# Clinical trial results:
# SSAT058: A phase IV, open-label, multi centre pilot study to assess changes in cerebral function parameters in patients without perceived Central Nervous System (CNS) symptoms when switched from tenofovir/emtricitabine/efavirenz (Atripla®) to a fixed dose combination of tenofovir/emtricitabine/rilpivirine (Eviplera®).

## Summary

| | |
|---|---|
| EudraCT number | 2014-002284-15 |
| Trial protocol | GB |
| Global end of trial date | 10 February 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 June 2018 |
| First version publication date | 28 June 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | SSAT058 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02529059 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | St Stephen's AIDS Trust |
| Sponsor organisation address | Chelsea Chambers, 262a Fulham Road, London, United Kingdom, SW10 9EL |
| Public contact | Marita Marshall, St Stephen's AIDS Trust, +44 2038280567, marita.marshall@ststcr.com |
| Scientific contact | Prof. Mark Nelson, Chelsea and Westminster Hospital, mark.nelson@chelwest.nhs.uk |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 18 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 February 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 February 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess changes in neuropsychiatric and central nervous system (CNS) parameters in patients without perceived Central Nervous System (CNS) symptoms after 4 weeks of switching from Atripla (TDF/FTC/EFV) to Eviplera (TDF/FTC/RPV).

Protection of trial subjects:

The protocol was written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice, E6 and the principles of the Declaration of Helsinki. The protocol was approved by the National Regulator and an Independent Ethics Committee as required by national legislation.

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were encouraged to ask questions concerning all portions of the conduct of the study to ensure understanding. The purpose of the study together with the procedures benefits and risks of the study; any discomforts and the precautions taken was described during the consent process; allowing subject to make an informed decision about participation. Subjects were also informed of their right to discontinue from the study at any time without any detriment.

The inclusion/exclusion criteria were designed to eliminate subjects who may have been put at risk by participating in the study. Women of childbearing potential were required to have a negative pregnancy test at screening in order to exclude any participants who may have been pregnant, and these participants (along with heterosexually active males) were required to use effective birth control for the duration of the study.

Safety and tolerability of medications were assessed by questions, physical examination (as required) and laboratory parameters. Any changes in health status during the study were recorded and followed up by the clinical team.

Background therapy:

Only patients who were taking Atripla for at least 12 weeks, with established viral load suppression to undetectable levels (by local assay), were included in this study.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 December 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 42 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 42 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were competitively recruited from 4 sites in the UK; Elton John Centre (Brighton), Chelsea & Westminster Hospital (London), St Mary's Hospital (London) and Guy's & St. Thomas' Hospital (London).

42 patients were recruited from Dec 2015 to June 2016. One patient was deemed non-evaluable at baseline and is not included in the analysis.

### Pre-assignment

Screening details:

Four patients screened for the study were deemed ineligible:
- Due to previous nRTI treatment
- Could not comply with contraception requirements
- Could not comply with treatment switch requirements
- Presented with pre-existing cognitive issues at screening

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Experimental Arm |

Arm description:

Single Arm Study - all patients were switched from tenofovir/emtricitabine/efavirenz (Atripla®) to a fixed dose combination of tenofovir/emtricitabine/rilpivirine (Eviplera®).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Eviplera |
| Investigational medicinal product code | J05AR08 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

A single-pill fixed dose combination of tenofovir 245mg, emtricitabine 200mg and rilpivirine 25mg once daily.

| **Number of subjects in period 1** | Experimental Arm |
|---|---|
| Started | 42 |
| Week 4 | 40 |
| Week 12 | 39 |
| week 24 | 39 |
| Completed | 39 |
| Not completed | 3 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |

| | |
|---|---|
| Determined ineligible | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 42 | 42 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 40 | 40 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 47.3 | | |
| full range (min-max) | 31.2 to 68.4 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 39 | 39 | |
| Ethnicity<br>Units: Subjects | | | |
| Unknown | 2 | 2 | |
| English/Welsh/Scottish/Northern Irish/British | 26 | 26 | |
| Irish | 1 | 1 | |
| other White | 7 | 7 | |
| White & Black African | 1 | 1 | |
| Mixed/multiple ethnicity) | 1 | 1 | |
| African | 2 | 2 | |
| Caribbean | 1 | 1 | |
| other | 1 | 1 | |
| Duration of prior Atripla treatment<br>Units: Days | | | |
| median | 1778 | | |
| inter-quartile range (Q1-Q3) | 938 to 2656 | - | |

## End points

### End points reporting groups

| Reporting group title | Experimental Arm |
|---|---|

Reporting group description:

Single Arm Study - all patients were switched from tenofovir/emtricitabine/efavirenz (Atripla®) to a fixed dose combination of tenofovir/emtricitabine/rilpivirine (Eviplera®).

| Subject analysis set title | Baseline |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients attending baseline visit (pre-switch).

Note: 1 patient excluded from analysis due to protocol deviation

| Subject analysis set title | Week 4 |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients attending Week 4 visit post switch

| Subject analysis set title | Week 12 |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients attending Week 12 visit post switch

| Subject analysis set title | Week 24 |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients attending Week 24 visit (post switch)

### Primary: Proportion of patients with grade 2-4 CNS AE at Baseline, Week 4 and Week 12 , as reported in the CNS questionnaire:

| End point title | Proportion of patients with grade 2-4 CNS AE at Baseline, Week 4 and Week 12 , as reported in the CNS questionnaire:[1] |
|---|---|

End point description:

AEs were graded using a study questionnaire based on the AIDS Clinical Trials Group (ACTG) grading scale.

These were then coded as:
0 - None
1 - Mild
2 - Moderate
3 - Severe

The following results represent frequency of patients with at least one moderate (or severe) AE from this questionnaire.

McNemars Chi squared value for change in individual toxicities given in attached report.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline, Week 4 and Week 12 post switch

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A summary listing of the 'proportion of patients affected' is the only measure required by protocol

| End point values | Baseline | Week 4 | Week 12 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 40 | 39 | |
| Units: Patients | | | | |
| Any | 14 | 7 | 9 | |
| Dizziness | 3 | 1 | 1 | |
| Depression/low mood | 3 | 1 | 3 | |
| Insomnia/sleeplessness | 5 | 4 | 5 | |
| Anxiety/nervousness | 3 | 1 | 0 | |
| Confusion | 1 | 1 | 0 | |
| Impaired concentration/attention | 3 | 1 | 1 | |
| Headache | 3 | 1 | 1 | |
| Somnolence/daytime sleepiness | 2 | 5 | 2 | |
| Aggressive mood/behaviour | 2 | 0 | 1 | |
| Abnormal dreams | 9 | 1 | 1 | |

| Attachments (see zip file) | SSAT058 CNS Questionnaire results.pdf |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Primary: Median number of grade 2+ neuropsychiatric and CNS AEs, as reported in the CNS questionnaire at Baseline, Week 4 and Week 12

| End point title | Median number of grade 2+ neuropsychiatric and CNS AEs, as reported in the CNS questionnaire at Baseline, Week 4 and Week 12 |
|---|---|

End point description:

Please note that this was not considered a normalised dataset, and therefore range is given instead of the originally intended 95% CI. Incidence of grade 2+ AEs were transformed into a score out of 100 to facilitate comparison.

| End point type | Primary |
|---|---|

End point timeframe:

Basseline, Week 4 and Week 12

| End point values | Baseline | Week 4 | Week 12 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 40 | 39 | |
| Units: Score (/100) | | | | |
| median (full range (min-max)) | 0 (0 to 30) | 0 (0 to 25) | 0 (0 to 25) | |

## Statistical analyses

| **Statistical analysis title** | Baseline to week 4 |
|---|---|
| Statistical analysis description:<br>% improvement in total CNS score from baseline | |
| Comparison groups | Baseline v Week 4 |
| Number of subjects included in analysis | 81 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | = 0.064 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 12 |
|---|---|
| Statistical analysis description:<br>% improvement in total CNS score from baseline | |
| Comparison groups | Baseline v Week 12 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | = 0.022 |
| Method | Wilcoxon (Mann-Whitney) |

