**Supplemental Digital Content 1.docx**

Withdrawal criteria for confirmed virologic failure or inadequate virologic response.(Original criteria that were changed are indicated by italics and are followed by the updated criteriaa)

|  |
| --- |
| **Virologic failure or non-response defined as an HIV-1 RNA level (confirmed within 14 daysb of the original failing viral load) that met any of the following criteria:** |
| HIV-1 RNA <1 log10 c/ml below baseline at week 4, unless the viral load is <50 c/ml |
| HIV-1 RNA >1 log10 c/ml above nadir value after week 4 |
| HIV-1 RNA >400 c/ml at any time on or after week 12 |
| *HIV-1 RNA >50 c/ml at any time on or after week 24*Protocol amendment:HIV-1 RNA >50 c/ml at any time on or after week 24 and with HIV‑1 RNA >400 c/ml at the second (confirmatory) visit |
| *HIV-1 RNA ≥50 c/ml after suppression to <50 c/ml on two consecutive visits*Protocol amendment: HIV-1 RNA ≥50 c/ml after confirmed suppression to <50 c/ml and with HIV-1 RNA >400 c/ml at the second (confirmatory) visit |

c/ml, copies/ml; FDA, Food and Drug Administration.

aOriginal withdrawal criteria was changed (Protocol Amendment #6) prior to unblinding by the sponsor, following FDA agreement and concurrence of the Data Monitoring Committee.

bPrior to protocol amendment, it was defined as ‘7–14 days’.

**Supplemental Digital Content 2.eps**

**Screening and subject disposition in the study (CONSORT diagram)**

CONSORT, CONsolidated Standards Of Reporting Trials; CVC, cenicriviroc; EFV, efavirenz; FTC, emtricitabine; IEC, Independent Ethics Committee; IRB, Institutional Review Board; TDF, tenofovir disoproxil fumarate.

a99 subjects did not meet entry criteria.

bSubject took CVC 200 mg due to dispensing of incorrect treatment kit. The subject discontinued study medication on day 9 as instructed by the sponsor, due to an exclusionary entry criterion (history of an abnormal electrocardiogram).

cSubject took prohibited medication.

**Supplemental Digital Content 3.eps**

Proportion of subjects with HIV-1 RNA <50 c/mla in each treatment group up to week 48

BL, baseline; c/ml, copies/ml; CVC, cenicriviroc; EFV, efavirenz; SE, standard error.

aSubjects considered to have HIV-1 RNA <50 c/ml, if the last on-treatment HIV-1 RNA value in the window was <50 c/ml and the subject did not have a protocol-excluded change in antiviral therapy prior to that value.

**Supplemental Digital Content 4.eps**

Change from baselinea in CD4+/CD8+ cell ratio in each treatment group up to week 48

 BL, baseline; CVC, cenicriviroc; EFV, efavirenz; SE, standard error.

aBaseline defined as the average of the baseline and screening visit 2 values. If only one value existed, this was considered the baseline.

**Supplemental Digital Content 5.docx**

**Graded laboratory abnormalities observed during the study in each treatment group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *n* (%) | CVC 100 mg (*n*=58) | CVC 200 mg(*n*=57) | EFV 600 mg(*n*=28) | *P* valuea |
| Any graded abnormality | 51 (88) | 55 (96) | 25 (89) | 0.227 |
| Grade 1 | 21 (36) | 16 (28) | 13 (46) |  |
| Grade 2 | 23 (40) | 27 (47) | 8 (29) |  |
| Grade 3 | 4 (7) | 9 (16) | 3 (11) |  |
| Grade 4 | 3 (5) | 3 (5) | 1 (4) |  |
| Grade ≥3 laboratory abnormalities | 7 (12) | 12 (21) | 4 (14) | 0.409 |
| Creatine phosphokinase increased | 3 (5) | 9 (16) | 2 (7) | 0.141 |
| Grade 3 | 2 (3) | 6 (11) | 2 (7) |  |
| Grade 4 | 1 (2) | 3 (5) | 0 (0) |  |
| Aspartate aminotransferase increased | 1 (2) | 0 (0) | 0 (0) | 0.481 |
| Grade 3 | 1 (2) | 0 (0) | 0 (0) |  |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |  |
| Phosphate decreased | 2 (3) | 2 (4) | 1 (4) | >0.999 |
| Grade 3 | 2 (3) | 2 (4) | 1 (4) |  |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |  |
| Prothrombin time/international normalized ratio increased | 1 (2) | 0 (0) | 0 (0) | 0.481 |
| Grade 3 | 0 (0) | 0 (0) | 0 (0) |  |
| Grade 4 | 1 (2) | 0 (0) | 0 (0) |  |
| Fibrinogen decreased | 0 (0) | 2 (4) | 0 (0) | 0.219 |
| Grade 3 | 0 (0) | 2 (4) | 0 (0) |  |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |  |
| Hemoglobin decreased | 1 (2) | 0 (0) | 0 (0) | 0.481 |
| Grade 3 | 0 (0) | 0 (0) | 0 (0) |  |
| Grade 4 | 1 (2) | 0 (0) | 0 (0) |  |
| Neutrophils decreased | 2 (3) | 0 (0) | 1 (4) | 0.365 |
| Grade 3 | 2 (3) | 0 (0) | 0 (0) |  |
| Grade 4 | 0 (0) | 0 (0) | 1 (4) |  |

CVC, cenicriviroc; EFV, efavirenz.

aThe *P* values were assessed using a Cochran–Mantel–Haenszel test for differences between treatment groups in number of subjects with the given toxicity.

**Supplemental Digital Content 6.eps**

**Change from baselinea in fasting glucose parameters (a) HbA1c (b) HOMA-IR in each treatment group up to week 48 (safety population)**

CVC, cenicriviroc; EFV, efavirenz; HbA1c, hemoglobin type A1c; HOMA-IR, homeostasis model of assessment; SE, standard error.

aDefined as the last non-missing assessment prior to initiation of study treatment.

**Supplemental Digital Content 7.eps**

Change from baselinea in inflammation biomarkers (a) MCP-1 and (b) sCD14b in each treatment group up to week 48 (ITT population)

BL, baseline; CVC, cenicriviroc; EFV, efavirenz; ITT, intention to treat; LS, least squares; MCP‑1, monocyte chemotactic protein-1; sCD14, soluble CD14; SE, standard error.

aDefined as the last non-missing assessment prior to initiation of study treatment.

bThe samples were originally tested in two separate batches; however, a reanalysis of sCD14 was performed in one single batch for consistency in analysis across time points. To adjust for the effects of covariates, LS means were calculated from a linear mixed model that included treatment, baseline sCD14 value, baseline HIV-1 RNA, visit, and treatment by visit interaction as fixed effects.

**Supplemental Digital Content 8.eps**

Change from baseline in sCD14 vs. HIV-1 RNA (log10) at week 48

CVC, cenicriviroc; EFV, efavirenz; sCD14, soluble CD14.

**Supplemental Digital Content 9.eps**

Pharmacokinetic/pharmacodynamic modeling at weeks 24 and 48.

Relationship between the number of subjects with (a) virologic non-response and Cmin at week 24 (b) virologic failure and Cmin at week 48 (c) virologic failure and Cavg at week 48

Cavg, average plasma concentration; Cmin, minimum plasma concentration.