# 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<br>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<br>Units: years | | | |
| arithmetic mean | 33.6 | 34.4 | |
| standard deviation | ± 9.15 | ± 10 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 1 | 5 |
| Male | 103 | 105 | 208 |
| Sexual orientation<br>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.<br><br>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.<br><br>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.<br><br>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<br>• Change of PI in The Claude Nicol Unit, Brighton and Sussex University Hospitals NHS Trust, Brighton<br>• 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