Clinical trial results:
Randomised controlled trial of the tolerability and completion of maraviroc compared to Kaletra© in combination with Truvada© for HIV post-exposure prophylaxis

Summary

EudraCT number	2011-003447-21
Trial protocol	GB
Global end of trial date	24 April 2015

Results information

Result version number	v1 (current)
This version publication date	03 June 2016
First version publication date	03 June 2016

Trial information

Trial identification

Sponsor protocol code	MMC001

Additional study identifiers

ISRCTN number	ISRCTN63350011
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Central and North West London NHS Foundation Trust
Sponsor organisation address	1st Floor, Bloomsbury Building, St Pancras Hospital, 4 St Pancras Way, London, United Kingdom, NW1 0PE
Public contact	Angela Williams, Central & North West London NHS Foundation Trust, 44 203 317 3765 , mipep.noclor@nhs.net
Scientific contact	Dr Richard Gilson, University College London, 44 203 108 2103, r.gilson@ucl.ac.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	14 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2014
Global end of trial reached?	Yes
Global end of trial date	24 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patients taking current combinations of PEP frequently report side effects and the completion rate of the full 28 day course of medication is often poor. This may compromise the protective effect of PEP. The availability of a better tolerated combination would be beneficial to patients. The principal study objective is to compare the tolerability and completion rate between the standard PEP drug combination and maraviroc-based PEP. The primary endpoint was a composite of completion of 28 days of the allocated PEP regimen without grade 3 or 4 clinical or laboratory adverse events related to the PEP medication. The site investigators determined whether clinical or laboratory adverse events were related to the PEP medication at the time of occurrence. All adverse events were also reviewed by an independent panel.

Protection of trial subjects:

Venepuncture may be associated with discomfort and may leave a temporary bruise. Every effort was made to minimise this; no additional venepunction was required in this trial beyond routine care.
Both maraviroc-based PEP and the standard of care combination with Kaletra may cause side effects, including gastrointestinal symptoms, such as diarrhoea or nausea. However it was anticipated that maraviroc may be better tolerated than Kaletra®, and both treatments were to be given for a short time (28days). Participants were advised on the appropriate management of any side-effects.
Although common practice within the NHS, the efficacy of PEP has not been proven. Maraviroc has not been used as a part of HIV PEP so its efficacy has not been documented. An Independent Data Monitoring Committee monitored any potential risk for participants in this study and would have advised stopping the trial on grounds of safety if appropriate.

Background therapy:

Truvada® (tenofovir disoproxil -as fumarate- 245 mg, emtricitabine 200 mg), one tablet once daily

Evidence for comparator:

The purpose of this study was to test whether a PEP combination containing the antiretroviral drug maraviroc is superior to the standard PEP regimen containing Kaletra, in terms of the proportion of patients who complete a full course of PEP, without serious toxicity.
Maraviroc works in a different way to other antiretroviral agents currently used for PEP. It prevents HIV entering immune cells which in theory may be advantageous in terms of preventing acquisition of HIV infection. Maraviroc has been shown to be highly effective in treating patients with HIV infection (MOTIVATE and MERIT studies) and is generally well tolerated with very few people experiencing serious side effects. Animal data demonstrates that the use of drugs which work in the same way as maraviroc reduced the likelihood of macaques SIV following vaginal exposure. Maraviroc has also been shown to acheive high drug levels in the tissue compartments (male and female genital tract and rectum) exposed to HIV following sexual intercourse which suggests that it may be an effective agent when used as PEP after sexual exposure.

Actual start date of recruitment	02 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 213
Worldwide total number of subjects	213
EEA total number of subjects	213

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)	213
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified from among patients presenting to the clinic asking for PEP, or for whom PEP was recommended after a consultation with a healthcare worker.
We enrolled participants attending 5 sexual health clinics in the England.
First participant recruited: 02 Aug 2012, Last participant recruited: 24 Dec 2014.

Pre-assignment

Screening details:

Patients for whom PEP was indicated and who were not taking any concomitant medication which precluded use of the study medication

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental arm

Arm description:

Patients randomised to the experimental arm received maraviroc (300 mg) one tablet twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.

Arm type	Experimental
Investigational medicinal product name	Maraviroc
Investigational medicinal product code	EU/1/07/418/011-005
Other name	Celsentri
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Maraviroc (300 mg) one tablet twice daily

Arm title	Control arm

Arm description:

Patients randomised to the control arm received Kaletra® (lopinavir 200 mg, ritonavir 50 mg)two tablets twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.

Arm type	Active comparator
Investigational medicinal product name	Kaletra
Investigational medicinal product code	
Other name	Lopinavir/Ritonavir
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Kaletra® (lopinavir 200 mg, ritonavir 50 mg) two tablets twice daily.

Number of subjects in period 1	Experimental arm	Control arm
Started	107	106
Completed	98	98
Not completed	9	8
Lost to follow-up	9	8

Baseline characteristics

Reporting groups	
Reporting group title	Experimental arm
Reporting group description:	
Patients randomised to the experimental arm received maraviroc (300 mg) one tablet twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.	
Reporting group title	Control arm
Reporting group description:	
Patients randomised to the control arm received Kaletra® (lopinavir 200 mg, ritonavir 50 mg)two tablets twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.	

Reporting group values	Experimental arm	Control arm	Total
Number of subjects	107	106	213
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	107	106	213
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.6	34.4	
standard deviation	± 9.15	± 10	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	103	105	208
Sexual orientation Units: Subjects			
Bisexual	12	10	22
Heterosexual	6	4	10
Homosexual	83	89	172
Not recorded	6	3	9

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description:	
Patients randomised to the experimental arm received maraviroc (300 mg) one tablet twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.	
Reporting group title	Control arm
Reporting group description:	
Patients randomised to the control arm received Kaletra® (lopinavir 200 mg, ritonavir 50 mg)two tablets twice daily with Truvada® (tenofovir disoproxil - as fumarate - 245 mg, emtricitabine 200 mg), one tablet once daily for 28 days.	

Primary: Composite end point of completion of 28 days allocated PEP regimen without grade 3,4 clinical event or laboratory adverse event

End point title	Composite end point of completion of 28 days allocated PEP regimen without grade 3,4 clinical event or laboratory adverse event
End point description:	
Composite end point of completion of 28 days allocated PEP regimen without grade 3,4 clinical event or laboratory adverse event	
End point type	Primary
End point timeframe:	
Any time from randomization to 28 days	

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: People	98	98		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
Study designed to demonstrate the superiority of maraviroc based PEP relative to Kaletra based PEP, if under maraviroc the prevalence of the primary outcome improves to 70% and its current level is 50% in Kaletra arm.	
Comparison groups	Experimental arm v Control arm

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.262
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.65

Notes:

[1] - To calculate odds ratios we used logistic regression for binary outcomes Odds ratios were adjusted for age and site . Analysis was performed by 'intention-to-treat'. The primary outcome was missing in participants who attended the 14 day visit but no further visits. We performed multiple imputation of the primary outcome using data from participants who attended the 14 day visit. This imputation was conducted separately in each randomisation arm.

Secondary: Completion of 28 days allocated PEP

End point title	Completion of 28 days allocated PEP

End point description:

End point type	Secondary

End point timeframe:

Any time from randomization to 28 days after randomization

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: People	98	98		

Statistical analyses

Statistical analysis title	PEP completion rate at day 28

Statistical analysis description:

Study designed to demonstrate the superiority of maraviroc based PEP relative to Kaletra based PEP, if under maraviroc the prevalence of the primary outcome improves to 70% and its current level is 50% in Kaletra arm.

Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.309
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	3.04

Notes:

[2] - To calculate odds ratios we used logistic regression for binary outcomes Odds ratios were adjusted for age and site . Analysis was performed by 'intention-to-treat'.

Secondary: Laboratory abnormalities related to PEP

End point title	Laboratory abnormalities related to PEP

End point description:

Laboratory abnormalities highest grade reported

End point type	Secondary

End point timeframe:

Any time from randomization to 28 days after randomization

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Events	118	152		

Statistical analyses

Statistical analysis title	Laboratory abnormalities at 28 days
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.079
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.05

Notes:

[3] - We used ordinal logistic regression. The ordinal outcome is the highest grade reported between 0 and 4.

