



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9350-Boosted Atazanavir Versus Ritonavir-Boosted Atazanavir Each Administered with Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2009-016759-22                   |
| Trial protocol           | DE BE NL FR PT GB AT ES DK IT SE |
| Global end of trial date | 17 April 2015                    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 01 May 2016  |
| First version publication date | 01 May 2016  |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-216-0114 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01108510 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                   |
|------------------------------|---------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Gilead Sciences                                                                                   |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404                                         |
| Public contact               | Clinical Trial Mailbox, Gilead Sciences International Ltd,<br>ClinicalTrialDisclosures@gilead.com |
| Scientific contact           | Clinical Trial Mailbox, Gilead Sciences International Ltd,<br>ClinicalTrialDisclosures@gilead.com |

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                       | 17 April 2015 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 April 2015 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the safety and efficacy of a regimen containing cobicistat-boosted atazanavir (ATV+COBI) plus emtricitabine/tenofovir disoproxil fumarate (Truvada®; FTC/TDF) fixed-dose combination (FDC) versus ritonavir-boosted atazanavir (ATV+RTV) plus FTC/TDF FDC in HIV-1 infected, antiretroviral treatment-naïve adults.

Participants were randomized in a 1:1 ratio. Randomization was stratified by HIV-1 RNA level ( $\leq$  100,000 copies/mL or  $>$  100,000 copies/mL) at screening.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 26 April 2010 |
| 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 States: 248     |
| Country: Number of subjects enrolled | Thailand: 66           |
| Country: Number of subjects enrolled | Dominican Republic: 58 |
| Country: Number of subjects enrolled | Canada: 44             |
| Country: Number of subjects enrolled | Germany: 38            |
| Country: Number of subjects enrolled | Brazil: 35             |
| Country: Number of subjects enrolled | Mexico: 35             |
| Country: Number of subjects enrolled | United Kingdom: 32     |
| Country: Number of subjects enrolled | France: 31             |
| Country: Number of subjects enrolled | Italy: 21              |
| Country: Number of subjects enrolled | Austria: 18            |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Belgium: 18     |
| Country: Number of subjects enrolled | Australia: 15   |
| Country: Number of subjects enrolled | Switzerland: 15 |
| Country: Number of subjects enrolled | Portugal: 14    |
| Country: Number of subjects enrolled | Spain: 7        |
| Country: Number of subjects enrolled | Denmark: 2      |
| Country: Number of subjects enrolled | Netherlands: 1  |
| Worldwide total number of subjects   | 698             |
| EEA total number of subjects         | 182             |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 694 |
| From 65 to 84 years                       | 4   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled in a total of 144 study sites in Asia, Australia, Europe, and South and North America. The first participant was screened on 26 April 2010. The last study visit occurred on 17 April 2015.

### Pre-assignment

Screening details:

867 participants were screened.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Study (overall period)  |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Double blind                    |
| Roles blinded                | Subject, Investigator, Assessor |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | ATV+COBI+FTC/TDF |

Arm description:

COBI + RTV placebo + ATV + FTC/TDF once daily

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Cobicistat   |
| Investigational medicinal product code |              |
| Other name                             | Tybost®      |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Cobicistat (COBI) (150 mg) once daily

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Atazanavir |
| Investigational medicinal product code |            |
| Other name                             | Reyataz®   |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

Atazanavir (ATV) (300 mg) once daily

|                                        |                                             |
|----------------------------------------|---------------------------------------------|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code |                                             |
| Other name                             | Truvada®                                    |
| Pharmaceutical forms                   | Tablet                                      |
| Routes of administration               | Oral use                                    |

Dosage and administration details:

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (200/300 mg) FDC once daily

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Ritonavir placebo |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Ritonavir placebo once daily

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | ATV+RTV+FTC/TDF |
|------------------|-----------------|

Arm description:

RTV + COBI placebo + ATV + FTC/TDF once daily

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Ritonavir         |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Ritonavir (RTV) (100 mg) once daily

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Atazanavir |
| Investigational medicinal product code |            |
| Other name                             | Reyataz®   |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

Atazanavir (ATV) (300 mg) once daily

|                                        |                                             |
|----------------------------------------|---------------------------------------------|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code |                                             |
| Other name                             | Truvada®                                    |
| Pharmaceutical forms                   | Tablet                                      |
| Routes of administration               | Oral use                                    |