**Primary: Median CNS toxicity score (from CNS questionnaire) from baseline compared to Week 4 and Week 12**

| End point title | Median CNS toxicity score (from CNS questionnaire) from baseline compared to Week 4 and Week 12 |
|---|---|
| End point description:<br>All grades of CNS adverse events reported in the questionnaire were summed together. This total was then transformed into a score from 0 to 100, where a score of 0 represents no adverse events, and 100 is all events reported as 'Severe'. Due to this dataset not being normalised, inter-quartile range is given instead of the protocol specified 95% CI. | |
| End point type | Primary |
| End point timeframe:<br>Baseline to Week 4 and Week 12 | |

| **End point values** | Baseline | Week 4 | Week 12 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 40 | 39 | |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | 10 (3 to 23) | 7 (3 to 13) | 10 (3 to 17) | |

**Statistical analyses**

| Statistical analysis title | Baseline to week 4 |
|---|---|
| Comparison groups | Baseline v Week 4 |
| Number of subjects included in analysis | 81 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | = 0.028 |
| Method | Wilcoxon (Mann-Whitney) |

| Statistical analysis title | Baseline to week 12 |
|---|---|
| Comparison groups | Baseline v Week 12 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| P-value | = 0.064 |
| Method | Wilcoxon (Mann-Whitney) |

**Primary: Rate of toxicity as measured by change in sleep score from baseline to Week 4, Week 12 & Week 24**

| End point title | Rate of toxicity as measured by change in sleep score from baseline to Week 4, Week 12 & Week 24 |
|---|---|

End point description:

Please note that this was not considered a normalised dataset, and therefore inter-quartile range is given instead of the originally intended 95% CI.

All reported sleep adverse effects were transformed into a score out of 100 for ease of comparison.

'Change from baseline' measures the improvement in responses. A positive value indicates a reduction in reported adverse events.

Note: Week 24 time-point is considered a secondary endpoint.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline to week 4 / week 12

| End point values | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39[2] |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Sleep score | 22 (20 to 32) | 20 (14 to 29) | 19 (14 to 27) | 20 (14 to 26) |
| Change from baseline | 0 (0 to 0) | 2 (-1 to 8) | 4 (-1 to 10) | 3 (-2 to 10) |

Notes:

[2] - Secondary endpoint

| | |
|---|---|
| **Attachments (see zip file)** | SSAT058 Sleep questionnaire results.pdf |

**Statistical analyses**

| **Statistical analysis title** | Baseline to week 4 |
|---|---|
| Comparison groups | Baseline v Week 4 |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.008 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 12 |
|---|---|
| Comparison groups | Week 12 v Baseline |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 24 |
|---|---|
| Comparison groups | Week 24 v Baseline |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.009 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Friedman's test |
|---|---|
| Comparison groups | Baseline v Week 4 v Week 12 v Week 24 |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.03 |
| Method | Friedman's test |

**Secondary: Proportion of patients with grade 2-4 CNS AE at Week 24 , as reported in the CNS questionnaire:**

| End point title | Proportion of patients with grade 2-4 CNS AE at Week 24 , as reported in the CNS questionnaire: |
|---|---|

| | |
|---|---|
| End point description: | |
| McNemars Chi squared value for change in individual toxicities given in attached report. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 24 post treatment switch | |

| **End point values** | Week 24 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37[3] | | | |
| Units: Patients | | | | |
| Any | 10 | | | |
| Dizziness | 0 | | | |
| Depression/low mood | 2 | | | |
| Insomnia/sleeplessness | 6 | | | |
| Anxiety/nervousness | 2 | | | |
| Confusion | 0 | | | |
| Impaired concentration/attention | 1 | | | |
| Headache | 1 | | | |
| Somnolence/daytime sleepiness | 3 | | | |

Notes:

[3] - 2 patients DNA

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Median number of grade 2+ neuropsychiatric and CNS AEs, as reported in the CNS questionnaire at Week 24**

| | |
|---|---|
| End point title | Median number of grade 2+ neuropsychiatric and CNS AEs, as reported in the CNS questionnaire at Week 24 |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Week 24 visit only | |

| **End point values** | Week 24 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37[4] | | | |
| Units: Adverse Events | | | | |
| median (full range (min-max)) | 0 (0 to 5) | | | |

Notes:

[4] - 2 patients DNA

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median CNS toxicity score (from CNS questionnaire) at Week 24

| End point title | Median CNS toxicity score (from CNS questionnaire) at Week 24 |
|---|---|

End point description:

All grades of CNS adverse events reported in the questionnaire were summed together. This total was then transformed into a score from 0 to 100, where a score of 0 represents no adverse events, and 100 is all events reported as 'Severe'. Due to this dataset not being normalised, inter-quartile range is given instead of the protocol specified 95% CI.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 24

| End point values | Week 24 | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37[5] | | | |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | 7 (3 to 17) | | | |

Notes:

[5] - 2 patients DNA

### Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of change in CNS parameters as measured using the Hospital Anxiety and Depression Scale (HADS) at Week12/24 compared to baseline

| End point title | Rate of change in CNS parameters as measured using the Hospital Anxiety and Depression Scale (HADS) at Week12/24 compared to baseline |
|---|---|

End point description:

A HAD score was derived based on responses in the HAD scale questionnaire. The responses to each question were given scores that ranged from 0 to 3 where response with a score of 0 gave a positive response while 3 gave negative response. All missing responses were scored 3.

The total HAD scores from each patient responses were taken as a fraction of the observed HAD score relative to the expected total HAD score. These have been expressed as that out of 100. So the minimum possible score that could be observed could be 0 and maximum possible score that could be observed is 100 (‘worse’).

Please note that this was not considered a normalised dataset, and therefore inter-quartile range is given instead of the originally intended 95% CI.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Week 12 / Week 24

| End point values | Baseline | Week 12 | Week 24 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 39 | 39 | |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Absolute value | 14.3 (7.1 to 26.2) | 16.7 (2.4 to 23.8) | 9.5 (0.0 to 26.2) | |
| Change from Baselnie | 0.0 (0.0 to 0.0) | 2.4 (-2.4 to 7.1) | 2.4 (0.0 to 7.1) | |

| Attachments (see zip file) | SSAT058 HAD Results.pdf |
|---|---|

**Statistical analyses**

| Statistical analysis title | Baseline to week 12 |
|---|---|
| Comparison groups | Baseline v Week 12 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.049 |
| Method | Wilcoxon (Mann-Whitney) |

| Statistical analysis title | Baseline to week 24 |
|---|---|
| Comparison groups | Baseline v Week 24 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.024 |
| Method | Wilcoxon (Mann-Whitney) |

| Statistical analysis title | Friedman's test |
|---|---|
| Comparison groups | Baseline v Week 12 v Week 24 |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | Friedman's test |

**Secondary: Proportion of patients with undetectable viral load at weeks 4, 12 and 24**

| End point title | Proportion of patients with undetectable viral load at weeks 4, 12 and 24 |
|---|---|

| | |
|---|---|
| End point description:<br>Undetectable by local assay | |
| End point type | Secondary |
| End point timeframe:<br>Weeks 4, 12 and 24 | |

| **End point values** | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: Patients | 40 | 40 | 38 | 39 |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Proportion of patients with viral load below 400 copies/ml at Weeks 4, 12 and 24**

| | |
|---|---|
| End point title | Proportion of patients with viral load below 400 copies/ml at Weeks 4, 12 and 24 |
| End point description: | |
| End point type | Secondary |
| End point timeframe:<br>Weeks 4, 12 and 24. | |

| **End point values** | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: Patients | | | | |
| <400 | 41 | 40 | 39 | 39 |
| >=400 | 0 | 0 | 0 | 0 |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from baseline CD4+ count at Week 12 and Week 24**

| | |
|---|---|
| End point title | Change from baseline CD4+ count at Week 12 and Week 24 |
| End point description: | |
| End point type | Secondary |

End point timeframe:
Baseline to Weeks 12 and 24

| **End point values** | Baseline | Week 12 | Week 24 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 39 | 39 | |
| Units: cells/millilitre | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Absolute value | 563 (465 to 679) | 590 (481 to 719) | 600 (488 to 682) | |
| Change from baseline | 0 (0 to 0) | 16 (-34 to 60) | -2 (-55 to 75) | |

**Statistical analyses**

| **Statistical analysis title** | Baseline to week 12 |
|---|---|
| Comparison groups | Week 12 v Baseline |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.238 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 24 |
|---|---|
| Comparison groups | Baseline v Week 24 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.995 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Proportion of patients with grade 2-4 non-lipid laboratory AEs at Weeks, 4, 12 and 24 compared with Baseline**

| End point title | Proportion of patients with grade 2-4 non-lipid laboratory AEs at Weeks, 4, 12 and 24 compared with Baseline |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
Baseline to Weeks 4, 12 and 24

| End point values | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: Patients | | | | |
| Sodium (high) | 0 | 0 | 0 | 0 |
| Sodium (low) | 0 | 0 | 0 | 0 |
| Potassium (high) | 0 | 0 | 0 | 0 |
| Potassium (low) | 0 | 0 | 0 | 0 |
| Creatinine | 0 | 1 | 2 | 1 |
| Albumin | 0 | 0 | 0 | 0 |
| glucose | 1 | 2 | 2 | 2 |
| ALT | 0 | 0 | 0 | 0 |
| ALP | 0 | 0 | 0 | 0 |
| AST | 0 | 0 | 0 | 0 |
| Total Bilirubin | 0 | 0 | 0 | 0 |
| Serum Phosphate | 4 | 4 | 1 | 3 |
| Haemoglobin | 0 | 0 | 0 | 0 |
| White Blood Cells | 0 | 0 | 0 | 0 |
| Platelets | 0 | 0 | 0 | 0 |
| Neutrophils | 0 | 0 | 0 | 0 |

| Attachments (see zip file) | SSAT058 Lab reults.pdf |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of patients with grade 2-4 non-CNS adverse events at Weeks, 4, 12 and 24 compared with Baseline

| End point title | Proportion of patients with grade 2-4 non-CNS adverse events at Weeks, 4, 12 and 24 compared with Baseline |
|---|---|

End point description:

Proportion of patients experiencing at least one Grade 2+ (moderate or severe) AE. As assessed by the CNS questionnaire.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 4,12 and 24

| End point values | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 37 |
| Units: Patients | | | | |
| None | 27 | 33 | 30 | 27 |
| 1+ Moderate/Severe | 14 | 7 | 9 | 10 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in lipid parameters from Baseline to Weeks 4, 12 and 24

| End point title | Change in lipid parameters from Baseline to Weeks 4, 12 and 24 |
|---|---|

End point description:

p-values from Wilcoxon signed rank tests listed in attached lab data table.

Additionally this analysis has been performed both with and without protocol deviating patients, as listed in the table attached to the first laboratory parameters endpoint.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Weeks 4, 12 and 24.

| End point values | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: mmol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Total cholesterol values | 5.2 (4.6 to 5.7) | 4.7 (4.2 to 5.0) | 4.5 (3.8 to 5.0) | 4.4 (4.0 to 5.2) |
| Total cholesterol change from baseline | 0.0 (0.0 to 0.0) | -0.6 (-0.8 to -0.2) | -0.7 (-1.0 to -0.5) | -0.8 (-1.2 to -0.3) |
| HDL | 1.4 (1.2 to 1.6) | 1.3 (1.1 to 1.5) | 1.3 (1.1 to 1.5) | 1.3 (1.1 to 1.5) |
| HDL change from baseline | 0.0 (0.0 to 0.0) | -0.11 (-0.23 to 0.02) | -0.10 (-0.26 to 0.00) | -0.13 (-0.30 to 0.06) |
| LDL | 3.1 (2.4 to 3.5) | 2.8 (2.2 to 3.1) | 2.5 (2.1 to 3.1) | 2.7 (2.1 to 3.3) |
| LDL change from baseline | 0.0 (0.0 to 0.0) | -0.36 (-0.61 to -0.07) | -0.50 (-0.79 to -0.28) | -0.40 (-0.80 to -0.08) |
| total:HDL ratio | 3.6 (3.2 to 4.2) | 3.4 (2.8 to 4.2) | 3.6 (3.0 to 4.1) | 3.5 (2.8 to 4.3) |
| total:HDL ratio change from baseline | 0.0 (0.0 to 0.0) | -0.12 (-0.49 to -0.10) | -0.24 (-0.50 to 0.01) | -0.19 (-0.47 to 0.21) |
| Triglycerides | 1.3 (0.8 to 2.4) | 0.9 (0.7 to 1.8) | 1.3 (0.6 to 1.6) | 0.9 (0.7 to 1.6) |
| Triglycerides change from baseline | 0.0 (0.0 to 0.0) | -0.26 (-0.71 to 0.01) | -0.17 (-0.82 to 0.10) | -0.28 (-0.72 to 0.08) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in quality of life 4, 12 and 24 weeks post switch, as measured by the EuroQOL questionnaire

| End point title | Change in quality of life 4, 12 and 24 weeks post switch, as measured by the EuroQOL questionnaire |
|---|---|

End point description:

Scores were converted to (/100) to facilitate comparison
Max possible=100 (best imaginable health state)
Min possible=0 (worst imaginable health state)

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Weeks 4, 12 and 24

| End point values | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Absolute score | 80 (75 to 90) | 90 (73 to 94) | 89 (80 to 90) | 90 (75 to 95) |
| Change from baseline | 0 (0 to 0) | -2 (-10 to 0) | -5 (-10 to 0) | -3 (-10 to 0) |

| Attachments (see zip file) | SSAT058 EQ5d results.pdf |
|---|---|

### Statistical analyses

| Statistical analysis title | Friedman's test |
|---|---|
| Comparison groups | Week 4 v Baseline v Week 12 v Week 24 |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.002 |
| Method | Friedman's test |

| Statistical analysis title | Baseline to week 4 |
|---|---|
| Comparison groups | Baseline v Week 4 |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.003 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 12 |
|---|---|
| Comparison groups | Baseline v Week 12 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.007 |
| Method | Wilcoxon (Mann-Whitney) |

| **Statistical analysis title** | Baseline to week 24 |
|---|---|
| Comparison groups | Baseline v Week 24 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.005 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: Change in neurocognitive function from baseline to Weeks 4, 12 and 24. As measured by Instrumental Activities of Daily Life questionnaire**

| End point title | Change in neurocognitive function from baseline to Weeks 4, 12 and 24. As measured by Instrumental Activities of Daily Life questionnaire |
|---|---|

End point description:

Scores were converted to (/100) to facilitate comparison
Max possible=100 (best imaginable health state)
Min possible=0 (worst imaginable health state)

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Weeks 4, 12 and 24

| **End point values** | Baseline | Week 4 | Week 12 | Week 24 |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 40 | 39 | 39 |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Absolute score | 100 (100 to 100) | 100 (100 to 100) | 100 (100 to 100) | 100 (100 to 100) |
| Change from Baseline | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) |

| Attachments (see zip file) | SSAT058 IADL Results.pdf |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in medication adherence from Baseline to Weeks 12 and 24. As measured by the adherence questionnaire

| End point title | Change in medication adherence from Baseline to Weeks 12 and 24. As measured by the adherence questionnaire |
|---|---|

End point description:

Adherence to study medication as measured by the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline to Week 12/24

| End point values | Week 12 | Week 24 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 39 | 39 | | |
| Units: % improvement | | | | |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 1) | 0 (0 to 5) | | |

| Attachments (see zip file) | SSAT 058 Analysis v3.3 MMASRI.pdf |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in cerebral MRI modalities from Baseline to Week 24

| End point title | Change in cerebral MRI modalities from Baseline to Week 24 |
|---|---|

End point description:

Imaging modalities given as absolute values, then as change from baseline (difference)

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline to Week 24

| End point values | Baseline | Week 24 | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 10 | | |
| Units: Ratio | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |

| | | | | |
|---|---|---|---|---|
| ThalbasNAACr | 0.96 (0.70 to 1.08) | 1.07 (0.95 to 1.41) | | |
| Difference ThalbasNAACr | 0 (0 to 0) | 0.19 (-0.11 to 0.44) | | |
| Tha cholCr | 0.23 (0.19 to 0.25) | 0.23 (0.21 to 0.27) | | |
| Difference Tha cholCr | 0 (0 to 0) | 0.01 (-0.04 to 0.04) | | |
| Thal GlxCr | 0.80 (0.73 to 1.16) | 0.98 (0.84 to 1.38) | | |
| Difference Thal GlxCr | 0 (0 to 0) | 0.22 (-0.28 to 0.65) | | |
| FW NAACr | 1.24 (1.07 to 1.33) | 1.12 (1.01 to 1.23) | | |
| Difference FW NAACr | 0 (0 to 0) | -0.05 (-0.17 to 0.02) | | |
| FW CholCr | 0.31 (0.27 to 0.34) | 0.27 (0.24 to 0.34) | | |
| Difference FW CholCr | 0 (0 to 0) | -0.04 (-0.08 to 0.01) | | |
| FW GlxCr | 0.88 (0.62 to 1.00) | 0.90 (0.85 to 0.96) | | |
| Difference FW GlxCr | 0 (0 to 0) | 0.10 (-0.02 to 0.40) | | |
| FW InsCr | 0.59 (0.53 to 0.71) | 0.61 (0.58 to 0.85) | | |
| Difference FW InsCr | 0 (0 to 0) | 0.106 (-0.01 to 0.19) | | |
| FG NAACr | 1.09 (1.04 to 1.14) | 1.06 (0.94 to 1.13) | | |
| Difference FG NAACr | 0 (0 to 0) | -0.02 (-0.15 to 0.05) | | |
| FG choCr | 0.25 (0.23 to 0.26) | 0.22 (0.21 to 0.26) | | |
| Difference FG choCr | 0 (0 to 0) | -0.01 (-0.05 to 0.02) | | |
| FG InsCr | 0.61 (0.53 to 0.64) | 0.62 (0.57 to 0.68) | | |
| Difference FG InsCr | 0 (0 to 0) | -0.04 (-0.05 to 0.10) | | |

| | |
|---|---|
| **Attachments (see zip file)** | SSAT058 MR results.pdf |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in neurocognitive function from baseline to Weeks 4 and 24. As measured by computerised cognitive testing

| | |
|---|---|
| End point title | Change in neurocognitive function from baseline to Weeks 4 and 24. As measured by computerised cognitive testing |

End point description:

CogState cognitive tasks use novel visual and verbal stimuli to ensure assessment is culture-neutral and not limited by a subject or participant’s level of education. All Cogstate tasks are designed for repeated administration with minimal practice or learning effects.

A Cogstate battery comprises a number of individual tasks – each designed to test a specific area of

cognition. When a number of these individual tests are put together to form a test battery, a more complete picture of a person’s cognitive state can be defined.

Each participants score was measured against available normative data, and is shown as a summary below. Individual comparisons for each test are given in the attached table.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Weeks 4 and 24.

| **End point values** | Baseline | Week 4 | Week 24 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 | 40 | 39 | |
| Units: Score (/100) | | | | |
| median (inter-quartile range (Q1-Q3)) | -0.01 (-0.71 to 0.80) | -0.06 (-0.71 to 0.72) | -0.15 (-0.62 to 0.78) | |

| **Attachments (see zip file)** | SSAT058 Cogstate.pdf |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From consent to follow-up (Week 24+30 days)

Adverse event reporting additional description:

Adverse event incidence for laboratory and CNS categories, are further detailed in the endpoints section.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | ACTG Adverse Events |
| Dictionary version | 1.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Experimental Arm |

Reporting group description:

Single Arm Study - all patients were switched from tenofovir/emtricitabine/efavirenz (Atripla®) to a fixed dose combination of tenofovir/emtricitabine/rilpivirine (Eviplera®).

| Serious adverse events | Experimental Arm | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Trauma (foot) | Additional description: Hospitalisation | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Epiglotitis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Experimental Arm | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 40 (100.00%) | | |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Tiredness | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Ear and labyrinth disorders | | | |
| Hayfever | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Toothache | Additional description: including tooth pain | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Renal and urinary disorders | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | | |
| occurrences (all) | 6 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Cold | | | |
| subjects affected / exposed | 4 / 40 (10.00%) | | |
| occurrences (all) | 4 | | |
| Influenza | | | |
| subjects affected / exposed | 5 / 40 (12.50%) | | |
| occurrences (all) | 5 | | |
| Viral infection | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | | |
| Gonorrhea | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 October 2015 | Principal Investigator change |
| 08 February 2016 | Addition of an interim analysis post after all patients had completed their Week 4 visit |
| 07 December 2016 | Addition of an interim analysis after all participants had completed the Week 12 visit |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported