



## Clinical trial results:

### **Pre-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men**

#### **Summary**

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-002373-56  |
| Trial protocol           | GB              |
| Global end of trial date | 28 October 2016 |

#### **Results information**

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)                                  |
| This version publication date     | 23 December 2017                              |
| First version publication date    | 23 December 2017                              |
| Summary attachment (see zip file) | PROUD_Lancet_2015 (PROUDmainpaper_Lancet.pdf) |

#### **Trial information**

##### **Trial identification**

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | PROUD |
|-----------------------|-------|

##### **Additional study identifiers**

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN94465371 |
| ClinicalTrials.gov id (NCT number) | NCT02065986    |
| WHO universal trial number (UTN)   | -              |

Notes:

##### **Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Medical Research Council  |
| Sponsor organisation address | 2nd Floor, David Phillips Building, Polaris House, North Star Avenue, Swindon, United Kingdom, SN2 1FL          |
| Public contact               | PROUD trial team, Medical Research Council Clinical Trials Unit at UCL, +44 02076704783, proud.mrcctu@ucl.ac.uk |
| Scientific contact           | PROUD trial team, Medical Research Council Clinical Trials Unit at UCL, +44 02076704783, proud.mrcctu@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                       | 10 June 2015    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 10 June 2015    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 28 October 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this pilot is to determine whether it is feasible to conduct a large trial in the UK to determine whether the immediate inclusion of anti-retroviral pre-exposure prophylaxis (PrEP) as part of the HIV risk reduction package for men who have sex with men is clinically effective and cost-effective in reducing the risk of acquiring HIV.

Protection of trial subjects:

The protocol was amended to accommodate and implement the IDMC and Trial Steering Committee recommendation in October 2014, namely that daily oral Truvada be offered to all participants in the PROUD pilot study as soon as possible and continued through to the end of the study. The recommendation was made primarily on the basis of safety, and was based on a significant and potentially preventable risk of HIV infection in the deferred group compared to the immediate group.

Note: Follow-up was scheduled to end in May 2016 but continued to Oct 2016 in order to provide PrEP to participants that still needed it.

Background therapy: -

Evidence for comparator: -

|   |                     |
|---|---------------------|
| Actual start date of recruitment                          | 29 November 2012    |
| Long term follow-up planned                               | Yes                 |
| Long term follow-up rationale                             | Scientific research |
| Long term follow-up duration                              | 2 Years             |
| Independent data monitoring committee (IDMC) involvement? | Yes                 |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 544 |
| Worldwide total number of subjects   | 544                 |
| EEA total number of subjects         | 544                 |

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          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 538 |
| From 65 to 84 years       | 6   |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment ran between November 29, 2012 and continued until April 30, 2014 in 13 sexual health clinics in England

### Pre-assignment

Screening details:

Eligibility criteria: male at birth, 18 years or older, previously attended enrolling clinic, screened for HIV and other sexually transmitted infections, HIV negative by routinely used assay in previous 4 weeks or on day of enrolment, reported anal intercourse without a condom in the previous 90 days and likely to occur again in next 90 days.

### Period 1

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

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Immediate |

Arm description:

Participants received prescription of PrEP at randomisation

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Truvada            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Fixed dose combination of 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir) once daily

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Deferred |
|------------------|----------|

Arm description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b> | Immediate | Deferred |
|---------------------------------------|-----------|----------|
| Started                               | 275       | 269      |
| Completed                             | 247       | 235      |
| Not completed                         | 28        | 34       |
| Adverse event, serious fatal          | 1         | -        |
| Consent withdrawn by subject          | 3         | 4        |

|                           |    |    |
|---------------------------|----|----|
| HIV infection at baseline | 2  | 1  |
| Lost to follow-up         | 22 | 29 |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Immediate |
|-----------------------|-----------|

Reporting group description:

Participants received prescription of PrEP at randomisation

|                       |          |
|-----------------------|----------|
| Reporting group title | Deferred |
|-----------------------|----------|

Reporting group description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

| Reporting group values                             | Immediate | Deferred | Total |
|--|-----------|----------|-------|
| Number of subjects                                 | 275       | 269      | 544   |
| 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)                               | 271       | 267      | 538   |
| From 65-84 years                                   | 4         | 2        | 6     |
| 85 years and over                                  | 0         | 0        | 0     |
| Gender categorical                                 |           |          |       |
| Units: Subjects                                    |           |          |       |
| Female   | 0         | 0        | 0     |
| Male   | 272       | 265      | 537   |
| Missing  | 3         | 4        | 7     |
| Employment status                                  |           |          |       |
| Units: Subjects                                    |           |          |       |
| Employed   | 249       | 245      | 494   |
| Unemployed   | 24        | 20       | 44    |
| Missing  | 2         | 4        | 6     |
| Education status                                   |           |          |       |
| Units: Subjects                                    |           |          |       |
| University degree                                  | 161       | 166      | 327   |
| No University degree                               | 111       | 101      | 212   |
| Missing  | 3         | 2        | 5     |
| Country of birth                                   |           |          |       |
| Units: Subjects                                    |           |          |       |
| UK   | 162       | 160      | 322   |
| Outside of UK                                      | 110       | 107      | 217   |
| Missing  | 3         | 2        | 5     |
| Relationship status                                |           |          |       |
| Units: Subjects                                    |           |          |       |

|   |        |        |     |
|---|--------|--------|-----|
| Partner, living together  | 87     | 73     | 160 |
| Partner, living separately  | 40     | 46     | 86  |
| No partner  | 146    | 147    | 293 |
| Missing   | 2      | 3      | 5   |
| Circumcision status   |        |        |     |
| Units: Subjects   |        |        |     |
| Circumcised   | 77     | 79     | 156 |
| Not circumcised   | 194    | 186    | 380 |
| Missing   | 4      | 4      | 8   |
| Chemsex in past 90 days   |        |        |     |
| Use of either $\gamma$ -hydroxybutyrate, 4-methylmethcathinone, or methamphetamine to facilitate or enhance sex |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 115    | 116    | 231 |
| No  | 151    | 143    | 294 |
| Missing   | 9      | 10     | 19  |
| Used post-exposure prophylaxis in past 12 months  |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 91     | 93     | 184 |
| No  | 167    | 159    | 326 |
| Missing   | 17     | 17     | 34  |
| Ethnicity   |        |        |     |
| Units: Subjects   |        |        |     |
| White   | 220    | 219    | 439 |
| Asian   | 14     | 15     | 29  |
| Black   | 11     | 10     | 21  |
| Other   | 28     | 21     | 49  |
| Missing   | 2      | 4      | 6   |
| Any STI diagnosed in past 12 months   |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 164    | 167    | 331 |
| No  | 98     | 92     | 190 |
| Missing   | 13     | 10     | 23  |
| Bacterial STI diagnosed in the past 12 months   |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 150    | 155    | 305 |
| No  | 112    | 104    | 216 |
| Missing   | 13     | 10     | 23  |
| Rectal gonorrhoea or chlamydia diagnosed in past 12 months  |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 89     | 83     | 172 |
| No  | 173    | 176    | 349 |
| Missing   | 13     | 10     | 23  |
| HIV tests in past 12 months   |        |        |     |
| Units: Number   |        |        |     |
| median  | 3      | 3      |     |
| inter-quartile range (Q1-Q3)  | 2 to 4 | 2 to 4 | -   |

## End points

### End points reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Immediate |
|-----------------------|-----------|

Reporting group description:

Participants received prescription of PrEP at randomisation

|                       |          |
|-----------------------|----------|
| Reporting group title | Deferred |
|-----------------------|----------|

Reporting group description:

Deferred PrEP initiation until week 48 or 13 October 2014, whichever was earliest.

Note: The deferred period was originally planned to last for 12 months. The change reflects the IDMC and TSC recommendation to offer all participants PrEP in October 2014.

### Primary: HIV infections

|                 |                |
|-----------------|----------------|
| End point title | HIV infections |
|-----------------|----------------|

End point description:

Compare HIV infections between trial arms during the deferred phase

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Deferred phase

| End point values                 | Immediate        | Deferred          |  |  |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type               | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed      | 247              | 235               |  |  |
| Units: Rate per 100PY            |                  |                   |  |  |
| number (confidence interval 90%) | 1.2 (0.4 to 2.9) | 9.0 (6.1 to 12.8) |  |  |

### Statistical analyses

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | Primary analysis         |
| Comparison groups                       | Immediate v Deferred     |
| Number of subjects included in analysis | 482                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.0001                 |
| Method                                  | Exact Poisson regression |
| Parameter estimate                      | Rate ratio (RR)          |
| Point estimate                          | 7.3                      |
| Confidence interval                     |                          |
| level                                   | 90 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 2.8                      |
| upper limit                             | 23.3                     |



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**Secondary: Bacterial sexually transmitted infections**

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|                 |   |
|-----------------|---|
| End point title | Bacterial sexually transmitted infections |
|-----------------|---|

End point description:

Compare rates of STIs between trial arms during the deferred phase

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the deferred phase

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| End point values               | Immediate       | Deferred        |  |  |
|--------------------------------|-----------------|-----------------|--|--|
| Subject group type             | Reporting group | Reporting group |  |  |
| Number of subjects analysed    | 265             | 247             |  |  |
| Units: No. of infections       |                 |                 |  |  |
| Any                            | 152             | 124             |  |  |
| Gonorrhoea                     | 103             | 89              |  |  |
| Chlamydia                      | 77              | 54              |  |  |
| Syphilis                       | 30              | 22              |  |  |
| Rectal gonorrhoea or chlamydia | 93              | 77              |  |  |

**Statistical analyses**

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Comparison of any bacterial STI |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Comparing proportion with STI using logistic regression, adjusting for number of screens

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Immediate v Deferred |
|-------------------|----------------------|

|   |     |
|---|-----|
| Number of subjects included in analysis | 512 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |       |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

|         |        |
|---------|--------|
| P-value | = 0.74 |
|---------|--------|

|        |                      |
|--------|----------------------|
| Method | Regression, Logistic |
|--------|----------------------|

|                    |                 |
|--------------------|-----------------|
| Parameter estimate | Odds ratio (OR) |
|--------------------|-----------------|

|                |      |
|----------------|------|
| Point estimate | 1.07 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 90 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.78 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.48 |
|-------------|------|

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | Comparison of gonorrhoea |
|-----------------------------------|--------------------------|

Statistical analysis description:

Comparing proportion with STI using logistic regression, adjusting for number of screens

|   |                      |
|---|----------------------|
| Comparison groups                       | Deferred v Immediate |
| Number of subjects included in analysis | 512                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other                |
| P-value                                 | = 0.46               |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 0.86                 |
| Confidence interval                     |                      |
| level                                   | 90 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.62                 |
| upper limit                             | 1.2                  |

|  |                         |
|--|-------------------------|
| <b>Statistical analysis title</b>  | Comparison of chlamydia |
| Statistical analysis description:  |                         |
| Comparing proportion with STI using logistic regression, adjusting for number of screens |                         |
| Comparison groups  | Deferred v Immediate    |
| Number of subjects included in analysis  | 512                     |
| Analysis specification   | Pre-specified           |
| Analysis type  | other                   |
| P-value  | = 0.27                  |
| Method   | Regression, Logistic    |
| Parameter estimate   | Odds ratio (OR)         |
| Point estimate   | 1.27                    |
| Confidence interval  |                         |
| level  | 90 %                    |
| sides  | 2-sided                 |
| lower limit  | 0.89                    |
| upper limit  | 1.8                     |

|  |                        |
|--|------------------------|
| <b>Statistical analysis title</b>  | Comparison of syphilis |
| Statistical analysis description:  |                        |
| Comparing proportion with STI using logistic regression, adjusting for number of screens |                        |
| Comparison groups  | Immediate v Deferred   |
| Number of subjects included in analysis  | 512                    |
| Analysis specification   | Pre-specified          |
| Analysis type  | other                  |
| P-value  | = 0.39                 |
| Method   | Regression, Logistic   |
| Parameter estimate   | Odds ratio (OR)        |
| Point estimate   | 1.29                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.79    |
| upper limit         | 2.1     |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Comparison of rectal gonorrhoea or chlamydia |
| Statistical analysis description:  |  |
| Comparing proportion with STI using logistic regression, adjusting for number of screens |  |
| Comparison groups  | Deferred v Immediate                         |
| Number of subjects included in analysis  | 512  |
| Analysis specification   | Pre-specified                                |
| Analysis type  | other  |
| P-value  | = 0.99                                       |
| Method   | Regression, Logistic                         |
| Parameter estimate   | Odds ratio (OR)                              |
| Point estimate   | 1  |
| Confidence interval  |  |
| level  | 90 %   |
| sides  | 2-sided                                      |
| lower limit  | 0.72   |
| upper limit  | 1.38   |

## Secondary: Sexual behaviour

|   |                  |
|---|------------------|
| End point title   | Sexual behaviour |
| End point description:  |                  |
| Compare the sexual behaviour between trial arms during the deferred phase |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| Deferred phase  |                  |

| End point values            | Immediate       | Deferred        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 210             | 193             |  |  |
| Units: Participants         |                 |                 |  |  |
| 0 partners                  | 41              | 42              |  |  |
| 1 partner                   | 46              | 51              |  |  |
| 2-4 partners                | 49              | 51              |  |  |
| 5-9 partners                | 30              | 25              |  |  |
| 10-19 partners              | 26              | 13              |  |  |
| 20+ partners                | 18              | 11              |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Comparison of change in sexual behaviour |
| Statistical analysis description:<br>Change in number of receptive anal intercourse partners without a partner from baseline to the end of the deferred phase |  |
| Comparison groups   | Immediate v Deferred                     |
| Number of subjects included in analysis   | 403                                      |
| Analysis specification  | Post-hoc                                 |
| Analysis type   | other <sup>[1]</sup>                     |
| P-value   | = 0.03                                   |
| Method  | Regression, Linear                       |

Notes:

[1] - Linear regression (for category number) adjusting for number of partners at baseline

## Secondary: PrEP prescription

|   |                                  |
|---|----------------------------------|
| End point title   | PrEP prescription <sup>[2]</sup> |
| End point description:<br>The mean percentage of days covered by prescription of study drug |                                  |
| End point type  | Secondary                        |
| End point timeframe:<br>Deferred phase  |                                  |

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is not a relevant outcome for the deferred arm since they did not have access to study drug during this period

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Immediate       |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 275             |  |  |  |
| Units: Percentage                    |                 |  |  |  |
| arithmetic mean (standard deviation) | 0.88 (± 0.25)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs - randomisation to end of the trial

AEs - randomisation to end of deferred phase in ppts in immediate group who interrupted/stopped treatment

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18     |

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Participants |
|-----------------------|--------------|

Reporting group description:

pooled over study arms

| Serious adverse events  | Participants      |  |  |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed   | 85 / 544 (15.63%) |  |  |
| number of deaths (all causes)                                       | 2                 |  |  |
| number of deaths resulting from adverse events                      | 2                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Colorectal cancer   |                   |  |  |
| subjects affected / exposed   | 1 / 544 (0.18%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Vascular disorders  |                   |  |  |
| Orthostatic hypotension   |                   |  |  |
| subjects affected / exposed   | 1 / 544 (0.18%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Pulmonary embolism  |                   |  |  |
| subjects affected / exposed   | 1 / 544 (0.18%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 1             |  |  |
| Surgical and medical procedures                                     |                   |  |  |
| Surgery   |                   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abscess drainage                                |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc operation                   |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Removal of internal fixation                    |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tendon operation                                |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Liver transplant                                |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune system disorders                         |                 |  |  |
| Anaphylactic reaction                           |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Social circumstances                            |                 |  |  |
| Physical assault                                |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| disorders                                       |                 |  |  |
| Epididymitis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Orchitis  |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Priapism  |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Testicular swelling                             |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Testicular torsion                              |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Chest pain                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Sinusitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional state                               |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Drug withdrawal syndrome                        |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Panic attack                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicidal ideation                               |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicide attempt                                 |                 |  |  |
| subjects affected / exposed                     | 4 / 544 (0.74%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychotic disorder                              |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Liver function test abnormal<br>subjects affected / exposed | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Injury, poisoning and procedural<br>complications           |                 |  |  |
| Accidental overdose   |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Accidental poisoning  |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Head injury   |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Overdose  |                 |  |  |
| subjects affected / exposed                                 | 5 / 544 (0.92%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 5           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Post procedural haematuria                                  |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Road traffic accident                                       |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |
| Substance-induced psychotic<br>disorder                     |                 |  |  |
| subjects affected / exposed                                 | 1 / 544 (0.18%) |  |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all               | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Nervous system disorders                        |                 |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Loss of consciousness                           |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Iron deficiency anaemia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anal abscess                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 3 / 544 (0.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Constipation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 3 / 544 (0.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Food poisoning                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric varices haemorrhage                     |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis acute                              |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis chronic                            |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Peritonitis bacterial                           |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Ascites   |                 |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Biliary sepsis                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal pain                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Hand fracture                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc protrusion                  |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal chest pain                      |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Arthropathy                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ankle fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Joint dislocation                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower limb fracture                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Multiple fractures                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal fracture                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Upper limb fracture                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Infections and infestations                     |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Acute hepatitis C                               |                 |  |  |  |
| subjects affected / exposed                     | 3 / 544 (0.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Acute HIV infection                             |                 |  |  |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Device related infection                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diarrhoea infectious                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis bacterial                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis shigella                        |                 |  |  |  |
| subjects affected / exposed                     | 3 / 544 (0.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Injection site abscess                          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Joint abscess                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Mumps   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Shigella infection                              |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Staphylococcal bacteraemia                      |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diabetes mellitus                               |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| Non-serious adverse events                            | Participants     |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 21 / 544 (3.86%) |  |  |
| Investigations  |                  |  |  |
| serum creatinine increased                            |                  |  |  |
| subjects affected / exposed <sup>[1]</sup>            | 3 / 275 (1.09%)  |  |  |
| occurrences (all)                                     | 3                |  |  |
| abnormal liver function tests                         |                  |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed <sup>[2]</sup><br>occurrences (all)   | 1 / 275 (0.36%)<br>1                             |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed <sup>[3]</sup><br>occurrences (all)   | 1 / 275 (0.36%)<br>1                             |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed <sup>[4]</sup><br>occurrences (all)   | 2 / 275 (0.73%)<br>3                             |  |  |
| General disorders and administration site conditions<br>Flu like illness<br>subjects affected / exposed <sup>[5]</sup><br>occurrences (all)   | 1 / 275 (0.36%)<br>1                             |  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed <sup>[6]</sup><br>occurrences (all)<br><br>Gastroenteritis<br>subjects affected / exposed <sup>[7]</sup><br>occurrences (all) | 4 / 275 (1.45%)<br>4<br><br>1 / 275 (0.36%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Chest pain<br>subjects affected / exposed <sup>[8]</sup><br>occurrences (all)  | 3 / 275 (1.09%)<br>3                             |  |  |
| Skin and subcutaneous tissue disorders<br>Lipoatrophy<br>subjects affected / exposed <sup>[9]</sup><br>occurrences (all)  | 1 / 275 (0.36%)<br>1                             |  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed <sup>[10]</sup><br>occurrences (all)<br><br>Anxiety<br>subjects affected / exposed <sup>[11]</sup><br>occurrences (all)        | 2 / 275 (0.73%)<br>2<br><br>2 / 275 (0.73%)<br>2 |  |  |



|  |  |  |  |
|--|--|--|--|
| Manic depression<br>subjects affected / exposed <sup>[12]</sup><br>occurrences (all)   | 1 / 275 (0.36%)<br>1   |  |  |
| Musculoskeletal and connective tissue disorders<br>chest pain musculoskeletal<br>subjects affected / exposed <sup>[13]</sup><br>occurrences (all)<br><br>polyarthralgia<br>subjects affected / exposed <sup>[14]</sup><br>occurrences (all)<br><br>Arthralgia<br>subjects affected / exposed <sup>[15]</sup><br>occurrences (all)<br><br>loin pain<br>subjects affected / exposed <sup>[16]</sup><br>occurrences (all) | 1 / 275 (0.36%)<br>1<br><br>1 / 275 (0.36%)<br>1<br><br>2 / 275 (0.73%)<br>2<br><br>1 / 275 (0.36%)<br>1 |  |  |
| Infections and infestations<br>Hospital acquired pneumonia<br>subjects affected / exposed <sup>[17]</sup><br>occurrences (all)   | 1 / 275 (0.36%)<br>1   |  |  |

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: reporting for ppts in immediate group who interrupted/stopped treatment

[2] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[3] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[4] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[5] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[6] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[7] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[8] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[9] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[10] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[11] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[12] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[13] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[14] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[15] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[16] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

[17] - 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: reporting for ppts in immediate group who interrupted/stopped treatment

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 27 February 2013  | Update to CTA - clarification that Truvada of primary use in the study is Gilead clinical trial stock. Commercial stock details added as use in emergency if clinical need   |
| 19 September 2013 | The update provided updated relevant results, clarified that the recruitment strategies would be broader than clinics and that follow-up data could be collected within the GUM clinic network as this is more convenient for the participants and provided additional detail on the quantitative and qualitative data collection. Section 5 was been updated as it may have been necessary to post drugs. Further details were provided about one to one and group discussions and included the related PIS, IC and one to one interview guide. The Investigators wished to clarify that discontinuation of Truvada is only a Serious Adverse Event when the clinician decided they would never prescribe Truvada again (section 7), and that soundex would be needed in addition to date of birth to cross-check the PHE database for HIV endpoints (section 8). In line with MRC CTU and international guidelines, we have expanded the oversight to include Participant Involvement meetings, and clarified the independent data monitoring that we have implemented on the recommendation of the Trial Steering Committee (section 14). |
| 17 October 2014   | Protocol 1.3 - The protocol was amended to accommodate and implement the Trial Steering Committee recommendation of 9th October 2014, namely that daily oral Truvada be offered to all participants in the PROUD pilot study as soon as possible and continued through to the end of the study.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26364263>