Dosage and administration details:

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (200/300 mg) FDC once daily

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Cobicistat placebo |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Cobicistat placebo once daily

| <b>Number of subjects in period 1<sup>[1]</sup></b> | ATV+COBI+FTC/TDF | ATV+RTV+FTC/TDF |
|-----------------------------------------------------|------------------|-----------------|
| Started                                             | 344              | 348             |
| Completed                                           | 70               | 81              |
| Not completed                                       | 274              | 267             |
| Withdrew Consent                                    | 21               | 15              |
| Adverse event, non-fatal                            | 26               | 19              |
| Participant Noncompliance                           | 5                | 7               |

|                                       |     |     |
|---------------------------------------|-----|-----|
| Death                                 | 1   | 1   |
| Investigator's Discretion             | 12  | 10  |
| Pregnancy                             | -   | 3   |
| Joined Another Gilead-sponsored Study | 186 | 195 |
| Lost to follow-up                     | 20  | 17  |
| Lack of efficacy                      | 3   | -   |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 5 participants in the ATV+COBI+FTC/TDF group and 1 participant in the ATV+RTV+FTC/TDF group who were randomized but not treated are not included in the subject disposition table.

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | ATV+COBI+FTC/TDF |
|-----------------------|------------------|

Reporting group description:

COBI + RTV placebo + ATV + FTC/TDF once daily

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | ATV+RTV+FTC/TDF |
|-----------------------|-----------------|

Reporting group description:

RTV + COBI placebo + ATV + FTC/TDF once daily

| Reporting group values | ATV+COBI+FTC/TDF | ATV+RTV+FTC/TDF | Total |
|------------------------|------------------|-----------------|-------|
| Number of subjects     | 344              | 348             | 692   |
| Age categorical        |                  |                 |       |
| Units: Subjects        |                  |                 |       |

|                                     |       |       |     |
|-------------------------------------|-------|-------|-----|
| Age Continuous                      |       |       |     |
| Units: years                        |       |       |     |
| arithmetic mean                     | 37    | 38    |     |
| standard deviation                  | ± 9.8 | ± 9.6 | -   |
| Gender, Male/Female                 |       |       |     |
| Units: participants                 |       |       |     |
| Female                              | 57    | 61    | 118 |
| Male                                | 287   | 287   | 574 |
| Ethnicity                           |       |       |     |
| Units: Subjects                     |       |       |     |
| Hispanic or Latino                  | 97    | 92    | 189 |
| Not Hispanic or Latino              | 245   | 253   | 498 |
| Unknown or Not Reported             | 2     | 3     | 5   |
| Race                                |       |       |     |
| Units: Subjects                     |       |       |     |
| American Indian or Alaska Native    | 1     | 2     | 3   |
| Asian                               | 44    | 37    | 81  |
| Black or African Heritage           | 65    | 63    | 128 |
| Native Hawaiian or Pacific Islander | 1     | 1     | 2   |
| White                               | 198   | 215   | 413 |
| Not Permitted                       | 2     | 3     | 5   |
| Other                               | 33    | 27    | 60  |
| HIV-1 RNA Category                  |       |       |     |
| Units: Subjects                     |       |       |     |
| ≤ 100,000 copies/mL                 | 212   | 205   | 417 |
| > 100,000 copies/mL                 | 132   | 143   | 275 |
| CD4 Cell Count Category             |       |       |     |
| Units: Subjects                     |       |       |     |
| ≤ 50 cells/μL                       | 11    | 12    | 23  |
| 51 to ≤ 200 cells/μL                | 49    | 45    | 94  |
| 201 to ≤ 350 cells/μL               | 114   | 126   | 240 |
| 351 to ≤ 500 cells/μL               | 123   | 117   | 240 |
| > 500 cells/μL                      | 47    | 48    | 95  |

|                                             |         |         |     |
|---------------------------------------------|---------|---------|-----|
| HIV Disease Status                          |         |         |     |
| Units: Subjects                             |         |         |     |
| Asymptomatic                                | 285     | 292     | 577 |
| Symptomatic HIV Infections                  | 31      | 32      | 63  |
| AIDS                                        | 28      | 24      | 52  |
| Hepatitis B Surface Antigen Status          |         |         |     |
| Units: Subjects                             |         |         |     |
| Positive                                    | 16      | 9       | 25  |
| Negative                                    | 328     | 339     | 667 |
| Hepatitis C Antibody Status                 |         |         |     |
| Units: Subjects                             |         |         |     |
| Positive                                    | 21      | 16      | 37  |
| Negative                                    | 323     | 331     | 654 |
| Indeterminate                               | 0       | 1       | 1   |
| HIV-1 RNA                                   |         |         |     |
| Units: log10 copies/mL                      |         |         |     |
| arithmetic mean                             | 4.81    | 4.84    |     |
| standard deviation                          | ± 0.585 | ± 0.594 | -   |
| Cluster of differentiation (CD4) Cell Count |         |         |     |
| Units: cells/μL                             |         |         |     |
| arithmetic mean                             | 353     | 351     |     |
| standard deviation                          | ± 170.5 | ± 175.5 | -   |



## End points

### End points reporting groups

|                                                                               |                  |
|-------------------------------------------------------------------------------|------------------|
| Reporting group title                                                         | ATV+COBI+FTC/TDF |
| Reporting group description:<br>COBI + RTV placebo + ATV + FTC/TDF once daily |                  |
| Reporting group title                                                         | ATV+RTV+FTC/TDF  |
| Reporting group description:<br>RTV + COBI placebo + ATV + FTC/TDF once daily |                  |

### Primary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48 |
| End point description:<br>The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a participant's virologic response status using only the viral load at the prespecified time point within an allowed window of time, along with study drug discontinuation status.<br><br>Intent-to-Treat (ITT) Analysis Set: participants who were randomized and received at least one dose of study drug |                                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Primary                                                             |
| End point timeframe:<br>Week 48                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                     |

| End point values                  | ATV+COBI+FTC/TDF | ATV+RTV+FTC/TDF |  |  |
|-----------------------------------|------------------|-----------------|--|--|
| Subject group type                | Reporting group  | Reporting group |  |  |
| Number of subjects analysed       | 344              | 348             |  |  |
| Units: percentage of participants |                  |                 |  |  |
| number (not applicable)           | 85.2             | 87.4            |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Difference in percentages          |
| Statistical analysis description:<br>700 planned subjects had 95% power to evaluate noninferiority assuming a response rate of 79.5% for both arms and a noninferiority margin of 12%. Null hypothesis: ATV+COBI+FTC/TDF group was at least 12% worse than the ATV+RTV+FTC/TDF group; alternative hypothesis: ATV+COBI+FTC/TDF group was less than 12% worse than the ATV+RTV+FTC/TDF group. ATV+COBI+FTC/TDF was noninferior if the lower bound of the 2-sided 95.2% confidence interval (CI) (COBI group - RTV group) was > -12%. |                                    |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ATV+RTV+FTC/TDF v ATV+COBI+FTC/TDF |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 692                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Parameter estimate                      | Difference in percentages      |
| Point estimate                          | -2.2                           |
| Confidence interval                     |                                |
| level                                   | 95.2 %                         |
| sides                                   | 2-sided                        |
| lower limit                             | -7.4                           |
| upper limit                             | 3                              |

Notes:

[1] - Difference in percentages of success and its 95.2% confidence interval (CI) were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.

### Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 96

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 96 |
|-----------------|---------------------------------------------------------------------|

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 96 was analyzed using the snapshot algorithm.

ITT Analysis Set

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

End point timeframe:

Week 96

| End point values                  | ATV+COBI+FTC/TDF | ATV+RTV+FTC/TDF |  |  |
|-----------------------------------|------------------|-----------------|--|--|
| Subject group type                | Reporting group  | Reporting group |  |  |
| Number of subjects analysed       | 344              | 348             |  |  |
| Units: percentage of participants |                  |                 |  |  |
| number (not applicable)           | 77.9             | 79.3            |  |  |

### Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Difference in percentages |
|----------------------------|---------------------------|

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 692                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[2]</sup>     |
| Parameter estimate                      | Difference in percentages          |
| Point estimate                          | -1.4                               |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -7.6    |
| upper limit         | 4.7     |

Notes:

[2] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

## Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 144

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 144 |
|-----------------|----------------------------------------------------------------------|

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 144 was analyzed using the snapshot algorithm.

ITT Analysis Set

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

End point timeframe:

Week 144

| End point values                  | ATV+COBI+FT<br>C/TDF | ATV+RTV+FTC<br>/TDF |  |  |
|-----------------------------------|----------------------|---------------------|--|--|
| Subject group type                | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed       | 344                  | 348                 |  |  |
| Units: percentage of participants |                      |                     |  |  |
| number (not applicable)           | 72.1                 | 74.1                |  |  |

## Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Difference in percentages |
|----------------------------|---------------------------|

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 692                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[3]</sup>     |
| Parameter estimate                      | Difference in percentages          |
| Point estimate                          | -2.1                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -8.7                               |
| upper limit                             | 4.5                                |

Notes:

[3] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

## Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 192

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 192 |
|-----------------|----------------------------------------------------------------------|

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 192 was analyzed using the snapshot algorithm.

Week 192 Modified ITT Analysis Set: includes participants in the ITT analysis set excluding those who either (1) transferred to other Gilead-sponsored studies after completing their Week 144 visit and before the lower limit of the Week 192 analysis window, or (2) prematurely discontinued study drug prior to the Week 144 visit.

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

End point timeframe:

Week 192

| End point values                  | ATV+COBI+FTC/TDF | ATV+RTV+FTC/TDF |  |  |
|-----------------------------------|------------------|-----------------|--|--|
| Subject group type                | Reporting group  | Reporting group |  |  |
| Number of subjects analysed       | 74               | 69              |  |  |
| Units: percentage of participants |                  |                 |  |  |
| number (not applicable)           | 71.6             | 79.7            |  |  |

## Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | Difference in percentages |
|----------------------------|---------------------------|

Statistical analysis description:

The null hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was at least 12% worse than the response rate in ATV+RTV+FTC/TDF group; the alternative hypothesis was that the response rate in the ATV+COBI+FTC/TDF group was less than 12% worse than that in the ATV+RTV+FTC/TDF group.

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 143                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[4]</sup>     |
| Parameter estimate                      | Difference in percentages          |
| Point estimate                          | -8                                 |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -22.2                              |
| upper limit                             | 6.3                                |

Notes:

[4] - Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

**Secondary: Change From Baseline in CD4 Cell Count at Week 48**

|                 |                                                   |
|-----------------|---------------------------------------------------|
| End point title | Change From Baseline in CD4 Cell Count at Week 48 |
|-----------------|---------------------------------------------------|

End point description:

Participants in the ITT Analysis Set with available change data at Week 48 were analyzed.

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

End point timeframe:

Baseline to Week 48

| End point values                     | ATV+COBI+FT<br>C/TDF | ATV+RTV+FTC<br>/TDF |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 313                  | 324                 |  |  |
| Units: cells/ $\mu$ L                |                      |                     |  |  |
| arithmetic mean (standard deviation) | 213 ( $\pm$ 151)     | 219 ( $\pm$ 150.4)  |  |  |

**Statistical analyses**

|                                         |                                        |
|-----------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>       | Difference in least squares mean (LSM) |
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF     |
| Number of subjects included in analysis | 637                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | other <sup>[5]</sup>                   |
| P-value                                 | = 0.67 <sup>[6]</sup>                  |
| Method                                  | ANOVA                                  |
| Parameter estimate                      | Difference in LSM                      |
| Point estimate                          | -5                                     |
| Confidence interval                     |                                        |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -28                                    |
| upper limit                             | 18                                     |

Notes:

[5] - Comparative analysis

[6] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

**Secondary: Change From Baseline in CD4 Cell Count at Week 96**

|                 |                                                   |
|-----------------|---------------------------------------------------|
| End point title | Change From Baseline in CD4 Cell Count at Week 96 |
|-----------------|---------------------------------------------------|

End point description:

Participants in the ITT Analysis Set with available change data at Week 96 were analyzed.

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

End point timeframe:

Baseline to Week 96

| End point values                     | ATV+COBI+FT<br>C/TDF | ATV+RTV+FTC<br>/TDF |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 300                  | 311                 |  |  |
| Units: cells/ $\mu$ L                |                      |                     |  |  |
| arithmetic mean (standard deviation) | 277 ( $\pm$ 176.8)   | 287 ( $\pm$ 181.5)  |  |  |

## Statistical analyses

| Statistical analysis title              | Difference in LSM                  |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 611                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other <sup>[7]</sup>               |
| P-value                                 | = 0.51 <sup>[8]</sup>              |
| Method                                  | ANOVA                              |
| Parameter estimate                      | Difference in LSM                  |
| Point estimate                          | -10                                |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -38                                |
| upper limit                             | 19                                 |

Notes:

[7] - Comparative analysis

[8] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

## Secondary: Change From Baseline in CD4 Cell Count at Week 144

| End point title        | Change From Baseline in CD4 Cell Count at Week 144                                         |
|------------------------|--------------------------------------------------------------------------------------------|
| End point description: | Participants in the ITT Analysis Set with available change data at Week 144 were analyzed. |
| End point type         | Secondary                                                                                  |
| End point timeframe:   | Baseline to Week 144                                                                       |

| End point values                     | ATV+COBI+FT<br>C/TDF | ATV+RTV+FTC<br>/TDF |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 275                  | 288                 |  |  |
| Units: cells/ $\mu$ L                |                      |                     |  |  |
| arithmetic mean (standard deviation) | 310 ( $\pm$ 188)     | 332 ( $\pm$ 199.8)  |  |  |

## Statistical analyses

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| <b>Statistical analysis title</b>       | Difference in LSM                  |
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 563                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other <sup>[9]</sup>               |
| P-value                                 | = 0.18 <sup>[10]</sup>             |
| Method                                  | ANOVA                              |
| Parameter estimate                      | Difference in LSM                  |
| Point estimate                          | -22                                |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -54                                |
| upper limit                             | 10                                 |

Notes:

[9] - Comparative analysis

[10] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.

### Secondary: Change From Baseline in CD4 Cell Count at Week 192

|                                                                                            |                                                    |
|--------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                            | Change From Baseline in CD4 Cell Count at Week 192 |
| End point description:                                                                     |                                                    |
| Participants in the ITT Analysis Set with available change data at Week 192 were analyzed. |                                                    |
| End point type                                                                             | Secondary                                          |
| End point timeframe:                                                                       |                                                    |
| Baseline to Week 192                                                                       |                                                    |

| End point values                     | ATV+COBI+FTC/TDF   | ATV+RTV+FTC/TDF    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 73                 | 83                 |  |  |
| Units: cells/ $\mu$ L                |                    |                    |  |  |
| arithmetic mean (standard deviation) | 350 ( $\pm$ 191.3) | 343 ( $\pm$ 190.7) |  |  |

### Statistical analyses

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| <b>Statistical analysis title</b>       | Difference in LSM                  |
| Comparison groups                       | ATV+COBI+FTC/TDF v ATV+RTV+FTC/TDF |
| Number of subjects included in analysis | 156                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other <sup>[11]</sup>              |
| P-value                                 | = 0.84 <sup>[12]</sup>             |
| Method                                  | ANOVA                              |
| Parameter estimate                      | Difference in LSM                  |
| Point estimate                          | 6                                  |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -55     |
| upper limit         | 67      |

Notes:

[11] - Comparative analysis

[12] - The p-value and difference in LSM and its 95% CI were computed using ANOVA model, including baseline HIV-1 RNA category in the model.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline through end of study drug treatment (average exposure: ATV+COBI+FTC/TDF group = 141.3 weeks; ATV+RTV+FTC/TDF group = 143.0 weeks) plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who were randomized and received at least one dose of study drug

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | ATV+COBI+FTC/TDF |
|-----------------------|------------------|

Reporting group description:

COBI + RTV placebo + ATV + FTC/TDF once daily

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | ATV+RTV+FTC/TDF |
|-----------------------|-----------------|

Reporting group description:

RTV + COBI placebo + ATV + FTC/TDF once daily

| Serious adverse events                                              | ATV+COBI+FTC/TDF  | ATV+RTV+FTC/TDF   |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 64 / 344 (18.60%) | 50 / 348 (14.37%) |  |
| number of deaths (all causes)                                       | 1                 | 1                 |  |
| number of deaths resulting from adverse events                      | 0                 | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Uterine leiomyoma                                                   |                   |                   |  |
| subjects affected / exposed                                         | 1 / 344 (0.29%)   | 1 / 348 (0.29%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Anogenital warts                                                    |                   |                   |  |
| subjects affected / exposed                                         | 1 / 344 (0.29%)   | 0 / 348 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Burkitt's lymphoma                                                  |                   |                   |  |
| subjects affected / exposed                                         | 1 / 344 (0.29%)   | 0 / 348 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Hodgkin's disease                                                   |                   |                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Hypovolaemic shock                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |  |
| Abortion spontaneous                                 |                 |                 |  |
| subjects affected / exposed                          | 2 / 344 (0.58%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain                                           |                 |                 |  |
| subjects affected / exposed                          | 3 / 344 (0.87%) | 3 / 348 (0.86%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia                                              |                 |                 |  |
| subjects affected / exposed                          | 3 / 344 (0.87%) | 3 / 348 (0.86%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Immune system disorders                              |                 |                 |  |
| Immune reconstitution inflammatory syndrome          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Cervical dysplasia                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Priapism                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colpocoele                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Asthma                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 344 (0.87%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anxiety disorder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug dependence                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alcohol withdrawal syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alcoholism                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post-traumatic stress disorder                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Schizophrenia                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Substance-induced psychotic disorder            |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicidal ideation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood creatine phosphokinase increased          |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coma scale abnormal                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                 |                 |                 |  |
|-----------------------------------------------------------------|-----------------|-----------------|--|
| White blood cell count increased<br>subjects affected / exposed | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications               |                 |                 |  |
| Ankle fracture                                                  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Carbon monoxide poisoning                                       |                 |                 |  |
| subjects affected / exposed                                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Clavicle fracture                                               |                 |                 |  |
| subjects affected / exposed                                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Femur fracture                                                  |                 |                 |  |
| subjects affected / exposed                                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Hand fracture                                                   |                 |                 |  |
| subjects affected / exposed                                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Ligament rupture                                                |                 |                 |  |
| subjects affected / exposed                                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                                       |                 |                 |  |
| subjects affected / exposed                                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Overdose                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal haematoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tendon rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Palpitations                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Ataxia                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Guillain-Barre syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Migraine                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient global amnesia                        |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anaemia</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Coagulopathy</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Leukocytosis</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thrombocytopenia</b>                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Ear and labyrinth disorders</b>              |                 |                 |  |
| <b>Deafness unilateral</b>                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Tinnitus</b>                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Vertigo</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal mass                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Crohn's disease                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food poisoning                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroduodenal ulcer                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoidal haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Angioedema                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash                                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash papular                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin abrasion                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vasculitic rash                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 4 / 348 (1.15%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus ureteric                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fanconi syndrome acquired                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephropathy                                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular acidosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 3 / 348 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 4 / 344 (1.16%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 2 / 348 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 344 (0.87%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii pneumonia                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal wall abscess                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess neck                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis perforated                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chancroid                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dengue fever                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis salmonella                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis shigella                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Genital abscess                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gonorrhoea                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Groin abscess                                   |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected dermal cyst                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infectious colitis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis toxoplasmal                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis viral                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal candidiasis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orchitis                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis acute                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media chronic                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perineal abscess                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis streptococcal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia mycoplasmal                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculosis                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Scrotal abscess                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 344 (0.58%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ketoacidosis                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertriglyceridaemia                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malnutrition                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 344 (0.29%) | 0 / 348 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic acidosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 344 (0.00%) | 1 / 348 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                                   | ATV+COBI+FTC/TDF   | ATV+RTV+FTC/TDF    |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                    |                    |  |
| subjects affected / exposed                                         | 311 / 344 (90.41%) | 312 / 348 (89.66%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Anogenital warts                                                    |                    |                    |  |
| subjects affected / exposed                                         | 24 / 344 (6.98%)   | 16 / 348 (4.60%)   |  |
| occurrences (all)                                                   | 26                 | 18                 |  |
| Vascular disorders                                                  |                    |                    |  |
| Hypertension                                                        |                    |                    |  |
| subjects affected / exposed                                         | 18 / 344 (5.23%)   | 23 / 348 (6.61%)   |  |
| occurrences (all)                                                   | 18                 | 29                 |  |
| General disorders and administration site conditions                |                    |                    |  |
| Fatigue                                                             |                    |                    |  |
| subjects affected / exposed                                         | 38 / 344 (11.05%)  | 34 / 348 (9.77%)   |  |
| occurrences (all)                                                   | 41                 | 36                 |  |
| Pyrexia                                                             |                    |                    |  |
| subjects affected / exposed                                         | 36 / 344 (10.47%)  | 30 / 348 (8.62%)   |  |
| occurrences (all)                                                   | 43                 | 38                 |  |
| Respiratory, thoracic and mediastinal disorders                     |                    |                    |  |
| Cough                                                               |                    |                    |  |
| subjects affected / exposed                                         | 36 / 344 (10.47%)  | 29 / 348 (8.33%)   |  |
| occurrences (all)                                                   | 42                 | 35                 |  |
| Nasal congestion                                                    |                    |                    |  |
| subjects affected / exposed                                         | 15 / 344 (4.36%)   | 29 / 348 (8.33%)   |  |
| occurrences (all)                                                   | 16                 | 32                 |  |
| Oropharyngeal pain                                                  |                    |                    |  |
| subjects affected / exposed                                         | 20 / 344 (5.81%)   | 24 / 348 (6.90%)   |  |
| occurrences (all)                                                   | 22                 | 31                 |  |
| Psychiatric disorders                                               |                    |                    |  |
| Insomnia                                                            |                    |                    |  |
| subjects affected / exposed                                         | 26 / 344 (7.56%)   | 29 / 348 (8.33%)   |  |
| occurrences (all)                                                   | 29                 | 30                 |  |
| Depression                                                          |                    |                    |  |
| subjects affected / exposed                                         | 25 / 344 (7.27%)   | 28 / 348 (8.05%)   |  |
| occurrences (all)                                                   | 30                 | 29                 |  |
| Anxiety                                                             |                    |                    |  |

|                                                  |                        |                        |  |
|--------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 19 / 344 (5.52%)<br>19 | 16 / 348 (4.60%)<br>18 |  |
| Nervous system disorders                         |                        |                        |  |
| Headache                                         |                        |                        |  |
| subjects affected / exposed                      | 57 / 344 (16.57%)      | 73 / 348 (20.98%)      |  |
| occurrences (all)                                | 75                     | 111                    |  |
| Dizziness                                        |                        |                        |  |
| subjects affected / exposed                      | 32 / 344 (9.30%)       | 28 / 348 (8.05%)       |  |
| occurrences (all)                                | 36                     | 32                     |  |
| Blood and lymphatic system disorders             |                        |                        |  |
| Lymphadenopathy                                  |                        |                        |  |
| subjects affected / exposed                      | 18 / 344 (5.23%)       | 26 / 348 (7.47%)       |  |
| occurrences (all)                                | 21                     | 30                     |  |
| Eye disorders                                    |                        |                        |  |
| Ocular icterus                                   |                        |                        |  |
| subjects affected / exposed                      | 69 / 344 (20.06%)      | 79 / 348 (22.70%)      |  |
| occurrences (all)                                | 81                     | 88                     |  |
| Gastrointestinal disorders                       |                        |                        |  |
| Diarrhoea                                        |                        |                        |  |
| subjects affected / exposed                      | 76 / 344 (22.09%)      | 96 / 348 (27.59%)      |  |
| occurrences (all)                                | 105                    | 117                    |  |
| Nausea                                           |                        |                        |  |
| subjects affected / exposed                      | 66 / 344 (19.19%)      | 66 / 348 (18.97%)      |  |
| occurrences (all)                                | 79                     | 77                     |  |
| Vomiting                                         |                        |                        |  |
| subjects affected / exposed                      | 34 / 344 (9.88%)       | 25 / 348 (7.18%)       |  |
| occurrences (all)                                | 40                     | 28                     |  |
| Abdominal pain                                   |                        |                        |  |
| subjects affected / exposed                      | 22 / 344 (6.40%)       | 26 / 348 (7.47%)       |  |
| occurrences (all)                                | 22                     | 28                     |  |
| Haemorrhoids                                     |                        |                        |  |
| subjects affected / exposed                      | 23 / 344 (6.69%)       | 21 / 348 (6.03%)       |  |
| occurrences (all)                                | 24                     | 21                     |  |
| Abdominal pain upper                             |                        |                        |  |
| subjects affected / exposed                      | 19 / 344 (5.52%)       | 23 / 348 (6.61%)       |  |
| occurrences (all)                                | 25                     | 27                     |  |
| Flatulence                                       |                        |                        |  |

|                                                                                                                  |                          |                          |  |
|------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                 | 28 / 344 (8.14%)<br>29   | 10 / 348 (2.87%)<br>10   |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                                    | 15 / 344 (4.36%)<br>16   | 21 / 348 (6.03%)<br>26   |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)                                         | 16 / 344 (4.65%)<br>18   | 19 / 348 (5.46%)<br>19   |  |
| Hepatobiliary disorders<br>Jaundice<br>subjects affected / exposed<br>occurrences (all)                          | 76 / 344 (22.09%)<br>94  | 61 / 348 (17.53%)<br>68  |  |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)                                          | 42 / 344 (12.21%)<br>74  | 39 / 348 (11.21%)<br>68  |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)               | 26 / 344 (7.56%)<br>30   | 31 / 348 (8.91%)<br>32   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 34 / 344 (9.88%)<br>42   | 42 / 348 (12.07%)<br>52  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                   | 19 / 344 (5.52%)<br>23   | 19 / 348 (5.46%)<br>20   |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                      | 18 / 344 (5.23%)<br>18   | 20 / 348 (5.75%)<br>24   |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                            | 18 / 344 (5.23%)<br>22   | 15 / 348 (4.31%)<br>17   |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)               | 59 / 344 (17.15%)<br>108 | 79 / 348 (22.70%)<br>148 |  |

|                                                                                       |                         |                         |
|---------------------------------------------------------------------------------------|-------------------------|-------------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 67 / 344 (19.48%)<br>99 | 65 / 348 (18.68%)<br>77 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 33 / 344 (9.59%)<br>38  | 33 / 348 (9.48%)<br>44  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 28 / 344 (8.14%)<br>41  | 28 / 348 (8.05%)<br>33  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 25 / 344 (7.27%)<br>41  | 25 / 348 (7.18%)<br>36  |
| Syphilis<br>subjects affected / exposed<br>occurrences (all)                          | 23 / 344 (6.69%)<br>26  | 26 / 348 (7.47%)<br>32  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 25 / 344 (7.27%)<br>26  | 19 / 348 (5.46%)<br>23  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 17 / 344 (4.94%)<br>19  | 27 / 348 (7.76%)<br>31  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                  | 21 / 344 (6.10%)<br>29  | 19 / 348 (5.46%)<br>26  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 12 / 344 (3.49%)<br>13  | 20 / 348 (5.75%)<br>21  |
| Tinea pedis<br>subjects affected / exposed<br>occurrences (all)                       | 18 / 344 (5.23%)<br>19  | 11 / 348 (3.16%)<br>12  |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)                      | 18 / 344 (5.23%)<br>23  | 7 / 348 (2.01%)<br>7    |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 July 2010     | The first exclusion criterion was revised to clarify that subjects with an AIDS-defining diagnosis of a CD4-positive T lymphocyte count < 200/ $\mu$ L or a CD4-positive T lymphocyte count < 14% of the total lymphocyte count within 30 days prior to screening were not excluded from participation in the study.                                                                                                                                                                                                                                            |
| 03 February 2012 | Extended the blinded phase of the study from 96 weeks of treatment to 192 weeks of treatment; updated the introduction section of the protocol to reflect updated treatment guidelines, new information gathered from ongoing studies, and safety information included in the third edition of the COBI investigator's brochure; added additional testing for plasma storage samples and urine storage samples collected at baseline and at Weeks 2, 4, 24, and 48; updated the analysis schedule due to the extension of the blinded phase of study treatment. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23532097>

<http://www.ncbi.nlm.nih.gov/pubmed/26181707>