



## 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
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#### 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
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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 efavirin) 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

<b>Arm title</b>	Experimental
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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

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Consent withdrawn by subject	1

## Baseline characteristics

### Reporting groups

Reporting group title	Experimental
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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 <sup>[1]</sup>
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

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

Notes:

[2] - 1 subject withdrew 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 <sup>[3]</sup>
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

<b>End point values</b>	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	39 <sup>[4]</sup>			
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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Experimental Arm
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Reporting group description:

All subjects

<b>Serious adverse events</b>	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 %

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

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

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
sleep disturbances subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
<b>Nervous system disorders</b>			
Decreased range of movement in neck subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Decreased vision subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Fatigue subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 6		
Dysaesthesia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Headache subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
MRI head subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Neck pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Pins & needle subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
<b>Ear and labyrinth disorders</b>			
Dizziness subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 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		
<b>Gastrointestinal disorders</b>			
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 lymphagran 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 occurrences (all)	1 / 40 (2.50%) 1		
Loose stools subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 8		
Nausea subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Pain in lower abdomen subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Pain on swallowing subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Perianal ulcers subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
PR bleeds subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Recral bleeding 20 to lymphagram venereum (LGV) subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hepatobiliary disorders Elevated liver function subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Skin and subcutaneous tissue disorders acneform papules (face) subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Dry Scalp			

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

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

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

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### 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 $\leq 2$ ml & 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
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Notes: