Clinical trial results:
A phase III, open-label, multi centre pilot study to assess the feasibility of switching, individuals receiving Atripla or Kivexa plus Efavarinz with continuing Central Nervous System (CNS) toxicity, to a fixed dose combination of tenofovir/emtricitabine/rilpivirine (Eviplera)

Summary

EudraCT number	2012-002205-22
Trial protocol	GB
Global end of trial date	11 November 2013

Results information

Result version number	v1 (current)
This version publication date	22 November 2017
First version publication date	22 November 2017

Trial information

Trial identification

Sponsor protocol code	SSAT047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St Stephens Aids Trust
Sponsor organisation address	Chelsea Chambers, 262a Fulham Road, London, United Kingdom, SW10 9NH
Public contact	Marita Marshall, Head of Project Management, St Stephens Clinical Research, +44 0203 828 0567, marita.marshall@ststcr.com
Scientific contact	Prof Mark Nelson, St Stephen's Centre, Chelsea & Westminster Hospital, +44 0203 315 5610 , 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	15 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether switching individuals who have central nervous system (CNS) side effects from taking efavirenz-containing treatment (as Atripla or Kivexa plus efavarinz) to Eviplera resolves the CNS side effects after 12 weeks.

Protection of trial subjects:

The protocol was written, and the study was conducted according to the ICH GC P. 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. The inclusion/exclusion criteria were designed to eliminate subjects who may have been put at risk by participating in the study. Safety and tolerability of medications were assessed by questions, physical examination and laboratory parameters. Any changes in health status during the study were recorded and followed up by the clinical team.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2012
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	39

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited from 4 sites between 10/12/2012 & 18/03/2013

Pre-assignment

Screening details:

All subjects screened were randomised

Period 1

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

Arms

Arm title	Experimental

Arm description:

Single Arm study - all subjects

Arm type	Experimental
Investigational medicinal product name	Eviplera [tenofovir/emtricitabine/rilpivirine fixed dose combination]
Investigational medicinal product code	J05AR08
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg emtricitabine / 25mg rilpivirine/ 245mg tenofovir

Number of subjects in period 1	Experimental
Started	40
Completed	39
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Experimental

Reporting group description: -

Reporting group values	Experimental	Total	
Number of subjects	40	40	
Age categorical 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)	39	39	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	46.7		
full range (min-max)	24.4 to 72.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	36	36	
Ethnicity			
Self reported ethnicity			
Units: Subjects			
White/Caucasian	32	32	
Black African	1	1	
Black Caribbean	4	4	
Black Other	1	1	
Other	2	2	

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description:	
Single Arm study - all subjects	

Primary: Rate of Neuropsychiatric and CNS toxicity after 12 weeks of treatment

End point title	Rate of Neuropsychiatric and CNS toxicity after 12 weeks of treatment[1]
End point description:	
Measured by a questionnaire based on efavirenz SPC	
End point type	Primary
End point timeframe:	
Proportion change from baseline at 12 weeks	

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: Descriptive stats only

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	39[2]			
Units: % subjects	20			

Notes:

[2] - 1 subject withrew prior to wk12

Statistical analyses

No statistical analyses for this end point

Primary: Proportion with CNS side effects

End point title	Proportion with CNS side effects[3]
End point description:	

End point type	Primary
End point timeframe:	
at 12 weeks– compared to baseline	

Notes:

[3] - 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: Descriptive stats only

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	39[4]			
Units: % change				
No Change	20			
Base None/Mild to Mod/Severe	0			
Base Mod/Severe to None/Mild	19			

Notes:

[4] - One subject dropped out before week 12

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent to subjects final study visit.

Adverse event reporting additional description:

All CNS related AEs were captured on the CNS questionnaire only but were reviewed by the investigator to evaluate whether they met the SAE reporting criteria. Reasons for any Surgical procedures should be reported as AEs rather than the procedures themselves

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Experimental Arm

Reporting group description:

All subjects

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			
Vascular disorders			
Worsening Thrombocytopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Experimental Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 40 (90.00%)		
Vascular disorders			
Worsening thrombocytopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Abnormal gait			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Coryzal illness			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Fevers			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Immune system disorders			
Cough			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Cough with sputum			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dry cough			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hayfever			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Running nose			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Low tesrosterone			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Worsening of erectile dysfunchion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Worsening asthma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psychiatric disorders			
Low mood			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Low mood tearful demotivated			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Mood swings + depression			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
sleep disturbances			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Nervous system disorders			
Decreased range of movement in neck			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Decreased vision			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Dysaesthesia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
MRI head			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pins & needle			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Earache			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
fullness in both ears			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Acidic feeling in throat			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Bloating			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Diahorrea + vomiting			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Diahorrea secondary to lymphagram venereum (LGV)			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Heartburn			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Increased hunger			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Loose stools			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Pain in lower abdomen			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pain on swallowing			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Perianal ulcers			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
PR bleeds			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Recral bleeding 20 to lymphagram venereum (LGV)			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hepatobiliary disorders			
Elevated liver function			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
acneform papules (face)			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dry Scalp			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Sweating in morning			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Deteriorating renal funchion			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gout attack			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Smelly urine with			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Calf pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Loin pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Feet pain			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Fractured metatarsal in left			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Muscle aches with abnormal c			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Muscle pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pain in leg			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sciatic pain radiating to le			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sore Knee			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Sprained ankle			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Cellulitis left foot secondary burn			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Chest infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Dental abscess			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Fungal foot infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
LRTI subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Non specific viral illness subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
presumed upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Metabolism and nutrition disorders Diabetes Mellitus subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Leg swelling subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2013	Addition of an interim analysis once all subjects had completed week 12.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Volume of plasma from each patient & time point was ≤2ml & insufficient for running the HIV-1 RNA assay in its standard format. This was addressed by undertaking extensive assay validation experiments to optimise the nucleic acid extraction protocol

Notes: