAD) in $\log_{10}$ viral load at Weeks 16, 24, 48 and 96.

- Immunological Response:

    - Changes in CD4+ T lymphocyte (CD4) cell counts from Baseline through Weeks 16, 24, 48 and 96 for each treatment arm.

    - Changes in CD8+ T lymphocyte (CD8) cell counts from Baseline through Weeks 16, 24, 48 and 96 for each treatment arm.

- Evolution of viral resistance and tropism:

    - Genotyping and phenotyping at the time of failure.

    - HIV-1 tropism (Trofile™ assay) at Baseline and at the time of treatment failure.

**Safety Evaluations:** Adverse events (AEs) were monitored throughout the study. Clinical laboratory tests (hematology and chemistry [including serum creatinine, blood urea nitrogen , and creatinine clearance as measures of renal function]) were performed at randomization, on Day 1, and at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96, or at early termination. Hepatitis B surface antigen and Hepatitis C antibody were assessed at screening. Fasting metabolic assessment (total cholesterol, high density lipoprotein /low density lipoprotein ratio, triglycerides, glucose, and glycosylated hemoglobin), and Framingham scores were performed at baseline and at Weeks 24, 48, and 96 (these

assessments were not required for early termination). Serum pregnancy tests were performed in women of childbearing potential at randomization, and urine pregnancy tests were performed on Day 1 (baseline), at Week 4, and at all of the scheduled study visits following the Week 4 Visit. Vital signs, including blood pressure and pulse, temperature, and weight were measured at screening, on Day 1, and at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96, or at early termination. A 12-lead electrocardiogram was taken on Day 1, at Weeks 48 and 96, or at early termination. Complete physical examination was performed at screening and symptom directed physical examination was performed on Day 1, on Days 4, 7, and 10 for the first 15 subjects enrolled in each treatment group, and at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96, or at early termination.

**Statistical Methods:** The full analysis set (FAS) included all subjects who had taken at least 1 dose of the study treatment, and had baseline and at least 1 post-baseline measurement. The FAS was used for performing the efficacy analyses on all endpoints. The safety analysis set included all subjects who received at least 1 dose of study treatment.

Descriptive summaries were provided for all efficacy parameters. Continuous measurements were summarized using descriptive statistics (number of subjects [N], mean, standard deviation, median, and range) and discrete data were summarized by counts (N, frequency, and percent).

If a subject discontinued the study at a given visit, they were considered as failures or non-responders in the primary endpoint analysis at that visit and at all visits thereafter. If a measurement for HIV-1 RNA was missing for a given visit but the subject continued in the study, then last observation carried forward approach was used in the analysis of the primary endpoint. No formal statistical testing was performed for the primary endpoint.

Secondary endpoints included safety and tolerability; change from baseline in HIV-1 RNA of the first 15 subjects enrolled in each treatment group at Days 4, 7, 10, and 14 (US sites only); PK of the first 15 subjects enrolled in each treatment group (US sites only). Virological and immunological response, and evolution of viral resistance in each treatment group were summarized.

Safety data were evaluated using descriptive statistics.

## RESULTS

**Subject Disposition and Demography:** The number of subjects treated, completed, and discontinued is presented in Table 2. Of the 129 subjects randomized, 121 subjects were treated, 60 in the maraviroc + atazanavir/ritonavir treatment group and 61 in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group. Eight (8) randomized subjects (5 subjects in maraviroc + atazanavir/ritonavir treatment group and 3 subjects in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group) were not eligible for participation in the study for the following reasons: 2 subjects did not meet the entrance criteria, 2 subjects were no longer willing to participate in the study, 1 subject was lost to follow-up, 1 subject had a protocol violation, 1 subject was unable to fulfill the scheduled visits, and 1 subject was unable to participate in the sub-study.

**Table 2. Subject Disposition**

| Number (%) Subjects | Maraviroc + Atazanavir/Ritonavir | Atazanavir/Ritonavir + Emtricitabine/Tenofovir |
|---|---|---|
| Assigned to treatment | 65 | 64 |
| Treated | 60 | 61 |
| Completed | 50 (83.3) | 52 (85.2) |
| Discontinued | 10 (16.7) | 9 (14.8) |
| Related to study treatment | 4 (6.7) | 0 |
| AEs | 2 (3.3) | 0 |
| Insufficient clinical response[a] | 2 (3.3) | 0 |
| Not related to study treatment | 6 (10.0) | 9 (14.8) |
| Lost to follow-up | 3 (5.0) | 2 (3.3) |
| No longer willing to participate in the study | 2 (3.3) | 1 (1.6) |
| Other | 1 (1.7)[b] | 3 (4.9)[c] |
| Protocol violation | 0 | 2 (3.3) |
| Withdrawn due to pregnancy | 0 | 1 (1.6) |
| Analyzed for safety | | |
| AEs | 60 (100.0) | 61 (100.0) |
| Laboratory data | 59 (98.3%)[d] | 61 (100.0) |

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
AE = adverse event.

a. As defined by the Investigator.
b. One subject was discontinued due to virological failure detected at Week 72, and the subject failed to return for laboratory re testing.
c. Subjects were discontinued for the following reasons: 1 subject due to non-compliance with the study treatment; 1 subject due to possible side effects of tenofovir as the cause of suspected kidney failure; and 1 subject due to subject travelling abroad for more than 3 months and not able to attend scheduled visits required by the protocol.
d. One subject was lost to follow-up after the Baseline Visit and was not included in the laboratory data analyses.

Demographic characteristics are summarized and were presented in Table 3. Subjects ranged in age from 18 to 68 years and the mean age was similar between the 2 treatment groups. The majority of subjects in both treatment groups were male.

**Table 3. Demographic Characteristics**

| Parameters | Maraviroc + Atazanavir/Ritonavir | | | Atazanavir/Ritonavir + Emtricitabine/Tenofovir | | |
|---|---|---|---|---|---|---|
| | Male (N=56) | Female (N=4) | Total (N=60) | Male (N=52) | Female (N=9) | Total (N=61) |
| Age (years), n (%) | | | | | | |
| 18-44 | 41 (73.2) | 2 (50.0) | 43 (71.7) | 42 (80.8) | 7 (77.8) | 49 (80.3) |
| 45-64 | 15 (26.8) | 2 (50.0) | 17 (28.3) | 9 (17.3) | 2 (22.2) | 11 (18.0) |
| ≥65 | 0 | 0 | 0 | 1 (1.9) | 0 | 1 (1.6) |
| Mean | 38.0 | 41.3 | 38.3 | 35.1 | 36.9 | 35.3 |
| SD | 9.9 | 16.2 | 10.2 | 10.3 | 12.3 | 10.5 |
| Range | 21-61 | 22-60 | 21-61 | 18-68 | 22-62 | 18-68 |
| Race, n (%) | | | | | | |
| White | 44 (78.6) | 1 (25.0) | 45 (75.0) | 41 (78.8) | 5 (55.6) | 46 (75.4) |
| Black | 10 (17.9) | 3 (75.0) | 13 (21.7) | 7 (13.5) | 4 (44.4) | 11 (18.0) |
| Asian | 0 | 0 | 0 | 3 (5.8) | 0 | 3 (4.9) |
| Other | 2 (3.6) | 0 | 2 (3.3) | 1 (1.9) | 0 | 1 (1.6) |
| Weight (kg) | | | | | | |
| Mean | 77.8 | 72.9 | 77.5 | 78.0 | 81.8 | 78.5 |
| SD | 12.8 | 12.0 | 12.7 | 17.4 | 24.3 | 18.3 |
| Range | 59.0-119.7 | 62.8-88.9 | 59.0-119.7 | 49.7-127.0 | 50.3-117.5 | 49.7-127.0 |
| Height (cm) | | | | | | |
| Mean | 176.7 | 165.3 | 175.9 | 175.9 | 165.8 | 174.4 |
| SD | 8.3 | 3.8 | 8.6 | 7.6 | 7.3 | 8.3 |
| Range | 157.0-193.0 | 160.0-169.0 | 157.0-193.0 | 152.0-190.0 | 157.0-175.0 | 152.0-190.0 |

N = number of subjects; n = number of evaluable subjects; SD = standard deviation.

**Efficacy Results:**

Primary Efficacy:

The overall proportion of subjects with HIV-1 RNA <50 copies/mL up to Week 96 is summarized in Table 4.

**Table 4. Overall Proportion of Subjects with HIV-1 RNA <50 copies/mL at Weeks 16, 24, 48, and 96 (Full Analysis Set)**

| Variables | Maraviroc+ Atazanavir/Ritonavir N[a]=59 | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir N[a]=61 |
|---|---|---|
| n/N (%) | HIV-1 RNA <50 copies/mL | HIV-1 RNA <50 copies/mL |
| Week 16 | 43/54 (72.9) | 45/58 (73.8) |
| Week 24 | 48/56 (81.4) | 54/58 (88.5) |
| Week 48 | 44/53 (74.6) | 51/54 (83.6) |
| Week 96 | 40/49 (67.8) | 50/51 (82.0) |

HIV-1 = human immunodeficiency virus Type 1; N = number of subjects; n = number of subjects with observation at specific time point; RNA = ribonucleic acid.
a. Number of subjects used to calculate the percentage.

Secondary Efficacy:

A summary of plasma HIV-1 RNA ($log_{10}$ copies/mL) absolute values for Baseline and Weeks 16, 24, 48, and 96 is presented in Table 5.

**Table 5. HIV-1 RNA ($Log_{10}$ copies/mL) at Baseline and Weeks 16, 24, 48, and 96 (Full Analysis Set)**

| Variables | Maraviroc + Atazanavir/Ritonavir (N=59) | Atazanavir/Ritonavir + Emtricitabine/Tenofovir (N=61) |
|---|---|---|
| Baseline | | |
| n | 59 | 61 |
| Mean (SD) | 4.60 (0.55) | 4.66 (0.68) |
| Median (Min, Max) | 4.54 (3.43, 5.86) | 4.80 (3.28, 5.92) |
| 95% CI (Lower, Upper) | 4.4546, 4.7389 | 4.4876, 4.8371 |
| Week 16 | | |
| n | 54 | 58 |
| Mean (SD) | 1.83 (0.44) | 1.78 (0.25) |
| Median (Min, Max) | 1.69 (1.69, 4.49) | 1.69 (1.69, 2.93) |
| 95% CI (Lower, Upper) | 1.7061, 1.9445 | 1.7155, 1.8457 |
| Week 24 | | |
| n | 56 | 58 |
| Mean (SD) | 1.80 (0.38) | 1.74 (0.22) |
| Median (Min, Max) | 1.69 (1.69, 4.13) | 1.69 (1.69, 3.23) |
| 95% CI (Lower, Upper) | 1.6932, 1.8987 | 1.6809, 1.7976 |
| Week 48 | | |
| n | 53 | 54 |
| Mean (SD) | 1.73 (0.11) | 1.71 (0.16) |
| Median (Min, Max) | 1.69 (1.69, 2.22) | 1.69 (1.69, 2.89) |
| 95% CI (Lower, Upper) | 1.6961, 1.7548 | 1.6692, 1.7585 |
| Week 96 | | |
| n | 49 | 51 |
| Mean (SD) | 1.83 (0.43) | 1.69 (0.03) |
| Median (Min, Max) | 1.69 (1.69, 3.88) | 1.69 (1.69, 1.89) |
| 95% CI (Lower, Upper) | 1.7063, 1.9556 | 1.6863, 1.7018 |

Baseline was calculated as the mean of screening, randomization, and Day 1.
If viral load was undetectable, then 399 for the value <400, and 49 for the value <50 were used to calculate the summaries.
One subject had a 1-day discrepancy on Days 7 and 14, but was included in the analysis for Days 7 and 14.
CI = confidence interval; HIV-1 = human immunodeficiency virus Type 1; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with an observation at a specified time point; RNA = ribonucleic acid; SD = standard deviation.

The response rate of the subjects included in the viral kinetics sub-study is shown in Table 6. Figures were based on the first 15 subjects in each treatment group (US sites only).

**Table 6. Proportion of Subjects with HIV-1 RNA <50 copies/mL and <400 copies/mL**

| n (%) | Maraviroc+ Atazanavir/Ritonavir | Atazanavir/ Ritonavir+ Emtricitabine/ Tenofovir | Maraviroc+Atazanavir/Ritonavir vs Atazanavir/Ritonavir+Emtricitabine/Tenofovir | |
|---|---|---|---|---|
| | | | Difference in Proportion | 95% CI for the Difference |
| **HIV-1 RNA <50 copies/mL** | | | | |
| Day 4 | 0 | 0 | 0 | 0, 0 |
| Day 7 | 0 | 0 | 0 | 0, 0 |
| Day 10 | 0 | 1 (6.3) | -0.0625 | -0.1811, 0.0561 |
| Day 14 | 0 | 2 (12.5) | -0.125 | -0.2871, 0.0371 |
| **HIV-1 RNA <400 copies/mL** | | | | |
| Day 4 | 0 | 0 | 0 | 0, 0 |
| Day 7 | 2 (13.3) | 5 (33.3) | -0.1792 | -0.4641, 0.1057 |
| Day 10 | 3 (20.0) | 7 (43.8) | -0.2375 | -0.5538, 0.0788 |
| Day 14 | 5 (33.3) | 8 (50.0) | -0.1667 | -0.5087, 0.1753 |

CI = confidence interval; HIV-1 = human immunodeficiency virus Type 1; n = number of subjects with an observation at a specified time point; RNA = ribonucleic acid.

Following multiple dose administration of maraviroc 150 mg QD to the first 15 subjects in the maraviroc+atazanavir/ritonavir treatment group, maraviroc concentration geometric means (%CV) for area under the plasma concentration time-curve from time zero to time 24 hours ($AUC_{24}$), predicted average concentration ($AUC_{24}$ divided by the dosing interval) [$C_{av}$], maximum plasma concentration ($C_{max}$) and minimum plasma concentration ($C_{min}$) were 4121 hr•ng/mL (43%), 172 ng/mL (43%), 644 ng/mL (53%), and 35.9 ng/mL (70%), respectively. Maraviroc absorption was rapid, with median $T_{max}$ of 2 hours (Table 7).

**Table 7. Summary of Plasma Maraviroc Pharmacokinetic Parameter Values**

| Parameter | Maraviroc+ Atazanavir/Ritonavir N=15 |
|---|---|
| N | 15 |
| $AUC_{24}$ (ng hr/mL) | 4330 (1930–7310) |
| $C_{av}$ (ng/mL) | 180.0 (80.3–305) |
| $C_{max}$ (ng/mL) | 650.0 (178–1490) |
| $C_{min}$ (ng/mL) | 37.0 (8.44–92.7) |
| $T_{max}$ (hr) | 2.00 (0.50–3.92) |

$AUC_{24}$ = area under the plasma concentration time-curve from time zero to time 24 hours; $C_{av}$ = predicted average concentration (AUC24 divided by the dosing interval); $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; N = number of subjects; $T_{max}$ = time to maximum plasma concentration.

The TAD in HIV-1 RNA ($log_{10}$ copies/mL) is summarized at Weeks 16, 24, 48, and 96 in Table 8. No treatment difference was detected at any time point in the study.

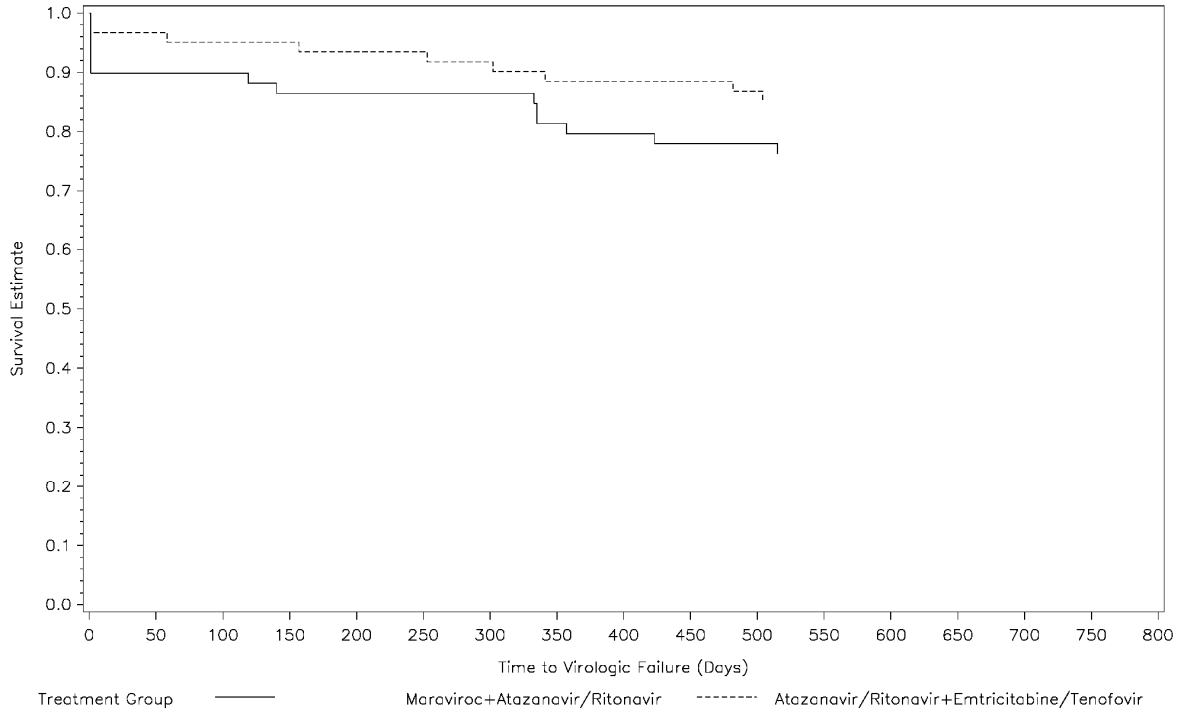
**Table 8. Time Averaged Difference (TAD) in Log10 Viral Load at Week 16, Week 24, Week 48 and Week 96 (Full Analysis Set)**

| Visit | Treatment | N | Change from Baseline | | | Treatment difference Maraviroc + Atazanavir/Ritonavir Atazanavir/Ritonavir+Emtricitabine/Tenofovir | |
|---|---|---|---|---|---|---|---|
| | | | Raw Mean (s.e.) | Median | Adjusted Mean* (s.e.) | Estimate (s.e.) | 95% CI |
| Week 16 | Maraviroc+Atazanavir /Ritonavir | 51 | -2.363 (0.0474) | -2.314 | -2.459 (0.0464) | -0.057 (0.0620) | (-0.180, 0.066) |
| | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir | 52 | -2.337 (0.0552) | -2.308 | -2.402 (0.0447) | | |
| Week 24 | Maraviroc+Atazanavir /Ritonavir | 51 | -2.532 (0.0537) | -2.485 | -2.663 (0.0481) | -0.037 (0.0642) | (-0.164, 0.090) |
| | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir | 52 | -2.536 (0.0635) | -2.56 | -2.626 (0.0463) | | |
| Week 48 | Maraviroc+Atazanavir /Ritonavir | 51 | -2.725 (0.0614) | -2.687 | -2.897 (0.0514) | -0.030 (0.0686) | (-0.166, 0.107) |
| | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir | 52 | -2.750 (0.0758) | -2.847 | -2.868 (0.0495) | | |
| Week 96 | Maraviroc+Atazanavir /Ritonavir | 51 | -2.802 (0.0685) | -2.757 | -2.998 (0.0554) | 0.002 (0.0739) | (-0.144, 0.149) |
| | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir | 52 | -2.867 (0.0840) | -2.988 | -3.001 (0.0533) | | |

* Mean was adjusted for viral load at Baseline category.
Discontinuations prior to the time point of analysis have been imputed as 0 for the purpose of analysis.
The baseline value used in the calculation of time averaged difference from baseline was the average of the pre-dose measurements collected at the screening visit, randomization visit and the baseline visit.
CI = confidence interval; N = number of subjects; s.e = standard of error.

The TLOVR through Week 96 is presented in Figure 1.

**Figure 1. Time to Loss of Virological Response - Week 96 (Full Analysis Set)**




Absolute CD4 and CD8 cell counts at baseline and Weeks 16, 24, 48, and 96 are summarized in Table 9 and Table 10 respectively.

**Table 9. Absolute CD4 Cell Counts (cells/μL) at Baseline and Weeks 16, 24, 48, and 96 (Full Analysis Set)**

| Parameters | Maraviroc + Atazanavir/Ritonavir (N=59) | Atazanavir/Ritonavir + Emtricitabine/Tenofovir (N=61) |
|---|---|---|
| Baseline | | |
| n | 59 | 61 |
| Mean (SD) | 357.7 (123.53) | 390.0 (152.34) |
| Median (Min, Max) | 345.5 (160.0, 744.0) | 358.0 (110.0, 901.5) |
| 95% CI (Lower, Upper) | 325.5281, 389.9126 | 351.0247, 429.0573 |
| Week 16 | | |
| n | 54 | 58 |
| Mean (SD) | 533.1 (145.66) | 536.8 (173.12) |
| Median (Min, Max) | 505.0 (273.0, 947.0) | 529.5 (198.0, 943.0) |
| 95% CI (Lower, Upper) | 493.2983, 572.8128 | 491.2403, 582.2769 |
| Week 24 | | |
| n | 54 | 57 |
| Mean (SD) | 550.2 (167.28) | 571.2 (199.58) |
| Median (Min, Max) | 550.0 (277.0, 972.0) | 542.0 (186.0, 1366.0) |
| 95% CI (Lower, Upper) | 504.5635, 595.8810 | 518.2901, 624.2011 |
| Week 48 | | |
| n | 52 | 53 |
| Mean (SD) | 582.8 (209.47) | 619.5 (229.84) |
| Median (Min, Max) | 588.0 (160.0, 1118.0) | 600.0 (274.0, 1335.0) |
| 95% CI (Lower, Upper) | 524.5093, 641.1445 | 556.1953, 682.8990 |
| Week 96 | | |
| n | 50 | 51 |
| Mean (SD) | 656.0 (216.73) | 700.6 (234.86) |
| Median (Min, Max) | 611.0 (184.0, 1410.0) | 671.0 (310.0, 1387.0) |
| 95% CI (Lower, Upper) | 594.4272, 717.6128 | 634.5134, 766.6238 |
| Week 16 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 520.6 (150.94) | 531.2 (171.20) |
| Median (Min, Max) | 501.5 (251.0, 947.0) | 515.0 (198.0, 943.0) |
| 95% CI (Lower, Upper) | (480.8638, 560.2396 | 487.3332, 575.0275 |
| Week 24 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 537.2 (177.16) | 560.6 (199.89) |
| Median (Min, Max) | 536.5 (251.0, 1027.0) | 536.0 (186.0, 1366.0) |
| 95% CI (Lower, Upper) | 490.6261, 583.7877 | 509.4284, 611.8175 |
| Week 48 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 571.0 (214.23) | 598.6 (227.62) |
| Median (Min, Max) | 579.5 (160.0, 1118.0) | 580.0 (247.0, 1335.0) |
| 95% CI (Lower, Upper) | 514.6716, 627.3284 | 540.3097, 656.9034 |
| Week 96 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 627.8 (227.50) | 662.3 (242.11) |
| Median (Min, Max) | 603.5 (184.0, 1410.0) | 635.0 (247.0, 1387.0) |
| 95% CI (Lower, Upper) | 567.9572, 687.5945 | 600.3198, 724.3360 |

CD = cluster of differentiation; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with an observation; SD = standard deviation.

**Table 10. Absolute CD8 Cell Counts (cells/μL) at Baseline and Weeks 16, 24, 48, and 96 (Full Analysis Set)**

| Parameters | Maraviroc + Atazanavir/Ritonavir (N=59) n (%) | Atazanavir/Ritonavir + Emtricitabine/Tenofovir (N=61) n (%) |
|---|---|---|
| Baseline | | |
| n | 59 | 61 |
| Mean (SD) | 931.1 (446.26) | 1125.6 (735.08) |
| Median (Min, Max) | 855.5 (346.5, 2583.0) | 890.0 (253.0, 3662.0) |
| 95% CI (Lower, Upper) | 814.8473, 1047.441 | 937.3188, 1313.845 |
| Week 16 | | |
| n | 54 | 58 |
| Mean (SD) | 998.8 (463.44) | 940.4 (443.05) |
| Median (Min, Max) | 886.0 (389.0, 3201.0) | 854.5 (293.0, 2511.0) |
| 95% CI (Lower, Upper) | (872.3022, 1125.290) | 823.9548, 1056.942 |
| Week 24 | | |
| n | 54 | 57 |
| Mean (SD) | 940.5 (374.88) | 935.7 (458.16) |
| Median (Min, Max) | 834.0 (341.0, 2355.0) | 855.0 (273.0, 2489.0) |
| 95% CI (Lower, Upper) | 838.1960, 1042.841 | 814.1705, 1057.303 |
| Week 48 | | |
| n | 52 | 53 |
| Mean (SD) | 866.8 (432.38) | 872.4 (416.11) |
| Median (Min, Max) | 751.0 (352.0, 2669.0) | 798.0 (335.0, 2175.0) |
| 95% CI (Lower, Upper) | 746.4525, 987.2013 | 757.7224, 987.1078 |
| Week 96 | | |
| n | 50 | 51 |
| Mean (SD) | 832.0 (325.71) | 858.1 (379.44) |
| Median (Min, Max) | 767.0 (407.0, 1995.0) | 803.0 (261.0, 2134.0) |
| 95% CI (Lower, Upper) | 739.4557, 924.5843 | 751.3802, 964.8158 |
| Week 16 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 985.7 (453.76) | 982.4 (488.96) |
| Median (Min, Max) | 886.0 (389.0, 3201.0) | 880.0 (293.0, 2632.0) |
| 95% CI (Lower, Upper) | 866.3963, 1105.018 | 857.1805, 1107.639 |
| Week 24 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 929.9 (378.52) | 951.5 (468.95) |
| Median (Min, Max) | 827.5 (341.0, 2355.0) | 882.0 (273.0, 2619.0) |
| 95% CI (Lower, Upper) | 830.3348, 1029.389 | 831.3544, 1071.564 |
| Week 48 (using LOCF approach) | | |
| n | 58 | 61 |
| Mean (SD) | 875.5 (421.40) | 870.1 (422.20) |
| Median (Min, Max) | 760.5 (352.0, 2669.0) | 798.0 (202.0, 2175.0) |
| 95% CI (Lower, Upper) | 764.7329, 986.3361 | 761.9525, 978.2114 |
| Week 96 (using LOCF approach) | | |
| N | 58 | 61 |
| Mean (SD) | 864.3 (350.92) | 860.5 (381.78) |
| Median (Min, Max) | 811.5 (407.0, 1995.0) | 803.0 (202.0, 2134.0) |
| 95% CI (Lower, Upper) | 772.0745, 956.6152 | 762.7457, 958.3034 |

CD = cluster of differentiation; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with an observation; SD = standard deviation.

For the virology analysis through Week 48, all subjects who discontinued therapy early or who reached Week 48 with sufficient plasma HIV-1 RNA for analysis (≥500 copies/mL) were submitted for analysis (maraviroc: n=3; TDF: n=3). The Monogram Biosciences assays PSGT™, Trofile and, for maraviroc-treated subjects, PhenoSense HIV-1 Entry™ were performed at Screening or Baseline and at the last on-treatment time point available. In all, no resistance to the respective regimens was reported (Table 11).

## Table 11. Virological Analysis of Plasma HIV-1 RNA from Subjects Through Week 48

| Group | Discontinuation Reason | Clade | Time point | Tropism; Phenotypic Susceptibility (MVC or TDF/FTC) | PI Mutations[a]; ATV Phenotypic Susceptibility |
|---|---|---|---|---|---|
| Maraviroc + ATV/r | AE | B | Screening | R5; Sensitive | M36I, Q58E, L63F/S; Sensitive[b] |
| | | | Week 12 | R5; Sensitive | M36I, Q58E, L63S; Sensitive[c] |
| | Lost to follow-up | B | Screening | R5; Sensitive | L10I, L63L/P, V77V/I; Sensitive |
| | | | Week 24 | R5; Sensitive | L10I, L63L/P; Sensitive |
| | Insufficient clinical response (never suppressed) | B | Screening | R5; Sensitive | L63S, V77V/I; Sensitive |
| | | | Week 24 | R5; Sensitive | L63S, V77I; Sensitive[d] |
| | | | Week 32 (E_Term) | R5; NR/NP | L63S; Sensitive |
| FTC/TDF + ATV/r | Lost to follow-up | B | Screening | R5; no NRTI RAMs, TDF and FTC sensitive | L63P; Sensitive |
| | | | Week 12 | NR; no NRTI RAMs, TDF and FTC sensitive | L63P; Sensitive |
| | Lost to follow-up | B | Screening | R5; No NRTI RAMs, TDF and FTC sensitive | V77I; Sensitive |
| | | | Week 12 (E term) | R5; No NRTI RAMs, TDF and FTC sensitive | V77I; Sensitive |
| | Protocol violation | B | Screening | R5; no NRTI RAMs, TDF and FTC sensitive | L33I, M46M/I, L63P; Sensitive |
| | | | Week 8 | DM; no NRTI RAMs, TDF and FTC sensitive | L33I, L63P; Sensitive |
| | | | Week 24 | R5; no NRTI RAMs, TDF and FTC sensitive | L33I, L63P; Sensitive |

For PI mutations, the International Union of Biochemistry single letter amino acid code is used to denote wild-type and variant amino acids at the positions described.
AE = adverse event; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; CCR5 = C-C chemokine receptor type 5; ddI = didanosine; DM = dual/mixed tropism; FTC = emtricitabine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; R5 = CCR5-tropic; RAM = resistance-associated mutation TDF = tenofovir disoproxil fumarate.

a. Mutations were provided as PI mutations as provided by Monogram Biosciences Inc.
b. Partial resistance to ddI with no NRTI RAMs observed.
c. Resistance to ddI, stavudine (d4T) and partial sensitivity to TDF observed; no NRTI RAMs observed.
d. Resistance to zidovudine observed; no NRTI RAMs observed.

For the virology analysis after Week 48 through Week 96, all subjects who discontinued therapy early or who reached Week 96 with sufficient plasma HIV-1 RNA for analysis were assessed. In addition, samples from those subjects with confirmed rebound during this

period were submitted for analysis. Overall, the analysis included a total of 5 subjects (4 subjects in the maraviroc + atazanavir/ritonavir treatment group and 1 subject in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group). One subject from each group had experienced confirmed virologic rebound followed by resuppression (Table 12). The Monogram Biosciences assays PhenoSense GT™, Trofile and, for maraviroc-treated subjects, PhenoSense HIV-1 Entry™ were performed at screening or baseline and at the last on-treatment time point available. In all, no resistance to the respective regimens was reported.

## Table 12. Virological Analysis of Plasma HIV-1 RNA From Subjects Through Week 96

| Group | Discontinuation Reason | Clade | Time Point Assessed | Tropism; Phenotypic Susceptibility (MVC or TDF/FTC) | PI Mutations[a]; ATV Phenotypic Susceptibility |
|---|---|---|---|---|---|
| Maraviroc + ATV/r | Completed | B | Screening | R5; Sensitive (99%) | E35D, L63S Sensitive |
| | | | Week 96 | R5; Sensitive (98%) | E35D, L63S Sensitive |
| | Insufficient clinical response | C | Screening | R5; Sensitive (95%) | M36I, K43K/T, H69K (I93L); Sensitive |
| | | | Week 96 | R5; Sensitive (100%) | M36I, H69K, L89M/V, (I93L); Sensitive |
| | Completed | B | Screening | R5; Sensitive (100%) | (I64V), V77V/I; Sensitive |
| | | | Week 96 | R5; Sensitive (100%) | (I64V); Sensitive |
| | Completed (resupressed after Week 72) | B | Screening | R5; Sensitive (100%) | I13I/V, I64I/V; Sensitive |
| | | | Week 60 | R5; Sensitive (100%) | I13I/V, I64I/V; Sensitive |
| FTC/TDF + ATV/r | Poor compliance | B | Screening | No NRTI RAMs, TDF and FTC sensitive | L63A; Sensitive |
| | | | Week 72 | No NRTI RAMs, TDF and FTC sensitive | L63A; sensitive |
| | | | Week 72 (Unplanned re-test) | No NRTI RAMs, TDF and FTC sensitive | L63A, N88N/T; Sensitive[b] |

For PI mutations, the International Union of Biochemistry single letter amino acid code is used to denote wild-type and variant amino acids at the positions described.
ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; FTC=emtricitabine; MVC = maraviroc; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; R5 = CCR5-tropic; RAM = resistance-associated mutation; TDF = tenofovir disoproxil fumarate.

a. PI mutations were listed as provided by Monogram Biosciences Inc.
b. Genotypic resistance noted to NFV and to unboosted ATV, but not to ATV/r, with N88N/T selected.

Subjects who had protocol-defined treatment failure are summarized in Table 13. All subjects discontinued after their protocol-defined treatment failure.

**Table 13. Summary of Protocol-Defined Treatment Failures**

| Protocol-Defined Failure Reason | Maraviroc+ Atazanavir/ Ritonavir N=59 | Atazanavir/ Ritonavir+ Emtricitabine/Tenofovir N=61 |
|---|---|---|
| HIV-1 RNA <1.0 $\log_{10}$ decrease from Baseline at Week 4 and thereafter | 1 (1.60) | 2 (3.20) |
| Failed to achieve HIV-1 RNA <400 copies/mL at Week 24 | 1 (1.60) | 0 |
| An increase in HIV-1 RNA to detectable levels ≥1000 copies/mL[a] | 0 | 0 |

One subject could contribute to 1 or more failure criteria.
HIV-1 = human immunodeficiency virus Type 1; N = number of subjects; RNA = ribonucleic acid.
a. On 2 consecutive measurements in subjects previously confirmed to have undetectable levels of <400 copies/mL on 2 consecutive visits.

Treatment outcomes at Week 96 are summarized by treatment group in Table 14.

**Table 14. Summary of Study Treatment Outcomes at Week 96 (Full Analysis Set)**

| Parameters | Maraviroc + Atazanavir/Ritonavir (N=59) n (%) | Atazanavir/Ritonavir + Emtricitabine/Tenofovir (N=61) n (%) |
|---|---|---|
| Responder[a] | 40 (67.8) | 50 (82.0) |
| Non-responder | 19 (32.2) | 11 (18.0) |
| Protocol-defined treatment failure | 3 (5.1) | 2 (3.3) |
| Never suppressed up to and including Week 96 | 3 (5.1) | 1 (1.6) |
| Discontinuation | 3 (5.1) | 6 (9.8) |
| Adverse event | 0 | 0 |
| Lost to follow-up | 1 (1.7) | 0 |
| No longer willing to participate in study | 1 (1.7) | 1 (1.6) |
| Protocol violation | 0 | 1 (1.6) |
| Withdrawn due to pregnancy | 0 | 1 (1.6) |
| Death | 0 | 0 |
| Other | 1 (1.7) | 3 (4.9) |
| Blippers[b] | 10 (16.9) | 2 (3.3) |

If a subject fell into more than 1 category, the precedence rule was applied based on the presentation of this table.
HIV-1 = human immunodeficiency virus Type 1; N = number of subjects; n = number of subjects with an observation; RNA = ribonucleic acid.
a. A responder was defined as a subject with HIV-1 RNA<50 copies/mL.
b. A blipper was defined as a subject who had previously achieved viral suppression to <50 copies/mL and experienced a brief episode of viremia followed by re-suppression to <50 copies/mL.

**Safety Results:** The most frequently reported (≥20% of subjects) all causality treatment emergent AEs (TEAEs) in the maraviroc + atazanavir/ritonavir treatment group were: hyperbilirubinemia (18 [30.0%] subjects); diarrhea (15 [25.0%] subjects); and ocular icterus (13 [21.7%] subjects). The most frequently reported all causality TEAEs in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group were: hyperbilirubinemia and nausea (16 [26.2%] subjects, each) and diarrhea (14 [23.0%] subjects; Table 15).

**Table 15. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5**

| System Organ Class<br>Preferred Term | Maraviroc+Atazanavir/ Ritonavir<br>n (%) | Atazanavir/ Ritonavir+Emtricitabine/Tenofovir<br>n (%) |
|---|---|---|
| Number (%) of subjects: evaluable for AEs | 60 | 61 |
| Number (%) of subjects: with AEs | 55 (91.7) | 58 (95.1) |
| Eye disorders | 13 (21.7) | 12 (19.7) |
| Conjunctivitis | 1 (1.7) | 5 (8.2) |
| Ocular icterus | 13 (21.7) | 7 (11.5) |
| Gastrointestinal disorders | 24 (40.0) | 28 (45.9) |
| Abdominal pain upper | 3 (5.0) | 0 |
| Constipation | 4 (6.7) | 1 (1.6) |
| Diarrhoea | 15 (25.0) | 14 (23.0) |
| Haemorrhoids | 4 (6.7) | 3 (4.9) |
| Nausea | 6 (10.0) | 16 (26.2) |
| Vomiting | 8 (13.3) | 6 (9.8) |
| General disorders and administration site conditions | 6 (10.0) | 9 (14.8) |
| Fatigue | 3 (5.0) | 7(11.5) |
| Pyrexia | 4 (6.7) | 3 (4.9) |
| Hepatobiliary disorders | 24 (40.0) | 21 (34.4) |
| Hyperbilirubinaemia | 18 (30.0) | 16 (26.2) |
| Jaundice | 10 (16.7) | 6 (9.8) |
| Infections and infestations | 31 (51.7) | 31 (50.8) |
| Anogenital warts | 4 (6.7) | 4 (6.6) |
| Bronchitis | 8 (13.3) | 5 (8.2) |
| Gonorrhoea | 4 (6.7) | 2 (3.3) |
| Herpes zoster | 3 (5.0) | 6 (9.8) |
| Influenza | 4 (6.7) | 6 (9.8) |
| Nasopharyngitis | 3 (5.0) | 6 (9.8) |
| Pharyngitis | 3 (5.0) | 3 (4.9) |
| Sinusitis | 10 (16.7) | 3 (4.9) |
| Syphilis | 3 (5.0) | 1 (1.6) |
| Tonsillitis | 4 (6.7) | 0 |
| Upper respiratory tract infection | 8 (13.3) | 8 (13.1) |
| Urinary tract infection | 3 (5.0) | 2 (3.3) |
| Investigations | 14 (23.3) | 8 (13.1) |
| Alanine aminotransferase increased | 3 (5.0) | 2 (3.3) |
| Aspartate aminotransferase increased | 4 (6.7) | 1 (1.6) |

**Table 15. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5**

| System Organ Class<br>Preferred Term | Maraviroc+Atazanavir/ Ritonavir<br>n (%) | Atazanavir/ Ritonavir+Emtricitabine/Tenofovir<br>n (%) |
|---|---|---|
| Blood amylase increased | 4 (6.7) | 2 (3.3) |
| Blood bilirubin increased | 7 (11.7) | 5 (8.2) |
| Blood creatine phosphokinase increased | 6 (10.0) | 0 |
| Blood creatinine increased | 3 (5.0) | 1 (1.6) |
| Blood uric acid increased | 4 (6.7) | 0 |
| Metabolism and nutrition disorders | 3 (5.0) | 3 (4.9) |
| Decreased appetite | 3 (5.0) | 3 (4.9) |
| Musculoskeletal and connective tissue disorders | 1 (1.7) | 4 (6.6) |
| Pain in extremity | 1 (1.7) | 4 (6.6) |
| Nervous system disorders | 6 (10.0) | 11 (18.0) |
| Dizziness | 2 (3.3) | 4 (6.6) |
| Headache | 6 (10.0) | 9 (14.8) |
| Psychiatric disorders | 11 (18.3) | 11 (18.0) |
| Depression | 7 (11.7) | 8 (13.1) |
| Insomnia | 5 (8.3) | 4 (6.6) |
| Respiratory, thoracic and mediastinal disorders | 6 (10.0) | 9 (14.8) |
| Cough | 4 (6.7) | 6 (9.8) |
| Rhinitis allergic | 2 (3.3) | 4 (6.6) |
| Skin and subcutaneous tissue disorders | 5 (8.3) | 4 (6.6) |
| Rash | 5 (8.3) | 4 (6.6) |

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; n = number of subjects with AEs.

Treatment-related TEAEs are summarized by system organ class in Table 16.

**Table 16. Treatment-Emergent Adverse Events by System Organ Class (Treatment-Related)**

| Number (%) of Subjects With AEs by System Organ Class | Maraviroc+Atazanavir/ Ritonavir n (%) | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir n (%) |
|---|---|---|
| Number (%) of subjects: evaluable for AEs | 60 | 61 |
| Number (%) of subjects: with AEs | 43 (71.7) | 40 (65.6) |
| Discontinued due to AEs | 2 (3.3) | 0 |
| Blood and lymphatic system disorders | 1 (1.7) | 0 |
| Ear and labyrinth disorders | 0 | 1 (1.6) |
| Eye disorders | 11 (18.3) | 8 (13.1) |
| Gastrointestinal disorders | 15 (25.0) | 18 (29.5) |
| General disorders and administration site conditions | 2 (3.3) | 2 (3.3) |
| Hepatobiliary disorders | 23 (38.3) | 20 (32.8) |
| Infections and infestations | 1 (1.7) | 0 |
| Investigations | 13 (21.7) | 7 (11.5) |
| Metabolism and nutrition disorders | 7 (11.7) | 2 (3.3) |
| Musculoskeletal and connective tissue disorders | 2 (3.3) | 1 (1.6) |
| Neoplasms benign, malignant and unspecified (inclusive cyst and polyps) | 2 (3.3) | 0 |
| Nervous system disorders | 3 (5.0) | 2 (3.3) |
| Psychiatric disorders | 1 (1.7) | 1 (1.6) |
| Renal and urinary disorders | 1 (1.7) | 2 (3.3) |
| Respiratory, thoracic and mediastinal disorders | 1 (1.7) | 0 |
| Skin and subcutaneous tissue disorders | 2 (3.3) | 6 (9.8) |
| Surgical and medical procedures | 0 | 1 (1.6) |
| Vascular disorders | 0 | 1 (1.6) |

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
AEs and SAEs are not separated out in this table.
MedDRA version 14.0 coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; n = number of subjects with pre-specified criteria; SAEs = serious adverse events.

Serious adverse events (SAEs) summarized by system organ class and preferred term are presented in Table 17.

## Table 17. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

| System Organ Class<br>Preferred Term | Maraviroc+Atazanavir/ Ritonavir<br>n (%) | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir<br>n (%) |
|---|---|---|
| Number (%) of subjects: evaluable for AEs | 60 | 61 |
| Number (%) of subjects: with AEs | 13 (21.7) | 11 (18.0) |
| Congenital, familial and genetic disorders | 1 (1.7) | 0 |
| Bronchogenic cyst | 1 (1.7) | 0 |
| Gastrointestinal disorders | 1 (1.7) | 3 (4.9) |
| Abdominal pain | 0 | 1 (1.6) |
| Enterocolitis | 0 | 1 (1.6) |
| Intestinal perforation | 1 (1.7) | 0 |
| Oesophageal stenosis | 0 | 1 (1.6) |
| Vomiting | 0 | 1 (1.6) |
| Hepatobiliary disorders | 1 (1.7) | 0 |
| Bile duct stone | 1 (1.7) | 0 |
| Cholelithiasis | 1 (1.7) | 0 |
| Infections and infestations | 4 (6.7) | 5 (8.2) |
| Anogenital warts | 1 (1.7) | 1 (1.6) |
| Bacteraemia | 0 | 1 (1.6) |
| Cellulitis | 1 (1.7) | 0 |
| Gastroenteritis viral | 1 (1.7) | 0 |
| Meningitis viral | 1 (1.7) | 0 |
| Parotitis | 0 | 1 (1.6) |
| Pneumonia | 0 | 1 (1.6) |
| Pyelonephritis | 0 | 1 (1.6) |
| Sepsis | 0 | 1 (1.6) |
| Sepsis syndrome | 0 | 1 (1.6) |
| Injury, poisoning and procedural complications | 1 (1.7) | 3 (4.9) |
| Concussion | 0 | 1 (1.6) |
| Foot fracture | 0 | 1 (1.6) |
| Hand fracture | 0 | 1 (1.6) |
| Tendon rupture | 1 (1.7) | 0 |
| Musculoskeletal and connective tissue disorders | 1 (1.7) | 0 |
| Costochondritis | 1 (1.7) | 0 |
| Nervous system disorders | 1 (1.7) | 1 (1.6) |
| Cognitive disorder | 1 (1.7) | 0 |
| Epilepsy | 0 | 1 (1.6) |
| Reversible ischaemic neurological deficit | 0 | 1 (1.6) |

**Table 17. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)**

| System Organ Class<br>Preferred Term | Maraviroc+Atazanavir/ Ritonavir<br>n (%) | Atazanavir/Ritonavir+ Emtricitabine/Tenofovir<br>n (%) |
|---|---|---|
| Psychiatric disorders | 1 (1.7) | 1 (1.6) |
| Mental status changes | 0 | 1 (1.6) |
| Psychotic disorder | 1 (1.7) | 0 |
| Renal and urinary disorders | 1 (1.7) | 2 (3.3) |
| Nephrolithiasis | 1 (1.7) | 0 |
| Renal colic | 0 | 1 (1.6) |
| Renal failure | 0 | 1 (1.6) |
| Respiratory, thoracic and mediastinal disorders | 3 (5.0) | 0 |
| Asthma | 2 (3.3) | 0 |
| Hypoxia | 1 (1.7) | 0 |
| Pulmonary sarcoidosis | 1 (1.7) | 0 |
| Vascular disorders | 0 | 1 (1.6) |
| Intra-abdominal haemorrhage | 0 | 1 (1.6) |

Subjects were only counted once per treatment for each row.
Included data up to 28 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = subjects with pre-defined criteria.

There were no deaths reported for subjects in this study. Thirteen (13) (21.7%) subjects in the maraviroc + atazanavir/ritonavir treatment group and 11 (18.0%) subjects in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group reported SAEs, none of which was considered by the Investigator to be treatment-related according to the clinical database. However, according to the safety database, one SAE of nephrolithiasis (maraviroc + atazanavir/ritonavir treatment group) was considered to be related to atazanavir. One subject in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group became pregnant during the study, and the child died (trisomy 13). These two additional SAEs (drug exposure during pregnancy and trisomy 13) were captured in the safety database.

Six (6) subjects had temporary discontinuations of study treatment due to AEs; none of the temporary discontinuations was considered by the Investigator to be related to the study treatment.

Two (2) subjects in the maraviroc + atazanavir/ritonavir treatment group permanently discontinued the study due to AEs (Table 18). There were no permanent discontinuations due to AEs in the atazanavir/ritonavir + emtricitabine/tenofovir treatment group.

**Table 18. Permanent Discontinuations due to Adverse Events (Safety Analysis Set)**

| Sl. No. | Gender (M/F) /Age (Years) | AE (Grade) MedDRA Preferred Term | Day of Onset[a] Stop Day of AE | Causality | Outcome | SAE (Yes/No) |
|---|---|---|---|---|---|---|
| Maraviroc + atazanavir/ritonavir treatment group | | | | | | |
| 1 | M/26 | Vomiting (2) | 86/98 | Related | Resolved | No |
| 2 | M/40 | Jaundice (2) | 2/(>7) | Related | Still present | No |

Age was recorded at screening.
Value in () was imputed from incomplete dates and times.
AE = adverse event; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities (version 14.0); SAE = serious adverse event (according to the investigator's assessment); Sl No. = serial number.
a. Day relative to start of study treatment. First day of study treatment was Day 1.

## CONCLUSIONS:

- The combination of maraviroc and atazanavir/ritonavir was effective in the treatment of treatment-naive HIV-1 infected subjects as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL at 96 weeks (67.8%) in comparison with atazanavir/ritonavir + emtricitabine/tenofovir (82.0%).

- In this 96-week study, there were no new tolerability or safety issues for maraviroc which would indicate a change in the benefit/risk balance of maraviroc for study subjects.

- A high proportion of maraviroc recipients achieved and maintained viral suppression through 24 weeks of treatment; at Week 24, 80.0% and 88.5% of subjects in the maraviroc+atazanavir/ritonavir and the atazanavir/ritonavir+emtricitabine/tenofovir treatment groups, respectively, had HIV-1 RNA <50 copies/mL.

- Maraviroc PK exposures achieved in the PK substudy appeared adequate.

- CD4 cell count increased from baseline to Week 96, with similar increases observed in both treatment groups.

- Of the 5 evaluable discontinuations, selection of resistance to maraviroc or to emtricitabine/tenofovir was not observed, and, while there was some minor variability of the protease encoding region in 2 subjects that might have been related to protease selective pressure, a resistance signal in terms of genotypic, phenotypic, or net susceptibility score to components of the regimens was not obtained. In addition, no change in tropism was observed in maraviroc recipients.