**Supplement on PK methods**

PK-sampling was performed during a 12 to 24 hours hospital admission and included blood collection at baseline before treatment intake with food and after 1, 2, 3, 4, 6, 8 and 12 hours for twice daily regimens (arms A and D) and additionally after 16 and 24 hours for once daily regimens (arms B and C). Blood was centrifuged within one hour after venepuncture and plasma was stored at -80°C. Urines were collected at baseline and after 4, 8, 12, and - for once daily regimens only - after 24 hours, and the total urine volume per collection period was recorded. Urines were initially stored at 4 to 8°C, aliquoted and aliquots transferred to the study laboratories for storage at -80°C.

All samples were assayed using a validated quantitative liquid chromatography-mass spectrometry (LC-MS/MS) method connected to a triple quadrupole mass spectrometer (Waters® Xevo™ TQ Mass Spectrometer) featuring high speed Multiple Reaction Monitoring. The lower limit of quantitation for FZD, ZDV and ZDV-glucuronide was 5, 1 and 24 ng/mL, respectively. Fluoro derivate FZD (Chiracon, Germany), AZT-[2-13C-1,3-15N] (Moravek Biochemicals, USA) and AZT-Glu-[Me d3] (Santa Cruz Biotechnology, USA) were used as internal standards for the quantification of FZD, ZDV and ZDV-Gluc, respectively

PK variables included the area under the time-concentration curve (AUC) calculated using the linear trapezoidal rule and extrapolated to infinity from the last concentration above or equal to the lower quantitation limit divided by the elimination rate constant lz. Average concentration (Cavg) was calculated using the AUC within the dose interval τ divided by τ. The residual concentration of FZD measured at steady-state (Ctrough ss) was calculated as the mean of concentrations at time point zero and τ of the kinetics at week 4. The apparent oral volume of distribution (Vz/F), apparent total clearance (Cl/F) and renal clearance (ClR/F) were estimated. CL/F of ZDV and ZDV-glucuronide apparent clearance was calculated on the basis of the transformation of the FZD dose in equivalent ZDV and ZDV-glucuronide, respectively. The elimination half-life (t1/2) was calculated by log-linear regression as t1/2 = Ln 2/λz. The maximum plasma concentrations (Cmax) and the time to Cmax (Tmax) were taken directly from the observed values.

**Supplemental table for Figure 2A:** Change in median HIV-RNA log10 compared to baseline in the intent-to-treat population (only study treatment emergent values reported)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Arm A** | | **Arm B** | | **Arm C** | | **Combined FZD arms** | | **Arm D** | |
| **N** | **Median HIV-RNA Log10 reduction (IQR)** | **N** | **Median HIV-RNA Log10 reduction (IQR)** | **N** | **Median HIV-RNA Log10 reduction (IQR)** | **N** | **Median HIV-RNA Log10 reduction (IQR)** | **N** | **Median HIV-RNA Log10 reduction (IQR)** |
| **Week 2** | 29 | -2·12 (-2·58 to -1·60) | 28 | -2·21 (-2·55 to -1·58) | 29 | -1·84 (-2·25 to -1·73) | 86 | -2.00 (-2.47 to -1.66) | 31 | -2·01 (-2·40 to -1·72) |
| **Week 4** | 27 | -2·47 (-2·99 to -1·83) | 27 | -2·44 (-2·75 to -2·01) | 28 | -2·34 (-2·76 to -2·06) | 82 | -2.40 (-2.77 to -2.01) | 31 | -2·49 (-2·83 to -2·09) |
| **Week 8** | 27 | -3·02 (-3·38 to -2·40) | 24 | -2·86 (-3·35 to -2·45) | 27 | -2·85 (-3·27 to -2·38) | 78 | -2.89 (-3.34 to -2.41) | 30 | -2·92 (-3·23 to -2·35) |
| **Week 12** | 27 | -3·18 (-3·70 to -3·01) | 24 | -3·40 (-3·84 to -2·65) | 27 | -3·35 (-4·06 to -2·63) | 78 | -3.36 (-3.83 to -2.76) | 30 | -3·46 (-3·98 to -2·92) |
| **Week 24** | 26 | -4·02 (-4·40 to -3·31) | 22 | -3·85 (-4·44 to -3·20) | 26 | -3·59 (-4·14 to -3·08) | 74 | -3.73 (-4.34 to - 3.20) | 29 | -4·03 (-4·30 to -3·43) |

**Supplemental table for Figure 2B:** Change in median CD4 cell count compared to baseline in the intent-to-treat population (only study treatment emergent values reported)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Arm A** | | **Arm B** | | **Arm C** | | **Combined FZD arms** | | **Arm D** | |
| **N** | **Median change of CD4 count (IQR)** | **N** | **Median change of CD4 count (IQR)** | **N** | **Median change of CD4 count (IQR)** | **N** | **Median change of CD4 count (IQR)** | **N** | **Median change of CD4 count (IQR)** |
| **Week 4** | 29 | 58 (-8 to 82) | 26 | 55 (21 to 99) | 28 | 41 (-16 to 115) | 83 | 53 (-4 to 98) | 30 | 60 (9 to 99) |
| **Week 8** | 28 | 78 (25 to 131) | 25 | 65 (11 to 119) | 27 | 92 (-11 to 175) | 80 | 79 (14 to 138) | 30 | 71 (41 to 137) |
| **Week 12** | 28 | 62 (-23 to 123) | 22 | 103 (50 to 149) | 27 | 110 (2 to 180) | 77 | 87 (6 to 150) | 28 | 66 (39 to 143) |
| **Week 24** | 25 | 125 (69 to 181) | 22 | 92 (46 to 143) | 26 | 100 (38 to 222) | 73 | 99 (52 to 181) | 29 | 79 (65 to 144) |

**Supplement Table 1:** Treatment adherence assessed by pill count for and study drug and for single study drug throughout the entire study period

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Arm A**  **FZD 600mg BID**  **(n=30)** | **Arm B**  **FZD 800mg QD**  **(n=29)** | **Arm C**  **FZD 1200mg QD**  **(n=29)** | **Arm D**  **ZDV 300mg BID**  **(n=31)** |
| Any study drug |  |  |  |  |
| good (95-<105%) | 24 (80%) | 24 (83%) | 26 (90%) | 30 (97%) |
| average (80-<95%) | 5 (17%) | 4 (14%) | 3 (10%) | 1 (3%) |
| low (below 80%) | 1 (3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fozivudine |  |  |  |  |
| good (95-<105%) | 24 (80%) | 25 (86%) | 26 (90%) | - |
| average (80-<95%) | 5 (17%) | 3 (10%) | 3 (10%) | - |
| low (below 80%) | 1 (3%) | 0 (0%) | 0 (0%) | - |
| Lamivudine |  |  |  |  |
| good (95-<105%) | 26 (87%) | 24 (83%) | 27 (93%) | - |
| average (80-<95%) | 4 (13%) | 4 (14%) | 2 (7%) | - |
| low (below 80%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Zidovudine/lamivudine |  |  |  |  |
| good (95-<105%) | - | - | - | 30 (97%) |
| average (80-<95%) | - | - | - | 1 (3%) |
| low (below 80%) | - | - | - | 0 (0%) |
| Efavirenz |  |  |  |  |
| good (95-<105%) | 26 (87%) | 25 (86%) | 27 (93%) | 31 (100%) |
| average (80-<95%) | 4 (13%) | 3(10%) | 2 (7%) | 0 (0%) |
| low (below 80%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Data shown are n (%)

**Supplemental table 4:** Treatment emergent adverse events by all study arms

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Arm A**  **FZD 600mg BID**  **(n=30)** | **Arm B**  **FZD 800mg QD**  **(n=29)** | **Arm C**  **FZD 1200mg QD**  **(n=29)** | **Combined FZD arms**  **(N=88)** | **Arm D**  **ZDV 300mg BID**  **(N=31)** |
| Weeks of treatment exposure, mean (SD) | 22·5 (4·70) | 20·1 (7·57) | 22·6 (5·20) | 21·7 (5·99) | 23·5 (2·48) |
| Any adverse event | 25 (83%) | 24 (83%) | 27 (93%) | 76 (86%) | 26 (84%) |
| Adverse events related to study treatment | 14 (47%) | 16 (55%) | 15 (52%) | 45 (51%) | 15 (48%) |
| Grade 3 or 4 adverse events | 3 (10%) | 6 (21%) | 3 (10%) | 12 (14%) | 6 (19%) |
| Serious adverse events | 1 (3%) | 7 (24%) | 2 (7%) | 10 (11%) | 7 (23%) # |
| Serious adverse events related to study treatment | 1 (3%) § | 5 (17%) § | 0 § | 6 (7%) | 6 (19%) § |
| Adverse events leading to study treatment discontinuation | 0 | 3 (10%) ‡ | 2 (7%) ‡ | 5 (6%) | 1 (3%) ‡ |
| Most common treatment emerging adverse events (>5% overall) |  |  |  |  |  |
| * Nausea, vomiting | 7 (23%) | 3 (10%) | 6 (21%) | 16 (18%) | 5 (16%) |
| * Dizziness, vertigo | 4 (13%) | 5 (17%) | 6 (21%) | 15 (17%) | 3 (10% ) |
| * Nasopharyngitis, Tonsillitis | 3 (10%) | 5 (17%) | 3 (10%) | 11 (13%) | 4 (13%) |
| * Upper respiratory tract infection | 2 (7%) | 1 (3%) | 4 (14%) | 7 (8%) | 7 (23%) |
| * Asthenia, fatigue, somnolence | 3 (10%) | 5 (17%) | 4 (14%) | 12 (14%) | 1 (3%) |
| * Headache | 2 (7%) | 4 (14%) | 4 (14%) | 10 (11%) | 3 (10%) |
| * Gastritis, dyspepsia, abdominal pain | 5 (17%) | 1 (3%) | 2 (7%) | 8 (9%) | 4 (13%) |
| * Gastroenteritis, diarrhoea | 2 (7%) | 1 (3%) | 5 (17%) | 8 (9%) | 2 (7%) |
| * Influenza like illness | 0 | 5 (17%) | 2 (7%) | 7 (8%) | 3 (10%) |
| * Cough | 1 (3%) | 1 (3%) | 2 (7%) | 4 (5%) | 3 (10%) |
| * Rash | 4 (13%) | 1 (3%) | 1 (3%) | 6 (7%) | 1 (3%) |
| * Genital infection, pelvic inflammatory disease | 2 (7%) | 3 (10%) | 2 (7%) | 7 (8%) | 2 (7%) |
| Laboratory abnormalities (new or worsening) |  |  |  |  |  |
| * Anaemia, any grade | 2 (7%) | 4 (14%) | 4 (14%) | 10 (11%) | 7 (23%) |
| * Anaemia, grade 3/4 | 0 | 1 (3%) | 0 | 1 (1%) | 1 (3%) |
| * Leukopenia, any grade | 18 (60%) | 21 (72%) | 18 (62%) | 57 (65%) | 26 (84%) |
| * Leukopenia, grade 3/4 | 0 | 1 (3%) | 2 (7%) | 3 (3%) | 4 (13%) |
| * Neutropenia, any grade | 18 (60%) | 18 (62%) | 17 (59%) | 53 (60%) | 23 (74%) |
| * Neutropenia, grade 3/4 | 5 (17%) | 8 (28%) | 6 (21%) | 19 (22%) | 13 (42%) |
| * Thrombocytopenia, any grade | 2 (7%) | 2 (7%) | 1 (3%) | 5 (6%) | 1 (3%) |
| * Thrombocytopenia, grade 3/4 | 0 | 0 | 1 (3%) | 1 (1%) | 0 |
| * Creatinine (µmol/L), any grade | 2 (7%) | 1 (3%) | 0 | 3 (3%) | 3 (10%) |
| * Alanine aminotransferase , any grade | 2 (7%) | 5 (17%) | 2 (7%) | 9 (10%) | 4 (13%) |
| * Aspartate aminotransferase, any grade | 4 (13%) | 4 (14%) | 2 (7%) | 10 (11%) | 3 (10%) |
| * Aspartate aminotransferase, grade 3/4 | 0 | 1 (3%) | 0 | 1 (1%) | 1 (3%) |
| * γ-Glutamyl transferase, any grade | 9 (30%) | 13 (45%) | 8 (28%) | 30 (34%) | 8 (26%) |
| * γ-Glutamyl transferase, grade 3/4 | 7 (6%) | 6 (7%) | 1 (3%) | 6 (7%) | 1 (3%) |
| * Hyperbilirubinaemia, any grade\* | 1 (3%) | 0 | 1 (3%) | 2 (2%) | 0 |
| * Amylasaemia, any grade | 2 (7%) | 0 | 4 (14%) | 6 (7%) | 0 |
| * Hyperglycaemia, any grade\* | 5 (17%) | 1 (3%) | 5 (17%) | 11 (13%) | 4 (13%) |
| * Hypoglycaemia, any grade\* | 5 (17%) | 3 (10%) | 4 (14%) | 12 (14%) | 2 (7%) |
| * Hypercholesterolaemia, any grade\* | 4 (13%)1 | 1 (3%)2 | 3 (10%)3 | 8 (9%)4 | 4 (13%) |
| * Hypertriglyderidaemia, any grade\* | 01 | 02 | 1 (3%)3 | 1 (1%)4 | 0 |
| * Hyperlactaemia, > local reference range †\* | 01 | 1 (3%)2 | 1 (3%)3 | 2 (2%)4 | 0 |

# One patients reported with 3 SAE’s (septicaemia secondary to urinary tract infections, cataract surgery and °IV neutropenia)

§ FZD Arm A: TB-IRIS (1); FZD Arm B: °IV anaemia (1), °IV GGT elevation (1), KS-IRIS (1), °IV neutropenia (2); ZDV arm: °IV anaemia (1), °IV neutropenia (5)

‡ FZD Arm B:°IV anaemia (1), °IV GGT elevation (1), Kaposi’s sarcoma and chemotherapy (1); FZD Arm C: death due to cholangiocellular carcinoma (1), severe rash probably related to efavirenz (1), ZDV arm: °IV anaemia (1)

† Local reference range Tanzania >6·0 mmol/L; Côte d’Ivoire >2·44 mmol/L

\* includes participants with missing pre-treatment values which were replaced with Grade=0

1 Two missing values; 2 Three missing values; 3 One missing value; 4 Six missing values

**Supplemental table for Figure 3A:** Change in median haemoglobin compared to baseline in the safety population (only study treatment emergent values reported)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Arm A** | | **Arm B** | | **Arm C** | | **Combined FZD arms** | | **Arm D** | |
| **N** | **Median Hb change (IQR)** | **N** | **Median Hb change (IQR)** | **N** | **Median Hb change (IQR)** | **N** | **Median Hb change (IQR)** | **N** | **Median Hb change (IQR)** |
| Week 2 | 29 | -0·30 (-0·70 to 0·10) | 28 | -0·10 (-1·10 to 0·25) | 29 | -0·30 (-0·90 to 0·20) | 86 | -0·30 (-0·90 to -0·20) | 31 | -0·40 (-1·00 to 0·10) |
| Week 4 | 29 | -0·40 (-1·10 to 0·20) | 27 | -0·50 (-1·10 to -0·20) | 28 | -0·35 (-0·65 to 0·45) | 84 | -0·40 (-1·05 to 0·20) | 31 | -0·90 (-1·40 to -0·20) |
| Week 8 | 28 | -0·40 (-1·20 to 0·60) | 25 | -0·30 (-1·20 to 0·40) | 27 | -0·30 (-1·30 to 0·30) | 80 | -0·40 (1·20 to 0·45) | 31 | -0·60 (-1·20 to 0·30) |
| Week 12 | 28 | -0·10 (-0·80 to 0·85) | 24 | -0·25 (-0·60 to 0·15) | 27 | -0·10 (-0·60 to 0·40) | 79 | -0·20 (-0·80 to 0·40) | 30 | -0·65 (-1·10 to 0·20) |
| Week 24 | 27 | -0·20 (-0·90 to 0·70) | 22 | 0·00 (-0·70 to 1·00) | 26 | 0·40 (-0·50 to 1·00) | 75 | 0·20 (-0·70 to 0·80) | 29 | 0·20 (-0·70 to 0·80) |

**Supplemental table for Figure 3B:** Change in median absolute neutrophil count (x 103) compared to baseline in the safety population (only study treatment emergent values reported)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Arm A** | | **Arm B** | | **Arm C** | | **Combined FZD arms** | | **Arm D** | |
| **N** | **Median neutrophil change (IQR)** | **N** | **Median neutrophil change (IQR)** | **N** | **Median neutrophil change (IQR)** | **N** | **Median neutrophil change (IQR)** | **N** | **Median neutrophil change (IQR)** |
| Week 2 | 29 | -0·07 (-0·50 to 0·12) | 28 | -0·17 (-0·54 to 0·22) | 29 | -0·36 (-0·83 to -0·08) | 86 | -0.17 (-0.61 to 0.12) | 31 | -0·69 (-1·15 to 0·00) |
| Week 4 | 29 | -0·18 (-0·54 to 0·46) | 27 | -0·21 (-0·43 to 0·21) | 28 | -0·53 (-1·60 to -0·07) | 84 | -0.27 (-0.75 to 0.15) | 31 | -0·86 (-1·26 to -0·15) |
| Week 8 | 28 | -0·03 (-0·66 to 0·13) | 25 | -0·07 (-0·31 to 0·31) | 27 | -0·34 (0·96 to 0·48) | 80 | -0.08 (-0.61 to 0.26) | 31 | -0·61 (-0·97 to -0·14) |
| Week 12 | 28 | -0·04 (-0·48 to 0·38) | 24 | -0·10 (-0·37 to 0·15) | 27 | -0·63 (-1·06 to 0·54) | 79 | -0.16 (0.65 to 0.31) | 30 | -0·14 (-0·76 to 0·56) |
| Week 24 | 27 | -0·02 (-0·59 to 0·17) | 22 | 0·07 (-0·31 to 0·21) | 26 | -0·07 (-0·85 to 0·29) | 75 | -0.02 (-0.63 to 0.27) | 29 | -0·13 (-0·57 to 0·08) |