



## Clinical trial results:

### Efficacy of Switch to Lopinavir/Ritonavir in Improving Cognitive function in Efavirenz treated patients

#### Summary

EudraCT number	2011-005581-37
Trial protocol	GB
Global end of trial date	31 December 2014

#### Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	06 February 2019

#### Trial information

##### Trial identification

Sponsor protocol code	5946
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##### Additional study identifiers

ISRCTN number	ISRCTN73411795
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 12/NE/0071

Notes:

#### Sponsors

Sponsor organisation name	Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Regent Point, Regent Farm Road, Newcastle Upon Tyne, United Kingdom, NE3 3HD
Public contact	Dr Ashley Price, The Newcastle upon Tyne Hospitals NHS Foundation Trust, +44 01912823854, david.price@nuth.nhs.uk
Scientific contact	Dr Ashley Price, The Newcastle upon Tyne Hospitals NHS Foundation Trust, +44 01912823854, david.price@nuth.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	27 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To explore whether chronic Efavirenz therapy is associated with mild cognitive impairment, and if it is improved by switch to Kaletra after 10 weeks.

Protection of trial subjects:

There were no specific measures put in place by the DMC to protect trial subjects.

On the 4th of Oct 2013 the chief investigator updated the DMC committee with a protocol deviation where the lipid profile and glucose blood tests were stipulated in the current protocol to be performed routinely in clinic within 12 weeks of the screening visit, however as part of routine care lipid profile and glucose blood tests were only checked every 12 months. Ashley informed the DMC that the issue was discussed with Sponsor and the TSC and both had agreed to an amendment to the protocol to allow lipid profile and glucose blood results for screening visit as long as it was completed as per clinical guidelines within the previous 12 months.

The Kaletra SmPC was also updated in this amendment.

The serious breach was discussed with the DMC on the 28th of November 2014 and there was no further comments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

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**Subjects enrolled per age group**

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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)	16
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A pilot phase IV open-label controlled trial in HIV-infected patients who had been on suppressive Efavirenz (EFV)-based Highly Active Anti-retroviral Therapy (HAART) for at least 6 months were observed at baseline + 10 weeks after a switch from EFV to Kaletra® (co-formulated lopinavir/ritonavir). To examine the effect of EFV on cognitive function.

### Pre-assignment

Screening details:

Patients with illicit drug use or excessive alcohol use were excluded. Patients were also unselected with respect to the presence or absence of cognitive symptoms.

### Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

### 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	Switch from EFV to Kaletra® for 10 weeks
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Arm description:

Single arm

Arm type	Experimental
Investigational medicinal product name	Kaletra®
Investigational medicinal product code	21-903
Other name	co-formulated lopinavir/ritonavir
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400/100mg (2 tablets) every twelve hours. Kaletra was dispensed at study visit immediately prior to treatment switch. Participants were given clear instructions at this time on which date to stop EFV and start Kaletra. This date was no more than 2 weeks following the date of dispensing.

<b>Number of subjects in period 1</b>	Switch from EFV to Kaletra® for 10 weeks
Started	16
Completed	16



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
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)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	48.9		
standard deviation	± 9.7	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	13	13	
Body Mass Index			
BMI was calculated for 12 of the 16 patients. Data was not available for 4 patients			
Units: kg/m2			
arithmetic mean	26.5		
standard deviation	± 3.5	-	
HIV-infected patients on HAART therapy (for at least 6 months)			
Time on Antiviral Therapy was calculated for 13 patients. Data was unavailable for 3 of the patients.			
Units: years			
arithmetic mean	5.2		
standard deviation	± 2.4	-	
HIV-infected patients on EFV therapy (for at least 6 months)			
Time on Antiviral Therapy was calculated for 13 patients. Data was not available for 3 of the 16 patients			
Units: Years			
arithmetic mean	5.3		
standard deviation	± 2.9	-	
Current CD4 Count			
Units: count			
arithmetic mean	650.6		
standard deviation	± 136.8	-	

EFV levels			
EFV levels was calculated for 12 patients. Data was not available for 4 of the 16 patients			
Units: ng/mL			
arithmetic mean	2950		
standard deviation	± 1948	-	