Secondary: Clinical adverse events

End point title	Clinical adverse events

End point description:

Clinical adverse events highest grade reported

End point type	Secondary

End point timeframe:

Any time from randomization to 28 days after randomization

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: events	123	175		

Statistical analyses

Statistical analysis title	Clinical adverse event at 28 days
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.59

Notes:

[4] - We used ordinal logistic regression. The outcome is the highest grade reported, between 0 and 2. There were no grade 3 or 4 clinical adverse events.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to month 4 visit after study entry

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Control Arm

Reporting group description:

Patients randomised to the control arm received 28 days treatment with Truvada® (tenofovir disoproxil -as fumarate- 245 mg, emtricitabine 200 mg), one tablet once daily in addition to Kaletra® (lopinavir 200 mg, ritonavir 50 mg) two tablets twice daily.

Reporting group title	Experimental arm

Reporting group description:

Patients randomised to the experimental arm received 28 days treatment with Truvada® (tenofovir disoproxil -as fumarate- 245 mg, emtricitabine 200 mg), one tablet once daily in addition to maraviroc (300 mg)one tablet twice daily.

Serious adverse events	Control Arm	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Control Arm	Experimental arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 106 (83.02%)	69 / 107 (64.49%)	
Nervous system disorders			
Headache/Sleeping disorder			
subjects affected / exposed	12 / 106 (11.32%)	11 / 107 (10.28%)	
occurrences (all)	18	14	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	45 / 106 (42.45%)	11 / 107 (10.28%)	
occurrences (all)	74	19	
Nausea/vomiting			
subjects affected / exposed	27 / 106 (25.47%)	25 / 107 (23.36%)	
occurrences (all)	38	30	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 106 (6.60%)	2 / 107 (1.87%)	
occurrences (all)	8	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2012	Addition of two clinical sites
03 December 2012	1. Sample size calculation was revisited as a result of a decision to exclude some of laboratory grade 3 events (lipid abnormalities) from the composite main study endpoint. Lipid abnormalities up to grade 3 are expected on taking Kaletra and would be not considered clinically relevant. They will revert to baseline levels after treatment discontinuation without any short or long term consequences. 2. Advertisement
10 July 2013	Research nurses to be allowed to consent patients.
23 September 2013	1. Exclusion criterion (5) in the protocol as currently drafted implies that the resistance status of the potential source of HIV infection for the participant is known or can be verified, so that this criterion can be met. In practice this information is rarely available as most contacts are unknown or of unknown resistance status. This is consistent with clinical practice. The entry criterion has been amended to make it clear that this information will not always available. 2. Exclusion criterion (7) refers to the results of screening blood tests which should be checked prior to the patient being randomised. However, the protocol does not have a separate screening visit; recruitment and initiation of therapy needs to occur at the first visit and within hours of presentation to be consistent with best practice. Results of bloods tests taken at baseline are not available in the time for randomisation, except the point of care HIV antibody test, which is referred to separately. This exclusion criterion has been reworded removing reference to screening blood tests. 3. The primary end point of the study is a combination of completion of the 28 day course and the absence of grade 3/4 adverse events. It is stated in the protocol that the patient reported completion would be corroborated by a return pill count. While every effort is being made to ensure that participants bring back their pill containers this will never be 100% and is currently only 50%. As such corroboration will be used where possible but it cannot be relied upon in all cases. The possibility that this data will not be available therefore needs to be included.
23 December 2013	Temporary Halt
29 January 2014	Change of the Name of the Sponsor
28 February 2014	Change of Chief Investigator • Change of PI in The Claude Nicol Unit, Brighton and Sussex University Hospitals NHS Trust, Brighton • Request for restart of the trial (we implemented a temporary halt in recruitment to the trial as from 3rd January 2014)
05 January 2015	Recruitment discontinued as of 5th January 2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 December 2013	Temporary halt in recruitment to the trial had been implemented from January -July 2014. The reason for this halt was because IMP expired on 31st January 2014 and we did not have in place arrangement for new supplies until 13th July 2014	13 July 2014

Notes:

Limitations and caveats

None reported