## End points

### End points reporting groups

Reporting group title	Switch from EFV to Kaletra® for 10 weeks
Reporting group description:	
Single arm	

### Primary: Change in cognitive test scores- Detection (DET)

End point title	Change in cognitive test scores- Detection (DET) <sup>[1]</sup>
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End point description:

Speed of performance; mean of the log10 transformed reaction times for correct responses.  
Data recorded at 2 visits and the change between the two measurements is the primary outcome.  
Lower score indicates better performance, change is defined as: Session 1 score – Session 2 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®

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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Log10milliseconds				
arithmetic mean (standard deviation)	-0.03 (± 0.12)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in cognitive test scores - Identification (IDN)

End point title	Change in cognitive test scores - Identification (IDN) <sup>[2]</sup>
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End point description:

Speed of performance; mean of the log10 transformed reaction times for correct responses.  
Data recorded at 2 visits and the change between the two measurements is the primary outcome.  
Lower score indicates better performance, change is defined as: Session 1 score – Session 2 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®



Notes:

[2] - 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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Log10 milliseconds				
arithmetic mean (standard deviation)	0.03 (± 0.09)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in cognitive test scores - One card learning (OCL)

End point title	Change in cognitive test scores - One card learning (OCL) <sup>[3]</sup>
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End point description:

Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses.

Data recorded at 2 visits and the change between the two measurements is the primary outcome.

Higher score indicates better performance, change is defined as: Session 2 score – Session 1 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®

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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Arcsine proportion correct				
arithmetic mean (standard deviation)	0.03 (± 0.07)			

## Statistical analyses

No statistical analyses for this end point

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**Primary: Change in cognitive test scores - Working memory (ONB)**

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End point title	Change in cognitive test scores - Working memory (ONB) <sup>[4]</sup>
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End point description:

Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses.

Data recorded at 2 visits and the change between the two measurements is the primary outcome. Higher score indicates better performance, change is defined as: Session 2 score – Session 1 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®

Notes:

[4] - 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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Arcsine proportion correct				
arithmetic mean (standard deviation)	-0.001 (± 0.13)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: Change in cognitive test scores - Associate learning (CPAL)**

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End point title	Change in cognitive test scores - Associate learning (CPAL) <sup>[5]</sup>
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End point description:

Accuracy of performance; total number of errors across five rounds.

Data recorded at 2 visits and the change between the two measurements is the primary outcome.

Lower score indicates better performance, change is defined as: Session 1 score – Session 2 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®

Notes:

[5] - 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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Total errors				
arithmetic mean (standard deviation)	13.6 (± 43.9)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in cognitive test scores - Executive function (GML)

End point title	Change in cognitive test scores - Executive function (GML) <sup>[6]</sup>
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End point description:

Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session.

Data recorded at 2 visits and the change between the two measurements is the primary outcome.

Lower score indicates better performance, change is defined as: Session 1 score – Session 2 score so that a positive change indicates improvement.

End point type	Primary
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End point timeframe:

10 weeks following switch from Efavirenz to Kaletra®

Notes:

[6] - 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: Due to small numbers formal statistical analysis beyond presentation of summary statistics was not considered appropriate.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Total errors				
arithmetic mean (standard deviation)	2.9 (± 12.2)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – Grey matter – Choline to Creatine ratio (Cho/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy) – Grey matter – Choline to Creatine ratio (Cho/Cre)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

Cho (choline) is a measure of cell turnover and inflammation. It has been reported to be increased in

HIV-associated cognitive impairment, and often is increased where NAA is decreased. Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived. Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit (week 1) – each participant had MRI scan to obtain baseline Cerebral metabolite profile (magnetic resonance spectroscopy) and functional Magnetic resonance imaging (fMRI) results.

Visit 3 (week 13) – each participant again had MRI scan to

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[7]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.01 (± 0.03)			

Notes:

[7] - Missing data from 2 patients

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – Grey matter – N-acetylaspartate to Creatine ratio (NAA/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy) – Grey matter – N-acetylaspartate to Creatine ratio (NAA/Cre)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

NAA (N-acetylaspartate) is a measure of neuronal integrity / viability. Previous MRS studies suggest that NAA in frontal brain areas may be decreased in HIV infection and associated with cognitive dysfunction. Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived.

Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit (week 1) – each participant had MRI scan to obtain baseline Cerebral metabolite profile (magnetic resonance spectroscopy) and functional Magnetic resonance imaging (fMRI) results.

Visit 3 (week 13) – each participant again had MRI scan to

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[8]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.16 (± 0.49)			

Notes:

[8] - missing data for 2 patients

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – White matter – Choline to Creatine ratio (Cho/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy) – White matter – Choline to Creatine ratio (Cho/Cre)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

Cho (choline) is a measure of cell turnover and inflammation. It has been reported to be increased in HIV-associated cognitive impairment, and often is increased where NAA is decreased.

Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived.

Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit (week 1) – each participant had MRI scan to obtain baseline Cerebral metabolite profile (magnetic resonance spectroscopy) and functional Magnetic resonance imaging (fMRI) results.

Visit 3 (week 13) - each participant again had MRI scan to

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	11 <sup>[9]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.03 (± 0.08)			

Notes:

[9] - Missing data for 5 patients

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – White matter – N-acetylaspartate to Creatine ratio (NAA/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

NAA (N-acetylaspartate) is a measure of neuronal integrity / viability. Previous MRS studies suggest that NAA in frontal brain areas may be decreased in HIV infection and associated with cognitive dysfunction. Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived.

Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit – each participant had MRI scan to obtain baseline Cerebral metabolite profile + fMRI results.

Visit 3 (week 13) - each participant again had MRI scan to obtain Cerebral metabolite profile and fMRI results.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	11 <sup>[10]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.11 (± 0.34)			

Notes:

[10] - Missing data from 5 patients

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – Basal Ganglia – N-acetylaspartate to Creatine ratio (NAA/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy) – Basal Ganglia – N-acetylaspartate to Creatine ratio (NAA/Cre)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

NAA (N-acetylaspartate) is a measure of neuronal integrity / viability. Previous MRS studies suggest that NAA in frontal brain areas may be decreased in HIV infection and associated with cognitive dysfunction. Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived.

Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit (week 1) – each participant had MRI scan to obtain baseline Cerebral metabolite profile and fMRI results.

Visit 3 (week 13) - each participant again had MRI scan to obtain Cerebral metabolite profile and fMRI results.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	8 <sup>[11]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.03 (± 0.42)			

Notes:

[11] - Missing data from 8 patients

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cerebral metabolite profile (magnetic resonance spectroscopy) – Basal Ganglia – Choline to Creatine ratio (Cho/Cre)

End point title	Cerebral metabolite profile (magnetic resonance spectroscopy) – Basal Ganglia – Choline to Creatine ratio (Cho/Cre)
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End point description:

MRS data will measure cerebral metabolites, each of which will be expressed as a ratio to creatine (Cre) to increase inter-scan standardisation.

Cho (choline) is a measure of cell turnover and inflammation. It has been reported to be increased in HIV-associated cognitive impairment, and often is increased where NAA is decreased.

Single voxel measurement gives the lowest coefficient of variance (CoV) on the measure and hence can detect smallest changes. Raw MRS data will first be registered against a standard model from which the metabolite concentrations will be derived.

Change is defined so that an increase from Visit 1 to Visit 3 is positive.

End point type	Secondary
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End point timeframe:

Baseline visit (week 1) – each participant had MRI scan to obtain baseline Cerebral metabolite profile and fMRI results. Visit 3 (week 13) - MRI scan to obtain Cerebral metabolite profile and fMRI results.

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	8 <sup>[12]</sup>			
Units: ratio				
arithmetic mean (standard deviation)	0.04 (± 0.07)			

Notes:

[12] - Missing data for 8 patients

## Statistical analyses

No statistical analyses for this end point

**Secondary: Sleep Quality - Sleep questionnaire (Epworth Sleepiness Scale [ESS])**

End point title	Sleep Quality - Sleep questionnaire (Epworth Sleepiness Scale [ESS])
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End point description:

Change (increase) between week 1 and week 13 scores

End point type	Secondary
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End point timeframe:

Questionnaire completed at baseline visit (week 1) and again at visit 3 (week 13).

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Change between 2 scores				
arithmetic mean (standard deviation)	-0.9 (± 3.4)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Sleep Quality - Pittsburgh Sleep Quality Index [PSQI]**

End point title	Sleep Quality - Pittsburgh Sleep Quality Index [PSQI]
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End point description:

Change (increase) between week 1 and week 13 scores

End point type	Secondary
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End point timeframe:

Questionnaire completed at baseline visit (week 1) and again at visit 3 (week 13).

<b>End point values</b>	Switch from EFV to Kaletra® for 10 weeks			
Subject group type	Reporting group			
Number of subjects analysed	14 <sup>[13]</sup>			
Units: Change between 2 scores				
arithmetic mean (standard deviation)	-3.4 (± 4.7)			

Notes:

[13] - Missing data from 2 patients

**Statistical analyses**

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first visit until final visit

Assessment type	Systematic
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### Dictionary used

Dictionary name	As reported
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Dictionary version	1
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### Reporting groups

Reporting group title	Rhinitis
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Reporting group description:

Please note the pdf generated from EudraCT is incorrect. 16 patients were exposed but only 1 patient reported Rhinitis.

Reporting group title	Weight gain to face and abdomen
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Reporting group description: -

Reporting group title	Increase in viral load to 69 copies/ml
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Reporting group description: -

Reporting group title	Increase in viral loads to 107 copies
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Reporting group description: -

Reporting group title	Abdominal bloating
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Reporting group description: -

Reporting group title	Abdominal discomfort/wind
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Reporting group description: -

Reporting group title	Abdominal cramps
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Reporting group description: -

Reporting group title	Increased fatigue
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Reporting group description: -

Reporting group title	Worsening low mood
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Reporting group description: -

Reporting group title	Under dose of Kaletra
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Reporting group description: -

Reporting group title	Inflamed throat
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Reporting group description: -

Reporting group title	Sore throat
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Reporting group description: -

Reporting group title	Pains in both hands
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Reporting group description: -

Reporting group title	Muscular pain
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Reporting group description:

Night time cramp in left thigh

Reporting group title	Muscle pains in thighs and hands
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Reporting group description: -

Reporting group title	Pain in abdomen and secondary to flatulence
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Reporting group description: -

Reporting group title	Aches and pains in legs
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Reporting group description: -

Reporting group title	Upper left Shoulder pain
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Reporting group description: -

Reporting group title	Lower right back pain
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Reporting group description: -	
Reporting group title	Night sweats
Reporting group description: -	
Reporting group title	Decreased sleep due to restlessness
Reporting group description: -	
Reporting group title	Infected spots on face
Reporting group description: -	
Reporting group title	Vomiting
Reporting group description: -	
Reporting group title	Dry Cough
Reporting group description: -	
Reporting group title	Hay fever
Reporting group description: -	
Reporting group title	Upper respiratory tract infection
Reporting group description: -	
Reporting group title	Productive Cough
Reporting group description: -	
Reporting group title	Stomach Cramp
Reporting group description: -	
Reporting group title	Oral trush
Reporting group description: -	
Reporting group title	Tiredness increased
Reporting group description: -	
Reporting group title	Headache
Reporting group description: -	
Reporting group title	Loss of appetite
Reporting group description: -	
Reporting group title	Flatulence
Reporting group description: -	
Reporting group title	Nausea (when having flatulence)
Reporting group description: -	
Reporting group title	Loose stool
Reporting group description: -	
Reporting group title	Dizziness/light-headedness
Reporting group description: -	
Reporting group title	Increased triglycerides
Reporting group description: -	
Reporting group title	Ring worm
Reporting group description:	
Rash on chest ring worm suspected	
Reporting group title	Ring worm
Reporting group description:	
Rash on chest not diagnosed	
Reporting group title	Nocturnal enuresis
Reporting group description: -	
Reporting group title	Nausea
Reporting group description: -	
Reporting group title	Tooth extraction
Reporting group description: -	
Reporting group title	Itching to upper body
Reporting group description: -	
Reporting group title	Swollen hands and feet (mild)

Reporting group description: -

Reporting group title	Dental Abcess
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Reporting group description: -

Reporting group title	On specific viral infection
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Reporting group description: -

Reporting group title	Cramp in left toe
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Reporting group description: -

Reporting group title	Under dose of study medication
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Reporting group description: -

Reporting group title	Aches in legs
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Reporting group description: -

Reporting group title	Numbness in arms
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Reporting group description: -

Reporting group title	Diarrohea
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Reporting group description: -

Serious adverse events	Rhinitis	Weight gain to face and abdomen	Increase in viral load to 69 copies/ml
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Increase in viral loads to 107 copies	Abdominal bloating	Abdominal dicomfort/wind
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Abdominal cramps	Increased fatigue	Worsening low mood
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Under dose of Kaletra	Inflamed throat	Sore throat
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
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<b>Serious adverse events</b>	Pains in both hands	Muscular pain	Muscle pains in thighs and hands
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Pain in abdomen and secondary to flatulence	Aches and pains in legs	Upper left Shoulder pain
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Lower right back pain	Night sweats	Decreased sleep due to restlessness
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Infected spots on face	Vomiting	Dry Cough
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Hay fever	Upper respiratory tract infection	Productive Cough
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Stomach Cramp	Oral thrush	Tiredness increased
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Headache	Loss of appetite	Flatulence
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Nausea (when having flatulence)	Loose stool	Dizziness/light-headedness
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Increased triglycerides	Ring worm	Ring worm
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Nocturnal enuresis	Nausea	Tooth extraction
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Itching to upper body	Swollen hands and feet (mild)	Dental Abscess
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

<b>Serious adverse events</b>	On specific viral infection	Cramp in left toe	Under dose of study medication
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Aches in legs	Numbness in arms	Diarrhoea
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

<b>Non-serious adverse events</b>	Rhinitis	Weight gain to face and abdomen	Increase in viral load to 69 copies/ml
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Increase in viral loads to 107 copies	Abdominal bloating	Abdominal discomfort/wind
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Abdominal cramps	Increased fatigue	Worsening low mood
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	5 / 16 (31.25%)	1 / 16 (6.25%)

General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	5 / 5 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Under dose of Kaletra	Inflamed throat	Sore throat
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Pains in both hands	Muscular pain	Muscle pains in thighs and hands
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Pain in abdomen and secondary to flatulence	Aches and pains in legs	Upper left Shoulder pain
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Lower right back pain	Night sweats	Decreased sleep due to restlessness
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Infected spots on face	Vomiting	Dry Cough
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	2 / 16 (12.50%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	3 / 3 (100.00%)	2 / 2 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Hay fever	Upper respiratory tract infection	Productive Cough
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Stomach Cramp	Oral thrush	Tiredness increased
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Headache	Loss of appetite	Flatulence
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	1 / 16 (6.25%)	3 / 16 (18.75%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	3 / 3 (100.00%)	1 / 1 (100.00%)	3 / 3 (100.00%)
occurrences (all)	1	1	1

<b>Non-serious adverse events</b>	Nausea (when having flatulence)	Loose stool	Dizziness/light-headedness
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions			



General disorders subjects affected / exposed <sup>[1]</sup> occurrences (all)	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1
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<b>Non-serious adverse events</b>	Increased triglycerides	Ring worm	Ring worm
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions General disorders subjects affected / exposed <sup>[1]</sup> occurrences (all)	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1

<b>Non-serious adverse events</b>	Nocturnal enuresis	Nausea	Tooth extraction
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	1 / 16 (6.25%)
General disorders and administration site conditions General disorders subjects affected / exposed <sup>[1]</sup> occurrences (all)	1 / 1 (100.00%)  1	3 / 3 (100.00%)  1	1 / 1 (100.00%)  1

<b>Non-serious adverse events</b>	Itching to upper body	Swollen hands and feet (mild)	Dental Abscess
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 1 (100.00%)
General disorders and administration site conditions General disorders subjects affected / exposed <sup>[1]</sup> occurrences (all)	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1

<b>Non-serious adverse events</b>	On specific viral infection	Cramp in left toe	Under dose of study medication
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
General disorders and administration site conditions General disorders subjects affected / exposed <sup>[1]</sup> occurrences (all)	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1	1 / 1 (100.00%)  1

<b>Non-serious adverse events</b>	Aches in legs	Numbness in arms	Diarrhea
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	13 / 16 (81.25%)
General disorders and administration site conditions			
General disorders			
subjects affected / exposed <sup>[1]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	13 / 13 (100.00%)
occurrences (all)	1	1	16

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The pdf created by EudracT gives unrepresentative information when numbers exposed under the general disorders is displayed.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2012	<p>The MHRA issued a Notice of Ground of Non-acceptance and Right to Amend Request letter dated 20th July 2012.</p> <p>The following medical points were raised, and were addressed in our response letter to MHRA dated 31st July 2012. Notice of Acceptance of Amended Request for a Clinical Trial Authorisation was granted on 06 August 2012. We have listed our responses, point by point below</p> <p>Point 1 - The Sponsor is required to enter the prohibited medications and medication not recommended to be co-administrated with efavirenz or Kaletra, as per respective SmPCs, in the exclusion criteria and in the list of prohibited medications during the trial.</p> <p>We have made changes to Section 10.2 Exclusion criteria and Section 12.3 Concomitant medication of the protocol as requested.</p> <p>Point 2 - The Sponsor is required to add breastfeeding to the exclusion criteria, in accordance with the SmPCs of efavirenz and lopinavir.</p> <p>We have added this information to the protocol as requested.</p> <p>Point 3 – the Sponsor is required to follow the SmPC of efavirenz and define the contraceptive methods and duration for both genders.</p> <p>We have made changes to Section 19.5 of the protocol as requested and agreed by Dr Steinberg MHRA. In addition to this we have changed the sub heading to 'Pregnancy and fertility' to further clarify this point</p> <p>Point 4 - The Sponsor is required to discontinue Kaletra if a diagnosis of pancreatitis is made during the trial.</p> <p>We have added this information to Section 17.2 Withdrawal of participants of the protocol as requested.</p> <p>Point 5 - The Sponsor must specify that patients who become pregnant during the trial whilst taking efavirenz must discontinue the efavirenz.</p> <p>We have made changes to Section 19.5 Pregnancy and fertility of the protocol as requested and agreed by Dr Steinberg MHRA. These changes are consistent with the BHIVA 2012 Guidelines for the management of HIV infection in pregnant women. In addition to this, we have added further information regarding pat</p>

24 October 2013	<p>A listed summary of changes is as follows:</p> <p>1) Change to the protocol section 10.1 Inclusion criteria to delete the first paragraph as it is repeated with the second paragraph.</p> <p>2) Changes to the protocol section 10.2 Exclusion criteria and 12.3 Concomitant medication to add Rivaroxaban to reflect the Kaletra SmPC update on 19 September 2012.</p> <p>3) Additional paragraph is added to the protocol section 11.1 Identification and screening of participants to allow the study adding additional Participant Identification Centres (PICs) if the recruitment rate is low.</p> <p>4) Change to the protocol section 15.1 schedule of events and second paragraph of Explanatory notes on table of events (page 30), screening visit, glucose and lipids blood results time limit to 12 months instead of 12 weeks from the screening visit. This is to bring it in line with the current clinical practice and British HIV Association Guidelines "Routine investigation and monitoring of adult HIV-1-infected individuals (2011). Section: 18.4.1 Recommendations for assessment and monitoring of lipid profile". Please see attached a copy of the BHIV guidelines for your information.</p> <p>5) Additional paragraph is added to the protocol section 19.2 Expected adverse reactions to cover the commonest anticipated adverse drug reaction – diarrhoea and suggest routine clinical treatment (Loperamide 2mg as needed).</p> <p>6) Change to the protocol appendix 1 Summary of Product Characteristics for Kaletra as Kaletra SmPC has been updated on 21 May 2013 on electronic Medicines Compendium (eMC) website. (Kaletra SmPC had been updated three times since the study was granted the REC favourable opinion and MHRA Clinical Trial Authorisation. SmPC dated 21 May 2013 is the most updated version.)</p> <p>7) Change to the protocol appendix 6 Study poster as a result of feedback from the lay representative for the study.</p> <p>8) The protocol has been updated to reflect the Marketing Authorisation transfer approval from Abbott Labora</p>
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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.

17 were recruited, 16 were eligible. Due to an error 1 patient received monotherapy for 4 weeks but was well on follow up. Viral load was not affected. A Serious breach was reported to the MHRA+REC, sponsor identified no other patients were affected.

Notes: