



## Clinical trial results:

### Safety, antiviral effect and pharmacokinetics of BI 207127 in combination with BI 201335 and with or without ribavirin for 4, 16, 24, 28 or 40 weeks in patients with chronic HCV genotype 1 infection (randomized Phase Ib/II).

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2009-018197-66  |
| Trial protocol           | PT FR DE AT ES  |
| Global end of trial date | 30 October 2014 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 05 May 2016  |
| First version publication date | 05 May 2016  |

## Trial information

### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 1241.21 |
|-----------------------|---------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01132313 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Boehringer Ingelheim   |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216   |
| Public contact               | Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.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                       | 11 December 2014 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 October 2014  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 October 2014  |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of Part 1 to 4 of this trial was to investigate safety, antiviral effect, and pharmacokinetics of deleobuvir (DBV/BI 207127) in combination with faldaprevir (FDV/BI 201335) and ribavirin (RBV) for 4, 16, 24, 28, or 40 weeks in patients with chronic hepatitis C virus (HCV) Genotype 1 (GT-1) infection.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 03 May 2010 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Efficacy    |
| Long term follow-up duration                              | 67 Months   |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 105 |
| Country: Number of subjects enrolled | France: 138        |
| Country: Number of subjects enrolled | Switzerland: 68    |
| Country: Number of subjects enrolled | Germany: 94        |
| Country: Number of subjects enrolled | Australia: 33      |
| Country: Number of subjects enrolled | New Zealand: 14    |
| Country: Number of subjects enrolled | Austria: 20        |
| Country: Number of subjects enrolled | Spain: 127         |
| Country: Number of subjects enrolled | Portugal: 37       |
| Country: Number of subjects enrolled | Romania: 71        |
| Worldwide total number of subjects   | 707                |
| EEA total number of subjects         | 487                |

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)                      | 648 |
| From 65 to 84 years                       | 59  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patients with chronic hepatitis C infection GT-1 were to be enrolled in the trial. Patients were recruited by hepatologists or infectious disease specialists experienced in treating HCV patients. This trial was conducted in 4 parts, each consisting of randomised, open-label treatments.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not allocated to trial treatment if any one of the specific entry criteria were violated.

### Period 1

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

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| Arm title                    | Part 1: 400mg DBV and 120mg FDV - 4w |

Arm description:

Part 1: 4 weeks of 400mg Deleobuvir tablet TID (Three times per day) and 120mg Faldaprevir soft gelatin capsule QD (Once daily) in combination with RBV tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period). Two patients were randomised to the Part 1: 400mg DBV and 120mg FDV - 4w arm, however these patients were not treated. Consequently, number of subject that started is 17 but only 15 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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

Dosage and administration details:

4 weeks of 400mg Deleobuvir tablet administered orally TID.

|  |                |
|--|----------------|
| Investigational medicinal product name | RBV (Copegus®) |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.

|  |                  |
|--|------------------|
| Investigational medicinal product name | PegIFN           |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

PegIFN 180µg per week was administered by injection subcutaneously.

|   |                                       |
|---|---------------------------------------|
| Investigational medicinal product name  | Faldaprevir                           |
| Investigational medicinal product code  |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Capsule, soft                         |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| 4 weeks of 120mg Faldaprevir soft gelatin capsule administered orally QD.   |                                       |
| <b>Arm title</b>  | Part 1: 600mg DBV and 120mg FDV - 4w  |
| Arm description:  |                                       |
| Part 1: 4 weeks of 600mg Deleobuvir (DBV, BI 207127) tablet three times per day (TID) and 120mg Faldaprevir (FDV, BI 201335) soft gelatin capsule once daily (QD) in combination with Ribavirin (RBV) tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period). |                                       |
| Arm type  | Experimental                          |
| Investigational medicinal product name  | Deleobuvir                            |
| Investigational medicinal product code  |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Tablet                                |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| 4 weeks of 600mg Deleobuvir tablet administered orally TID.   |                                       |
| Investigational medicinal product name  | PegIFN                                |
| Investigational medicinal product code  |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Injection                             |
| Routes of administration  | Subcutaneous use                      |
| Dosage and administration details:  |                                       |
| PegIFN 180µg per week was administered by injection subcutaneously.   |                                       |
| Investigational medicinal product name  | RBV (Copegus®)                        |
| Investigational medicinal product code  |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Tablet                                |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.   |                                       |
| Investigational medicinal product name  | Faldaprevir                           |
| Investigational medicinal product code  |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Capsule, soft                         |
| Routes of administration  | Oral use                              |
| Dosage and administration details:  |                                       |
| 16 weeks of 120mg Faldaprevir tablet orally QD.   |                                       |
| <b>Arm title</b>  | Part 2: 600mg DBV and 120mg FDV - 16w |
| Arm description:  |                                       |
| Part 2: 16 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.  |                                       |
| Arm type  | Experimental                          |

|  |   |
|--|---|
| Investigational medicinal product name   | Deleobuvir                                |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Tablet                                    |
| Routes of administration   | Oral use                                  |
| Dosage and administration details:   |   |
| 16 weeks of 600mg Deleobuvir tablet administered orally TID.   |   |
| Investigational medicinal product name   | Faldaprevir                               |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Capsule, soft                             |
| Routes of administration   | Oral use                                  |
| Dosage and administration details:   |   |
| 16 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.  |   |
| Investigational medicinal product name   | RBV (Copegus®)                            |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Tablet                                    |
| Routes of administration   | Oral use                                  |
| Dosage and administration details:   |   |
| Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.  |   |
| Investigational medicinal product name   | PegIFN                                    |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Injection                                 |
| Routes of administration   | Subcutaneous use                          |
| Dosage and administration details:   |   |
| PegIFN 180µg per week was administered by injection subcutaneously.  |   |
| <b>Arm title</b>   | Part 2: 600mg DBV TID and 120mg FDV - 28w |
| Arm description:   |   |
| Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. |   |
| Arm type   | Experimental                              |
| Investigational medicinal product name   | Deleobuvir                                |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Tablet                                    |
| Routes of administration   | Oral use                                  |
| Dosage and administration details:   |   |
| 28 weeks of 600mg Deleobuvir tablet orally TID.  |   |
| Investigational medicinal product name   | RBV (Copegus®)                            |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Tablet                                    |
| Routes of administration   | Oral use                                  |
| Dosage and administration details:   |   |
| Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.  |   |
| Investigational medicinal product name   | PegIFN                                    |
| Investigational medicinal product code   |   |
| Other name   |   |

|   |                                       |
|---|---------------------------------------|
| Pharmaceutical forms  | Injection                             |
| Routes of administration  | Subcutaneous use                      |
| Dosage and administration details:                                  |                                       |
| PegIFN 180µg per week was administered by injection subcutaneously. |                                       |
| Investigational medicinal product name                              | Faldaprevir                           |
| Investigational medicinal product code                              |                                       |
| Other name  |                                       |
| Pharmaceutical forms  | Capsule, soft                         |
| Routes of administration  | Oral use                              |
| Dosage and administration details:                                  |                                       |
| 28 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.       |                                       |
| <b>Arm title</b>  | Part 2: 600mg DBV and 120mg FDV - 40w |

Arm description:

Part 2: 40 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Two patients were randomised to the Part 2: 600mg DBV and 120mg FDV - 40w arm, however these patients were not treated. Consequently, number of subject that started is 79 but only 77 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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

Dosage and administration details:

40 weeks of 600mg Deleobuvir tablet orally TID.

|  |                  |
|--|------------------|
| Investigational medicinal product name | PegIFN           |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

PegIFN 180µg per week was administered by injection subcutaneously.

|  |                |
|--|----------------|
| Investigational medicinal product name | RBV (Copegus®) |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.

|  |               |
|--|---------------|
| Investigational medicinal product name | Faldaprevir   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

40 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Part 2: 600mg DBV BID and 120mg FDV - 28w |
|------------------|---|

Arm description:

Part 2: 28 weeks of 600mg Deleobuvir tablet twice a day (BID) and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early

due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. One patient was randomised to the Part 2: 600mg DBV BID and 120mg FDV - 28w arm, however this patient was not treated. Consequently, number of subject that started is 79 but only 78 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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

Dosage and administration details:

28 weeks of 600mg Deleobuvir tablet administered orally BID.

|  |                |
|--|----------------|
| Investigational medicinal product name | RBV (Copegus®) |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.

|  |                  |
|--|------------------|
| Investigational medicinal product name | PegIFN           |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

PegIFN 180µg per week was administered by injection subcutaneously.

|  |               |
|--|---------------|
| Investigational medicinal product name | Faldaprevir   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

28 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |
|------------------|---|

Arm description:

Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD, without RBV. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Three patients were randomised to the Part 2: 600mg DBV and 120mg FDV, no RBV - 28w arm, however these patients were not treated. Consequently, number of subject that started is 49 but only 46 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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

Dosage and administration details:

28 weeks of 600mg Deleobuvir tablet orally TID.

|  |           |
|--|-----------|
| Investigational medicinal product name | PegIFN    |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Injection |

|  |                                       |
|--|---------------------------------------|
| Routes of administration   | Subcutaneous use                      |
| Dosage and administration details:<br>PegIFN 180µg per week was administered by injection subcutaneously.  |                                       |
| Investigational medicinal product name   | Faldaprevir                           |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, soft                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>28 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.  |                                       |
| <b>Arm title</b>   | Part 3: 600mg DBV and 120mg FDV - 16w |
| Arm description:<br>Part 3: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. |                                       |
| Arm type   | Experimental                          |
| Investigational medicinal product name   | Deleobuvir                            |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>16 weeks of 600mg Deleobuvir tablet administered orally BID.   |                                       |
| Investigational medicinal product name   | Faldaprevir                           |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, soft                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>16 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.  |                                       |
| Investigational medicinal product name   | RBV (Copegus®)                        |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:<br>Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.  |                                       |
| Investigational medicinal product name   | PegIFN                                |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Injection                             |
| Routes of administration   | Subcutaneous use                      |
| Dosage and administration details:<br>PegIFN 180µg per week was administered by injection subcutaneously.  |                                       |
| <b>Arm title</b>   | Part 3: 800mg DBV and 120mg FDV - 24w |
| Arm description:<br>Part 3: 24 weeks of 800mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. |                                       |
| Arm type   | Experimental                          |

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name   | Deleobuvir                            |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| 24 weeks of 800mg Deleobuvir tablet orally BID.  |                                       |
| Investigational medicinal product name   | PegIFN                                |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Injection                             |
| Routes of administration   | Subcutaneous use                      |
| Dosage and administration details:   |                                       |
| PegIFN 180µg per week was administered by injection subcutaneously.  |                                       |
| Investigational medicinal product name   | RBV (Copegus®)                        |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.  |                                       |
| Investigational medicinal product name   | Faldaprevir                           |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Capsule, soft                         |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| 24 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.  |                                       |
| <b>Arm title</b>   | Part 3: 600mg DBV and 120mg FDV - 24w |
| Arm description:   |                                       |
| Part 3: 24 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. |                                       |
| Arm type   | Experimental                          |
| Investigational medicinal product name   | Deleobuvir                            |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| 24 weeks of 600mg Deleobuvir tablet orally TID.  |                                       |
| Investigational medicinal product name   | RBV (Copegus®)                        |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |
| Pharmaceutical forms   | Tablet                                |
| Routes of administration   | Oral use                              |
| Dosage and administration details:   |                                       |
| Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.  |                                       |
| Investigational medicinal product name   | PegIFN                                |
| Investigational medicinal product code   |                                       |
| Other name   |                                       |

|   |  |
|---|--|
| Pharmaceutical forms  | Injection                              |
| Routes of administration  | Subcutaneous use                       |
| Dosage and administration details:                                  |  |
| PegIFN 180µg per week was administered by injection subcutaneously. |  |
| Investigational medicinal product name                              | Faldaprevir                            |
| Investigational medicinal product code                              |  |
| Other name  |  |
| Pharmaceutical forms  | Capsule, soft                          |
| Routes of administration  | Oral use                               |
| Dosage and administration details:                                  |  |
| 24 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.       |  |
| <b>Arm title</b>  | Part 4: 600 mg DBV and 120mg FDV - 16w |

Arm description:

Part 4: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

|   |                |
|---|----------------|
| Arm type  | Experimental   |
| Investigational medicinal product name          | Deleobuvir     |
| Investigational medicinal product code          |                |
| Other name                                      |                |
| Pharmaceutical forms                            | Tablet         |
| Routes of administration                        | Oral use       |
| Dosage and administration details:              |                |
| 16 weeks of 600mg Deleobuvir tablet orally BID. |                |
| Investigational medicinal product name          | RBV (Copegus®) |
| Investigational medicinal product code          |                |
| Other name                                      |                |
| Pharmaceutical forms                            | Tablet         |
| Routes of administration                        | Oral use       |

Dosage and administration details:

Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.

|   |               |
|---|---------------|
| Investigational medicinal product name                        | Faldaprevir   |
| Investigational medicinal product code                        |               |
| Other name  |               |
| Pharmaceutical forms  | Capsule, soft |
| Routes of administration                                      | Oral use      |
| Dosage and administration details:                            |               |
| 16 weeks of 120mg Faldaprevir soft gelatin capsule orally QD. |               |

|                  |  |
|------------------|--|
| <b>Arm title</b> | Part 4: 600 mg DBV and 120mg FDV - 24w |
|------------------|--|

Arm description:

Part 4: 24 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

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

Dosage and administration details:

24 weeks of 600mg Deleobuvir tablet administered orally BID.

|  |                |
|--|----------------|
| Investigational medicinal product name | RBV (Copegus®) |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Ribavirin tablet 200mg tablets was administered as 1000mg if <75kg, or 1200mg if ≥75kg, distributed in 2 divided doses.

|  |               |
|--|---------------|
| Investigational medicinal product name | Faldaprevir   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

24 weeks of 120mg Faldaprevir soft gelatin capsule orally QD.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 1: 400mg DBV and 120mg FDV - 4w | Part 1: 600mg DBV and 120mg FDV - 4w | Part 2: 600mg DBV and 120mg FDV - 16w |
|---|--------------------------------------|--------------------------------------|---------------------------------------|
| Started   | 15                                   | 17                                   | 81                                    |
| Completed   | 14                                   | 17                                   | 61                                    |
| Not completed                                       | 1                                    | 0                                    | 20                                    |
| Adverse event, serious fatal                        | -                                    | -                                    | -                                     |
| Other reason not defined above                      | -                                    | -                                    | -                                     |
| Consent withdrawn by subject                        | -                                    | -                                    | 3                                     |
| Adverse event, non-fatal                            | -                                    | -                                    | 4                                     |
| Lack of antiviral response                          | -                                    | -                                    | 12                                    |
| Lost to follow-up                                   | -                                    | -                                    | 1                                     |
| Lack of efficacy                                    | 1                                    | -                                    | -                                     |
| Protocol deviation                                  | -                                    | -                                    | -                                     |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 2: 600mg DBV TID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w |
|---|---|---------------------------------------|---|
| Started   | 80  | 77                                    | 78  |
| Completed   | 48  | 34                                    | 54  |
| Not completed                                       | 32  | 43                                    | 24  |
| Adverse event, serious fatal                        | -   | -                                     | 1   |
| Other reason not defined above                      | -   | -                                     | -   |
| Consent withdrawn by subject                        | 3   | 6                                     | -   |
| Adverse event, non-fatal                            | 10  | 19                                    | 5   |
| Lack of antiviral response                          | 18  | 18                                    | 18  |
| Lost to follow-up                                   | -   | -                                     | -   |
| Lack of efficacy                                    | -   | -                                     | -   |
| Protocol deviation                                  | 1   | -                                     | -   |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w | Part 3: 600mg DBV and 120mg FDV - 16w | Part 3: 800mg DBV and 120mg FDV - 24w |
|---|---|---------------------------------------|---------------------------------------|
| Started   | 46  | 32                                    | 26                                    |
| Completed   | 19  | 24                                    | 5                                     |
| Not completed                                       | 27  | 8                                     | 21                                    |
| Adverse event, serious fatal                        | -   | -                                     | -                                     |
| Other reason not defined above                      | -   | 1                                     | -                                     |
| Consent withdrawn by subject                        | 1   | -                                     | -                                     |
| Adverse event, non-fatal                            | 5   | 3                                     | 7                                     |
| Lack of antiviral response                          | 21  | -                                     | -                                     |
| Lost to follow-up                                   | -   | 1                                     | -                                     |
| Lack of efficacy                                    | -   | 3                                     | 14                                    |
| Protocol deviation                                  | -   | -                                     | -                                     |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 3: 600mg DBV and 120mg FDV - 24w | Part 4: 600 mg DBV and 120mg FDV - 16w | Part 4: 600 mg DBV and 120mg FDV - 24w |
|---|---------------------------------------|--|--|
| Started   | 25                                    | 1                                      | 2                                      |
| Completed   | 5                                     | 0                                      | 2                                      |
| Not completed                                       | 20                                    | 1                                      | 0                                      |
| Adverse event, serious fatal                        | -                                     | -                                      | -                                      |
| Other reason not defined above                      | -                                     | -                                      | -                                      |
| Consent withdrawn by subject                        | 2                                     | -                                      | -                                      |
| Adverse event, non-fatal                            | 2                                     | -                                      | -                                      |
| Lack of antiviral response                          | -                                     | 1                                      | -                                      |
| Lost to follow-up                                   | -                                     | -                                      | -                                      |
| Lack of efficacy                                    | 16                                    | -                                      | -                                      |
| Protocol deviation                                  | -                                     | -                                      | -                                      |

**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: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

## Baseline characteristics

### Reporting groups

|  |   |
|--|---|
| Reporting group title  | Part 1: 400mg DBV and 120mg FDV - 4w          |
| Reporting group description:<br>Part 1: 4 weeks of 400mg Deleobuvir tablet TID (Three times per day) and 120mg Faldaprevir soft gelatin capsule QD (Once daily) in combination with RBV tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period). Two patients were randomised to the Part 1: 400mg DBV and 120mg FDV - 4w arm, however these patients were not treated. Consequently, number of subject that started is 17 but only 15 reported to ensure consistent reporting with baseline characteristics that includes only treated patients. |   |
| Reporting group title  | Part 1: 600mg DBV and 120mg FDV - 4w          |
| Reporting group description:<br>Part 1: 4 weeks of 600mg Deleobuvir (DBV, BI 207127) tablet three times per day (TID) and 120mg Faldaprevir (FDV, BI 201335) soft gelatin capsule once daily (QD) in combination with Ribavirin (RBV) tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period).  |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV - 16w         |
| Reporting group description:<br>Part 2: 16 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 2: 600mg DBV TID and 120mg FDV - 28w     |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV - 40w         |
| Reporting group description:<br>Part 2: 40 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Two patients were randomised to the Part 2: 600mg DBV and 120mg FDV - 40w arm, however these patients were not treated. Consequently, number of subject that started is 79 but only 77 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.                     |   |
| Reporting group title  | Part 2: 600mg DBV BID and 120mg FDV - 28w     |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet twice a day (BID) and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. One patient was randomised to the Part 2: 600mg DBV BID and 120mg FDV - 28w arm, however this patient was not treated. Consequently, number of subject that started is 79 but only 78 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.        |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD, without RBV. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Three patients were randomised to the Part 2: 600mg DBV and 120mg FDV, no RBV - 28w arm, however these patients were not treated. Consequently, number of subject that started is 49 but only 46 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.                             |   |
| Reporting group title  | Part 3: 600mg DBV and 120mg FDV - 16w         |
| Reporting group description:<br>Part 3: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 3: 800mg DBV and 120mg FDV - 24w         |

Reporting group description:

Part 3: 24 weeks of 800mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Part 3: 600mg DBV and 120mg FDV - 24w |
|-----------------------|---------------------------------------|

Reporting group description:

Part 3: 24 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Part 4: 600 mg DBV and 120mg FDV - 16w |
|-----------------------|--|

Reporting group description:

Part 4: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

|                       |  |
|-----------------------|--|
| Reporting group title | Part 4: 600 mg DBV and 120mg FDV - 24w |
|-----------------------|--|

Reporting group description:

Part 4: 24 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

| Reporting group values | Part 1: 400mg DBV and 120mg FDV - 4w | Part 1: 600mg DBV and 120mg FDV - 4w | Part 2: 600mg DBV and 120mg FDV - 16w |
|------------------------|--------------------------------------|--------------------------------------|---------------------------------------|
| Number of subjects     | 15                                   | 17                                   | 81                                    |
| Age categorical        |                                      |                                      |                                       |
| Units: Subjects        |                                      |                                      |                                       |

|   |      |        |        |
|---|------|--------|--------|
| Age Continuous  |      |        |        |
| Treated Set (TS): Treated set which included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment regardless of randomisation. 99999: SD is not calculable due to only one patient in treatment group. |      |        |        |
| Units: years  |      |        |        |
| arithmetic mean   | 50.8 | 50.8   | 48.6   |
| standard deviation  | ± 10 | ± 11.5 | ± 11.3 |
| Gender, Male/Female   |      |        |        |
| Units: Participants   |      |        |        |
| Female  | 7    | 7      | 36     |
| Male  | 8    | 10     | 45     |

| Reporting group values | Part 2: 600mg DBV TID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w |
|------------------------|---|---------------------------------------|---|
| Number of subjects     | 80  | 77                                    | 78  |
| Age categorical        |   |                                       |   |
| Units: Subjects        |   |                                       |   |

|   |        |        |        |
|---|--------|--------|--------|
| Age Continuous  |        |        |        |
| Treated Set (TS): Treated set which included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment regardless of randomisation. 99999: SD is not calculable due to only one patient in treatment group. |        |        |        |
| Units: years  |        |        |        |
| arithmetic mean   | 47.3   | 48.9   | 47.9   |
| standard deviation  | ± 11.2 | ± 10.7 | ± 11.1 |
| Gender, Male/Female   |        |        |        |
| Units: Participants   |        |        |        |
| Female  | 39     | 41     | 37     |

|      |    |    |    |
|------|----|----|----|
| Male | 41 | 36 | 41 |
|------|----|----|----|

| Reporting group values             | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w | Part 3: 600mg DBV and 120mg FDV - 16w | Part 3: 800mg DBV and 120mg FDV - 24w |
|------------------------------------|---|---------------------------------------|---------------------------------------|
| Number of subjects                 | 46  | 32                                    | 26                                    |
| Age categorical<br>Units: Subjects |   |                                       |                                       |

|   |      |        |        |
|---|------|--------|--------|
| Age Continuous  |      |        |        |
| Treated Set (TS): Treated set which included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment regardless of randomisation. 99999: SD is not calculable due to only one patient in treatment group. |      |        |        |
| Units: years  |      |        |        |
| arithmetic mean   | 45.3 | 48.9   | 47.2   |
| standard deviation  | ± 13 | ± 11.8 | ± 13.4 |
| Gender, Male/Female<br>Units: Participants  |      |        |        |
| Female  | 22   | 20     | 11     |
| Male  | 24   | 12     | 15     |

| Reporting group values             | Part 3: 600mg DBV and 120mg FDV - 24w | Part 4: 600 mg DBV and 120mg FDV - 16w | Part 4: 600 mg DBV and 120mg FDV - 24w |
|------------------------------------|---------------------------------------|--|--|
| Number of subjects                 | 25                                    | 1                                      | 2                                      |
| Age categorical<br>Units: Subjects |                                       |  |  |

|   |        |         |       |
|---|--------|---------|-------|
| Age Continuous  |        |         |       |
| Treated Set (TS): Treated set which included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment regardless of randomisation. 99999: SD is not calculable due to only one patient in treatment group. |        |         |       |
| Units: years  |        |         |       |
| arithmetic mean   | 46.5   | 59      | 52.5  |
| standard deviation  | ± 12.5 | ± 99999 | ± 4.9 |
| Gender, Male/Female<br>Units: Participants  |        |         |       |
| Female  | 11     | 1       | 2     |
| Male  | 14     | 0       | 0     |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 480   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |   |  |  |
|---|---|--|--|
| Age Continuous  |   |  |  |
| Treated Set (TS): Treated set which included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment regardless of randomisation. 99999: SD is not calculable due to only one patient in treatment group. |   |  |  |
| Units: years  |   |  |  |
| arithmetic mean   |   |  |  |
| standard deviation  | - |  |  |

|                     |     |  |  |
|---------------------|-----|--|--|
| Gender, Male/Female |     |  |  |
| Units: Participants |     |  |  |
| Female              | 234 |  |  |
| Male                | 246 |  |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Part 1: 400mg DBV and 120mg FDV - 4w          |
| Reporting group description:<br>Part 1: 4 weeks of 400mg Deleobuvir tablet TID (Three times per day) and 120mg Faldaprevir soft gelatin capsule QD (Once daily) in combination with RBV tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period). Two patients were randomised to the Part 1: 400mg DBV and 120mg FDV - 4w arm, however these patients were not treated. Consequently, number of subject that started is 17 but only 15 reported to ensure consistent reporting with baseline characteristics that includes only treated patients. |   |
| Reporting group title  | Part 1: 600mg DBV and 120mg FDV - 4w          |
| Reporting group description:<br>Part 1: 4 weeks of 600mg Deleobuvir (DBV, BI 207127) tablet three times per day (TID) and 120mg Faldaprevir (FDV, BI 201335) soft gelatin capsule once daily (QD) in combination with Ribavirin (RBV) tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period).  |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV - 16w         |
| Reporting group description:<br>Part 2: 16 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 2: 600mg DBV TID and 120mg FDV - 28w     |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV - 40w         |
| Reporting group description:<br>Part 2: 40 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Two patients were randomised to the Part 2: 600mg DBV and 120mg FDV - 40w arm, however these patients were not treated. Consequently, number of subject that started is 79 but only 77 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.                     |   |
| Reporting group title  | Part 2: 600mg DBV BID and 120mg FDV - 28w     |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet twice a day (BID) and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. One patient was randomised to the Part 2: 600mg DBV BID and 120mg FDV - 28w arm, however this patient was not treated. Consequently, number of subject that started is 79 but only 78 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.        |   |
| Reporting group title  | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |
| Reporting group description:<br>Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD, without RBV. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Three patients were randomised to the Part 2: 600mg DBV and 120mg FDV, no RBV - 28w arm, however these patients were not treated. Consequently, number of subject that started is 49 but only 46 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.                             |   |
| Reporting group title  | Part 3: 600mg DBV and 120mg FDV - 16w         |
| Reporting group description:<br>Part 3: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |   |
| Reporting group title  | Part 3: 800mg DBV and 120mg FDV - 24w         |

Reporting group description:

Part 3: 24 weeks of 800mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Part 3: 600mg DBV and 120mg FDV - 24w |
|-----------------------|---------------------------------------|

Reporting group description:

Part 3: 24 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Part 4: 600 mg DBV and 120mg FDV - 16w |
|-----------------------|--|

Reporting group description:

Part 4: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

|                       |  |
|-----------------------|--|
| Reporting group title | Part 4: 600 mg DBV and 120mg FDV - 24w |
|-----------------------|--|

Reporting group description:

Part 4: 24 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.

### Primary: Part 1: Rapid virological response (RVR)

|                 |  |
|-----------------|--|
| End point title | Part 1: Rapid virological response (RVR) <sup>[1][2]</sup> |
|-----------------|--|

End point description:

Part 1: Rapid virological response (RVR), defined as Hepatitis C Virus Ribonucleic acid (HCV RNA) <25IU/mL at Week 4 of treatment. Full Analysis Set (FAS): Full Analysis Set which included all randomised patients who were dispensed study medication and were documented to have taken at least one dose of study medication.

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

End point timeframe:

4 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 1: 400mg DBV and 120mg FDV - 4w | Part 1: 600mg DBV and 120mg FDV - 4w |  |  |
|-----------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                      |  |  |
| Number of subjects analysed       | 15 <sup>[3]</sup>                    | 17 <sup>[4]</sup>                    |  |  |
| Units: Percentage of participants |                                      |                                      |  |  |
| number (confidence interval 95%)  | 73.3 (47.6 to 89)                    | 100 (84.7 to 100)                    |  |  |

Notes:

[3] - FAS

[4] - FAS

### Statistical analyses

No statistical analyses for this end point

### Primary: Part 2: Sustained virological response (SVR)

|   |  |
|---|--|
| End point title   | Part 2: Sustained virological response (SVR) <sup>[5][6]</sup> |
| End point description:<br>Part 2: Sustained virological response (SVR), defined as HCV RNA <25 IU/mL and undetectable at 12 weeks after end of treatment. |  |
| End point type  | Primary  |
| End point timeframe:<br>From drug administration until 12 weeks after end of treatment, up to 52 weeks  |  |

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 2: 600mg DBV and 120mg FDV - 16w | Part 2: 600mg DBV TID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w |
|-----------------------------------|---------------------------------------|---|---------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                           | Reporting group                       | Reporting group                           |
| Number of subjects analysed       | 81 <sup>[7]</sup>                     | 80 <sup>[8]</sup>                         | 77 <sup>[9]</sup>                     | 78 <sup>[10]</sup>                        |
| Units: Percentage of participants |                                       |   |                                       |   |
| number (not applicable)           | 59.3                                  | 58.8                                      | 51.9                                  | 69.2                                      |

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

[10] - FAS

| End point values                  | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                               |  |  |  |
| Number of subjects analysed       | 46 <sup>[11]</sup>                            |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           | 39.1  |  |  |  |

Notes:

[11] - FAS

## Statistical analyses

No statistical analyses for this end point

## Primary: Part 3 and 4: Sustained virological response (SVR)

|  |  |
|--|--|
| End point title  | Part 3 and 4: Sustained virological response (SVR) <sup>[12][13]</sup> |
| End point description:<br>Part 3 and 4: Sustained virological response (SVR) defined as HCV RNA <25IU/mL and undetectable at 12 weeks after end of treatment. 99999: Summary statistics were not calculated due to early termination of study. |  |
| End point type   | Primary  |
| End point timeframe:<br>From drug administration until 12 weeks after end of treatment, up to 36 weeks   |  |

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 3: 600mg DBV and 120mg FDV - 16w | Part 3: 800mg DBV and 120mg FDV - 24w | Part 3: 600mg DBV and 120mg FDV - 24w | Part 4: 600 mg DBV and 120mg FDV - 16w |
|-----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| Subject group type                | Reporting group                       | Reporting group                       | Reporting group                       | Reporting group                        |
| Number of subjects analysed       | 32 <sup>[14]</sup>                    | 26 <sup>[15]</sup>                    | 25 <sup>[16]</sup>                    | 1 <sup>[17]</sup>                      |
| Units: Percentage of participants |                                       |                                       |                                       |  |
| number (confidence interval 95%)  | 65.6 (46.8 to 81.4)                   | 19.2 (6.6 to 39.4)                    | 12 (2.5 to 31.2)                      | 99999 (99999 to 99999)                 |

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

The study was stopped before data were collected from the participants in Part 4.

| End point values                  | Part 4: 600 mg DBV and 120mg FDV - 24w |  |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                        |  |  |  |
| Number of subjects analysed       | 2 <sup>[18]</sup>                      |  |  |  |
| Units: Percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 99999 (99999 to 99999)                 |  |  |  |

Notes:

[18] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Time to virological response

|   |  |
|---|--|
| End point title   | Part 1: Time to virological response <sup>[19]</sup> |
| End point description:  |  |
| Part 1: Time to virological response, defined as the timepoint of the first measurement of plasma HCV RNA level <25 IU/mL. The percentage of participants who achieved virological response within each time period are displayed for this outcome measure. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From drug administration until end of drug administration, up to 4 weeks  |  |

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 1: 400mg DBV and 120mg FDV - 4w | Part 1: 600mg DBV and 120mg FDV - 4w |  |  |
|-----------------------------------|--------------------------------------|--------------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                      |  |  |
| Number of subjects analysed       | 15 <sup>[20]</sup>                   | 17 <sup>[21]</sup>                   |  |  |
| Units: Percentage of participants |                                      |                                      |  |  |
| number (not applicable)           |                                      |                                      |  |  |
| <= 2 weeks                        | 6.7                                  | 11.8                                 |  |  |
| <= 4 weeks                        | 20                                   | 47.1                                 |  |  |
| <= 8 weeks                        | 53.3                                 | 41.2                                 |  |  |
| <= 12 weeks                       | 0                                    | 0                                    |  |  |
| <= 16 weeks                       | 6.7                                  | 0                                    |  |  |
| <= 28 weeks                       | 0                                    | 0                                    |  |  |
| <= 32 weeks                       | 6.7                                  | 0                                    |  |  |
| <= 40 weeks                       | 0                                    | 0                                    |  |  |
| > 40 weeks                        | 0                                    | 0                                    |  |  |
| Never                             | 6.7                                  | 0                                    |  |  |

Notes:

[20] - FAS

[21] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Time to virological response

|   |  |
|---|--|
| End point title   | Part 2: Time to virological response <sup>[22]</sup> |
| End point description:  |  |
| Part 2: Time to virological response, defined as the timepoint of the first measurement of plasma HCV RNA level <25 IU/mL. The percentage of participants who achieved virological response within each time period are displayed for this outcome measure. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From drug administration until end of drug administration, up to 40 weeks   |  |

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 2: 600mg DBV and 120mg FDV - 16w | Part 2: 600mg DBV TID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w |
|-----------------------------------|---------------------------------------|---|---------------------------------------|---|
| Subject group type                | Reporting group                       | Reporting group                           | Reporting group                       | Reporting group                           |
| Number of subjects analysed       | 81                                    | 80  | 77                                    | 78  |
| Units: Percentage of participants |                                       |   |                                       |   |

|                               |      |      |      |      |
|-------------------------------|------|------|------|------|
| number (not applicable)       |      |      |      |      |
| Day 0 (N=81, 80, 77, 78, 46)  | 0    | 0    | 0    | 0    |
| Day 8(N=75, 72, 72, 75, 44)   | 3.8  | 7.7  | 1.4  | 2.6  |
| Day 15 (N=62, 61, 63, 60, 33) | 19.4 | 20.7 | 9.9  | 22.1 |
| Day 29 (N=29, 32, 27, 32, 21) | 61.5 | 55.5 | 59.4 | 57.7 |
| Day 43 (N=16, 12, 13, 18, 12) | 78.8 | 83.3 | 80.5 | 76.2 |
| Day 57 (N=9, 8, 9, 11, 9)     | 88.1 | 88.9 | 85.1 | 85.5 |
| Day 85 (N=9, 7, 8, 11, 9)     | 88.1 | 90.3 | 86.8 | 85.5 |
| Day 113 (N=9, 7, 8, 11, 8)    | 88.1 | 90.3 | 86.8 | 85.5 |
| Day 141 (N=9, 7, 8, 11, 8)    | 88.1 | 90.3 | 86.8 | 85.5 |
| Day 169 (N=9, 7, 8, 11, 8)    | 88.1 | 90.3 | 86.8 | 85.5 |
| Day 197 (N=9, 7, 8, 11, 8)    | 88.1 | 90.3 | 86.8 | 85.5 |

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |  |  |  |
| Subject group type                | Reporting group                               |  |  |  |
| Number of subjects analysed       | 46  |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Day 0 (N=81, 80, 77, 78, 46)      | 0   |  |  |  |
| Day 8(N=75, 72, 72, 75, 44)       | 2.2   |  |  |  |
| Day 15 (N=62, 61, 63, 60, 33)     | 19.3  |  |  |  |
| Day 29 (N=29, 32, 27, 32, 21)     | 48.6  |  |  |  |
| Day 43 (N=16, 12, 13, 18, 12)     | 70.7  |  |  |  |
| Day 57 (N=9, 8, 9, 11, 9)         | 78  |  |  |  |
| Day 85 (N=9, 7, 8, 11, 9)         | 78  |  |  |  |
| Day 113 (N=9, 7, 8, 11, 8)        | 80.4  |  |  |  |
| Day 141 (N=9, 7, 8, 11, 8)        | 80.4  |  |  |  |
| Day 169 (N=9, 7, 8, 11, 8)        | 80.4  |  |  |  |
| Day 197 (N=9, 7, 8, 11, 8)        | 80.4  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1 and 2: Plasma HCV RNA level not detectable at Week 4

|                 |   |
|-----------------|---|
| End point title | Part 1 and 2: Plasma HCV RNA level not detectable at Week |
|-----------------|---|

End point description:

Part 1 and 2: Plasma Hepatitis C Virus Ribonucleic acid (HCV RNA) level not detectable at Week 4.

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

End point timeframe:

4 weeks

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                  | Part 1: 400mg DBV and 120mg FDV - 4w | Part 1: 600mg DBV and 120mg FDV - 4w | Part 2: 600mg DBV and 120mg FDV - 16w | Part 2: 600mg DBV TID and 120mg FDV - 28w |
|-----------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|---|
| Subject group type                | Reporting group                      | Reporting group                      | Reporting group                       | Reporting group                           |
| Number of subjects analysed       | 15 <sup>[24]</sup>                   | 17 <sup>[25]</sup>                   | 81 <sup>[26]</sup>                    | 80 <sup>[27]</sup>                        |
| Units: Percentage of participants |                                      |                                      |                                       |   |
| number (not applicable)           | 20                                   | 70.6                                 | 65.4                                  | 60  |

Notes:

[24] - FAS

[25] - FAS

[26] - FAS

[27] - FAS

| End point values                  | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |  |
|-----------------------------------|---------------------------------------|---|---|--|
| Subject group type                | Reporting group                       | Reporting group                           | Reporting group                               |  |
| Number of subjects analysed       | 77 <sup>[28]</sup>                    | 78 <sup>[29]</sup>                        | 46 <sup>[30]</sup>                            |  |
| Units: Percentage of participants |                                       |   |   |  |
| number (not applicable)           | 63.6                                  | 56.4                                      | 50  |  |

Notes:

[28] - FAS

[29] - FAS

[30] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Sustained virological response at 4 and 24 weeks after end of treatment

|                 |   |
|-----------------|---|
| End point title | Part 2: Sustained virological response at 4 and 24 weeks after end of treatment <sup>[31]</sup> |
|-----------------|---|

End point description:

Part 2: Sustained virological response at 4 and 24 weeks after end of treatment.

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

End point timeframe:

4 weeks and 24 weeks after the end of treatment, up to 64 weeks

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

|                                   |                                       |   |                                       |   |
|-----------------------------------|---------------------------------------|---|---------------------------------------|---|
| <b>End point values</b>           | Part 2: 600mg DBV and 120mg FDV - 16w | Part 2: 600mg DBV TID and 120mg FDV - 28w | Part 2: 600mg DBV and 120mg FDV - 40w | Part 2: 600mg DBV BID and 120mg FDV - 28w |
| Subject group type                | Reporting group                       | Reporting group                           | Reporting group                       | Reporting group                           |
| Number of subjects analysed       | 81 <sup>[32]</sup>                    | 80 <sup>[33]</sup>                        | 77 <sup>[34]</sup>                    | 78 <sup>[35]</sup>                        |
| Units: Percentage of participants |                                       |   |                                       |   |
| number (not applicable)           |                                       |   |                                       |   |
| SVR4                              | 60.5                                  | 62.5                                      | 54.5                                  | 69.2                                      |
| SVR24                             | 58                                    | 58.8                                      | 49.4                                  | 69.2                                      |

Notes:

[32] - FAS

[33] - FAS

[34] - FAS

[35] - FAS

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | Part 2: 600mg DBV and 120mg FDV, no RBV - 28w |  |  |  |
| Subject group type                | Reporting group                               |  |  |  |
| Number of subjects analysed       | 46 <sup>[36]</sup>                            |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| SVR4                              | 43.5  |  |  |  |
| SVR24                             | 39.1  |  |  |  |

Notes:

[36] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 3 and 4: Plasma HCV RNA level <25 IU/mL at week 4 and 12 of treatment

|                 |  |
|-----------------|--|
| End point title | Part 3 and 4: Plasma HCV RNA level <25 IU/mL at week 4 and 12 of treatment <sup>[37]</sup> |
|-----------------|--|

End point description:

Part 3 and 4: Plasma Hepatitis C Virus Ribonucleic acid (HCV RNA) level <25 IU/mL at week 4 and 12 of treatment. 99999: Summary statistics were not calculated due to early termination of study.

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

End point timeframe:

Week 4 and 12

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

|                                   |                                       |                                       |                                       |  |
|-----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| <b>End point values</b>           | Part 3: 600mg DBV and 120mg FDV - 16w | Part 3: 800mg DBV and 120mg FDV - 24w | Part 3: 600mg DBV and 120mg FDV - 24w | Part 4: 600 mg DBV and 120mg FDV - 16w |
| Subject group type                | Reporting group                       | Reporting group                       | Reporting group                       | Reporting group                        |
| Number of subjects analysed       | 32 <sup>[38]</sup>                    | 26 <sup>[39]</sup>                    | 25 <sup>[40]</sup>                    | 1 <sup>[41]</sup>                      |
| Units: Percentage of participants |                                       |                                       |                                       |  |
| number (not applicable)           | 75                                    | 26.9                                  | 32                                    | 99999                                  |

Notes:

[38] - FAS

[39] - FAS

[40] - FAS

[41] - FAS

The study was stopped before data were collected from the participants in Part 4.

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Part 4: 600 mg DBV and 120mg FDV - 24w |  |  |  |
| Subject group type                | Reporting group                        |  |  |  |
| Number of subjects analysed       | 2 <sup>[42]</sup>                      |  |  |  |
| Units: Percentage of participants |  |  |  |  |
| number (not applicable)           | 99999                                  |  |  |  |

Notes:

[42] - FAS

The study was stopped before data were collected from the participants in Part 4.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 3 and 4: Sustained virological response (SVR) at 4 weeks after end of treatment

|                 |  |
|-----------------|--|
| End point title | Part 3 and 4: Sustained virological response (SVR) at 4 weeks after end of treatment <sup>[43]</sup> |
|-----------------|--|

End point description:

Part 3 and 4: Sustained virological response (SVR) at 4 weeks after end of treatment. 99999: Summary statistics were not calculated due to early termination of study.

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

End point timeframe:

up to 28 weeks

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

|                                   |                                       |                                       |                                       |  |
|-----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| <b>End point values</b>           | Part 3: 600mg DBV and 120mg FDV - 16w | Part 3: 800mg DBV and 120mg FDV - 24w | Part 3: 600mg DBV and 120mg FDV - 24w | Part 4: 600 mg DBV and 120mg FDV - 16w |
| Subject group type                | Reporting group                       | Reporting group                       | Reporting group                       | Reporting group                        |
| Number of subjects analysed       | 32 <sup>[44]</sup>                    | 26 <sup>[45]</sup>                    | 25 <sup>[46]</sup>                    | 1 <sup>[47]</sup>                      |
| Units: Percentage of participants |                                       |                                       |                                       |  |
| number (confidence interval 95%)  | 75 (56.6 to 88.5)                     | 19.2 (6.6 to 39.4)                    | 12 (2.5 to 31.2)                      | 99999 (99999 to 99999)                 |

Notes:

[44] - FAS

[45] - FAS

[46] - FAS

[47] - FAS

The study was stopped before data were collected from the participants in Part 4.

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Part 4: 600 mg DBV and 120mg FDV - 24w |  |  |  |
| Subject group type                | Reporting group                        |  |  |  |
| Number of subjects analysed       | 2 <sup>[48]</sup>                      |  |  |  |
| Units: Percentage of participants |  |  |  |  |
| number (confidence interval 95%)  | 99999 (99999 to 99999)                 |  |  |  |

Notes:

[48] - FAS

The study was stopped before data were collected from the participants in Part 4.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 30 days after last drug administration for parts 1, 2 and 4 and until 28 days after last drug administration for part 3, up to 361 days.

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

### Dictionary used

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

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

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | P1:BI combi 400mg+RBV |
|-----------------------|-----------------------|

Reporting group description:

Part 1: 4 weeks of 400mg Deleobuvir tablet TID (Three times per day) and 120mg Faldaprevir soft gelatin capsule QD (Once daily) in combination with RBV tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period). Two patients were randomised to the Part 1: 400mg DBV and 120mg FDV - 4w arm, however these patients were not treated. Consequently, number of subject that started is 17 but only 15 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | P1:BI combi 600mg+RBV |
|-----------------------|-----------------------|

Reporting group description:

Part 1: 4 weeks of 600mg Deleobuvir (DBV, BI 207127) tablet three times per day (TID) and 120mg Faldaprevir (FDV, BI 201335) soft gelatin capsule once daily (QD) in combination with Ribavirin (RBV) tablet. From Week 5 to Week 24, patients received treatment with FDV 120 mg QD in combination with standard of care (SOC) PegIFN/RBV (triple therapy period).

|                       |              |
|-----------------------|--------------|
| Reporting group title | P2:TID_16wks |
|-----------------------|--------------|

Reporting group description:

Part 2: 16 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |              |
|-----------------------|--------------|
| Reporting group title | P2:TID_28wks |
|-----------------------|--------------|

Reporting group description:

Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|                       |              |
|-----------------------|--------------|
| Reporting group title | P2:TID_40wks |
|-----------------------|--------------|

Reporting group description:

Part 2: 40 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Two patients were randomised to the Part 2: 600mg DBV and 120mg FDV - 40w arm, however these patients were not treated. Consequently, number of subject that started is 79 but only 77 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

|                       |              |
|-----------------------|--------------|
| Reporting group title | P2:BID_28wks |
|-----------------------|--------------|

Reporting group description:

Part 2: 28 weeks of 600mg Deleobuvir tablet twice a day (BID) and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. One patient was randomised to the Part 2: 600mg DBV BID and 120mg FDV - 28w arm, however this patient was not treated. Consequently, number of subject that started is 79 but only 78 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | P3:BID600_16wks |
|-----------------------|-----------------|

Reporting group description:

Part 3: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.

|  |                 |
|--|-----------------|
| Reporting group title  | P2:NRBV_28wks   |
| Reporting group description:   |                 |
| Part 2: 28 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD, without RBV. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks. Three patients were randomised to the Part 2: 600mg DBV and 120mg FDV, no RBV - 28w arm, however these patients were not treated. Consequently, number of subject that started is 49 but only 46 reported to ensure consistent reporting with baseline characteristics that includes only treated patients. |                 |
| Reporting group title  | P3:BID800_24wks |
| Reporting group description:   |                 |
| Part 3: 24 weeks of 800mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |                 |
| Reporting group title  | P4:BID600_16wks |
| Reporting group description:   |                 |
| Part 4: 16 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.  |                 |
| Reporting group title  | P3:TID600_24wks |
| Reporting group description:   |                 |
| Part 3: 24 weeks of 600mg Deleobuvir tablet TID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet. Patients who discontinued their assigned treatment early due to lack of antiviral activity, could receive additional treatment with PegIFN/RBV for up to 24 weeks.   |                 |
| Reporting group title  | P4:BID600_24wks |
| Reporting group description:   |                 |
| Part 4: 24 weeks of 600mg Deleobuvir tablet BID and 120mg Faldaprevir soft gelatin capsule QD in combination with RBV tablet.  |                 |

| <b>Serious adverse events</b>                                       | <b>P1:BI combi<br/>400mg+RBV</b> | <b>P1:BI combi<br/>600mg+RBV</b> | <b>P2:TID_16wks</b> |
|---|----------------------------------|----------------------------------|---------------------|
| Total subjects affected by serious adverse events                   |                                  |                                  |                     |
| subjects affected / exposed   | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 3 / 81 (3.70%)      |
| number of deaths (all causes)                                       | 0                                | 0                                | 0                   |
| number of deaths resulting from adverse events                      | 0                                | 0                                | 0                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                                  |                     |
| B-cell lymphoma   |                                  |                                  |                     |
| subjects affected / exposed   | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 0 / 81 (0.00%)      |
| occurrences causally related to treatment / all                     | 0 / 0                            | 0 / 0                            | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                            | 0 / 0               |
| General disorders and administration site conditions                |                                  |                                  |                     |
| Asthenia  |                                  |                                  |                     |
| subjects affected / exposed   | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 0 / 81 (0.00%)      |
| occurrences causally related to treatment / all                     | 0 / 0                            | 0 / 0                            | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                            | 0 / 0               |
| Respiratory, thoracic and mediastinal disorders                     |                                  |                                  |                     |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychotic disorder                              |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| Blood potassium decre                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Electrocardiogram QT                            |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Accident at work                                |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gun shot wound                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb traumatic amputa                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Radius fracture                                 |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bundle branch block I                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiopulmonary failure                         |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery disease                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery steno                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular fibrillat                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Brain injury                                    |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Convulsion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Retinal tear                                    |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhoids                                    |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Drug eruption                                   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dry skin  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erythema nodosum                                |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Photosensitivity reac                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Purpura   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rash  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Toxic skin eruption                             |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Prerenal failure                                |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal failure acute                             |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis pharyngeal                           |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | P2:TID_28wks    | P2:TID_40wks   | P2:BID_28wks    |
|---|-----------------|----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                |                 |
| subjects affected / exposed   | 8 / 80 (10.00%) | 6 / 77 (7.79%) | 8 / 78 (10.26%) |
| number of deaths (all causes)                                       | 2               | 0              | 0               |
| number of deaths resulting from adverse events                      | 0               | 0              | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |                 |
| B-cell lymphoma   |                 |                |                 |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |
| Pulmonary embolism                                   |                |                |                |
| subjects affected / exposed                          | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                                  |                |                |                |
| subjects affected / exposed                          | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 1          |
| Psychiatric disorders                                |                |                |                |
| Depression   |                |                |                |
| subjects affected / exposed                          | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychotic disorder                                   |                |                |                |
| subjects affected / exposed                          | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                       |                |                |                |
| Blood potassium decre                                |                |                |                |
| subjects affected / exposed                          | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Electrocardiogram QT                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                           | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| Accident at work                                      |                |                |                |
| subjects affected / exposed                           | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Gun shot wound  |                |                |                |
| subjects affected / exposed                           | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb traumatic amputa                                 |                |                |                |
| subjects affected / exposed                           | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Radius fracture                                       |                |                |                |
| subjects affected / exposed                           | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Cardiac disorders</b>                              |                |                |                |
| Acute myocardial infa                                 |                |                |                |
| subjects affected / exposed                           | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                       |                |                |                |
| subjects affected / exposed                           | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Bundle branch block I                                 |                |                |                |
| subjects affected / exposed                           | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all       | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiopulmonary failu                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Coronary artery disea                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery steno                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular fibrillat                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Brain injury                                    |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Convulsion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Eye disorders</b>                            |                |                |                |
| Retinal tear                                    |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhoids                                    |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Nausea  |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Drug eruption                                   |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dry skin  |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erythema nodosum                                |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Photosensitivity reac                           |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Purpura   |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Rash  |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Toxic skin eruption                             |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 1 / 77 (1.30%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Prerenal failure                                |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal failure acute                             |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis pharyngeal                           |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 0 / 80 (0.00%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 80 (1.25%) | 0 / 77 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | P3:BID600_16wks | P2:NRBV_28wks  | P3:BID800_24wks |
|---|-----------------|----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                |                 |
| subjects affected / exposed   | 1 / 32 (3.13%)  | 3 / 46 (6.52%) | 3 / 26 (11.54%) |
| number of deaths (all causes)                                       | 0               | 0              | 0               |
| number of deaths resulting from adverse events                      | 0               | 0              | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |                 |
| B-cell lymphoma   |                 |                |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)  | 0 / 46 (0.00%) | 1 / 26 (3.85%)  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions                |                 |                |                 |
| Asthenia  |                 |                |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)  | 0 / 46 (0.00%) | 0 / 26 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders                     |                 |                |                 |
| Pulmonary embolism  |                 |                |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)  | 0 / 46 (0.00%) | 0 / 26 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory failure   |                 |                |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)  | 0 / 46 (0.00%) | 0 / 26 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| Psychiatric disorders   |                 |                |                 |
| Depression  |                 |                |                 |
| subjects affected / exposed   | 0 / 32 (0.00%)  | 0 / 46 (0.00%) | 0 / 26 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| Psychotic disorder  |                 |                |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Investigations</b>                                 |                |                |                |
| Blood potassium decre                                 |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Electrocardiogram QT                                  |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| Accident at work                                      |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Gun shot wound  |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 1 / 46 (2.17%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb traumatic amputa                                 |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Radius fracture                                       |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Cardiac disorders</b>                              |                |                |                |
| Acute myocardial infa                                 |                |                |                |
| subjects affected / exposed                           | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bundle branch block I                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiopulmonary failu                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery disea                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery steno                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ventricular fibrillat                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Brain injury                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Convulsion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Retinal tear                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhoids                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Drug eruption                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 46 (2.17%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dry skin  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Erythema nodosum                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Photosensitivity reac                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Purpura   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 46 (2.17%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rash  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Toxic skin eruption                             |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 46 (2.17%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Prerenal failure                                |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal failure acute                             |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis pharyngeal                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 46 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | P4:BID600_16wks | P3:TID600_24wks | P4:BID600_24wks |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                 |                 |
| subjects affected / exposed   | 0 / 1 (0.00%)   | 2 / 25 (8.00%)  | 0 / 2 (0.00%)   |
| number of deaths (all causes)                                       | 0               | 0               | 0               |
| number of deaths resulting from adverse events                      | 0               | 0               | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| B-cell lymphoma   |                 |                 |                 |
| subjects affected / exposed   | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions                |                 |                 |                 |
| Asthenia  |                 |                 |                 |
| subjects affected / exposed   | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders                     |                 |                 |                 |
| Pulmonary embolism  |                 |                 |                 |
| subjects affected / exposed   | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure   |                 |                 |                 |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Psychiatric disorders                           |               |                |               |
| Depression                                      |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Psychotic disorder                              |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Investigations                                  |               |                |               |
| Blood potassium decre                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Electrocardiogram QT                            |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Injury, poisoning and procedural complications  |               |                |               |
| Accident at work                                |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gun shot wound                                  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Limb traumatic amputa                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Radius fracture                                 |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiac disorders                               |               |                |               |
| Acute myocardial infa                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Angina unstable                                 |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Bundle branch block I                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiac arrest                                  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Cardiopulmonary failu                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Coronary artery disea                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Coronary artery steno                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Myocardial infarction                           |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Ventricular fibrillat                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nervous system disorders                        |               |                |               |
| Brain injury                                    |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Convulsion                                      |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Syncope   |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders            |               |                |               |
| Anaemia   |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Febrile neutropenia                             |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Eye disorders                                   |               |                |               |
| Retinal tear                                    |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Gastrointestinal disorders                      |               |                |               |
| Abdominal pain                                  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Diarrhoea                                       |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Gastritis                                       |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Haemorrhoids                                    |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Nausea  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Vomiting  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Hepatobiliary disorders                         |               |                |               |
| Cholecystitis                                   |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Skin and subcutaneous tissue disorders          |               |                |               |
| Drug eruption                                   |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Dry skin  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Erythema nodosum                                |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Photosensitivity reac                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Purpura   |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Rash  |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Toxic skin eruption                             |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Renal and urinary disorders                     |               |                |               |
| Prerenal failure                                |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| Renal failure acute                             |               |                |               |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| <b>Infections and infestations</b>              |               |                |               |
| Cellulitis pharyngeal                           |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| <b>Gastroenteritis</b>                          |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| <b>Herpes zoster</b>                            |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |
| <b>Metabolism and nutrition disorders</b>       |               |                |               |
| Dehydration                                     |               |                |               |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0         |

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

| <b>Non-serious adverse events</b>                           | <b>P1:BI combi<br/>400mg+RBV</b> | <b>P1:BI combi<br/>600mg+RBV</b> | <b>P2:TID_16wks</b> |
|---|----------------------------------|----------------------------------|---------------------|
| Total subjects affected by non-serious adverse events       |                                  |                                  |                     |
| subjects affected / exposed                                 | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 76 / 81 (93.83%)    |
| <b>General disorders and administration site conditions</b> |                                  |                                  |                     |
| Asthenia  |                                  |                                  |                     |
| subjects affected / exposed                                 | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 24 / 81 (29.63%)    |
| occurrences (all)   | 0                                | 0                                | 26                  |
| Chest pain  |                                  |                                  |                     |
| subjects affected / exposed                                 | 0 / 15 (0.00%)                   | 0 / 17 (0.00%)                   | 0 / 81 (0.00%)      |
| occurrences (all)   | 0                                | 0                                | 0                   |

|   |                |                |                  |
|---|----------------|----------------|------------------|
| Chills  |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 5 / 81 (6.17%)   |
| occurrences (all)                               | 0              | 0              | 5                |
| Fatigue   |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 18 / 81 (22.22%) |
| occurrences (all)                               | 0              | 0              | 18               |
| Influenza like illness                          |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 2 / 81 (2.47%)   |
| occurrences (all)                               | 0              | 0              | 2                |
| Irritability                                    |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 8 / 81 (9.88%)   |
| occurrences (all)                               | 0              | 0              | 8                |
| Oedema peripheral                               |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                               | 0              | 0              | 0                |
| Pyrexia   |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                               | 0              | 0              | 1                |
| Respiratory, thoracic and mediastinal disorders |                |                |                  |
| Cough   |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 7 / 81 (8.64%)   |
| occurrences (all)                               | 0              | 0              | 7                |
| Dyspnoea  |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 2 / 81 (2.47%)   |
| occurrences (all)                               | 0              | 0              | 2                |
| Epistaxis                                       |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                               | 0              | 0              | 1                |
| Psychiatric disorders                           |                |                |                  |
| Anxiety   |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 3 / 81 (3.70%)   |
| occurrences (all)                               | 0              | 0              | 3                |
| Depressed mood                                  |                |                |                  |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                               | 0              | 0              | 1                |
| Depression                                      |                |                |                  |

|   |                     |                     |                        |
|---|---------------------|---------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 11 / 81 (13.58%)<br>11 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 3 / 81 (3.70%)<br>3    |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 8 / 81 (9.88%)<br>8    |
| Injury, poisoning and procedural complications<br>Sunburn<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 6 / 81 (7.41%)<br>6    |
| Nervous system disorders<br>Disturbance in attent<br>subjects affected / exposed<br>occurrences (all)         | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 3 / 81 (3.70%)<br>3    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 4 / 81 (4.94%)<br>4    |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 3 / 81 (3.70%)<br>3    |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 11 / 81 (13.58%)<br>12 |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 81 (0.00%)<br>0    |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1    |
| Paraesthesia  |                     |                     |                        |

|                                      |                |                |                  |
|--------------------------------------|----------------|----------------|------------------|
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 10 / 81 (12.35%) |
| occurrences (all)                    | 0              | 0              | 10               |
| Somnolence                           |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Syncope                              |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                    | 0              | 0              | 1                |
| Tremor                               |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Blood and lymphatic system disorders |                |                |                  |
| Anaemia                              |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                    | 0              | 0              | 1                |
| Ear and labyrinth disorders          |                |                |                  |
| Tinnitus                             |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                    | 0              | 0              | 1                |
| Eye disorders                        |                |                |                  |
| Dry eye                              |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                    | 0              | 0              | 0                |
| Ocular icterus                       |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 2 / 81 (2.47%)   |
| occurrences (all)                    | 0              | 0              | 2                |
| Gastrointestinal disorders           |                |                |                  |
| Abdominal discomfort                 |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)                    | 0              | 0              | 1                |
| Abdominal distension                 |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 4 / 81 (4.94%)   |
| occurrences (all)                    | 0              | 0              | 4                |
| Abdominal pain                       |                |                |                  |
| subjects affected / exposed          | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 7 / 81 (8.64%)   |
| occurrences (all)                    | 0              | 0              | 7                |
| Abdominal pain upper                 |                |                |                  |

|                             |                |                |                  |
|-----------------------------|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 6 / 81 (7.41%)   |
| occurrences (all)           | 0              | 0              | 6                |
| Constipation                |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 4 / 81 (4.94%)   |
| occurrences (all)           | 0              | 0              | 4                |
| Diarrhoea                   |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 34 / 81 (41.98%) |
| occurrences (all)           | 0              | 0              | 39               |
| Dry mouth                   |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Dyspepsia                   |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 6 / 81 (7.41%)   |
| occurrences (all)           | 0              | 0              | 6                |
| Flatulence                  |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 3 / 81 (3.70%)   |
| occurrences (all)           | 0              | 0              | 3                |
| Gastrooesophageal ref       |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Hypoaesthesia oral          |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |
| Lip dry                     |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 1 / 81 (1.23%)   |
| occurrences (all)           | 0              | 0              | 1                |
| Nausea                      |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 41 / 81 (50.62%) |
| occurrences (all)           | 0              | 0              | 44               |
| Vomiting                    |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 24 / 81 (29.63%) |
| occurrences (all)           | 0              | 0              | 35               |
| Hepatobiliary disorders     |                |                |                  |
| Hyperbilirubinaemia         |                |                |                  |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)           | 0              | 0              | 0                |

|  |                |                |                  |
|--|----------------|----------------|------------------|
| Jaundice                               |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 25 / 81 (30.86%) |
| occurrences (all)                      | 0              | 0              | 25               |
| Skin and subcutaneous tissue disorders |                |                |                  |
| Alopecia                               |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                      | 0              | 0              | 0                |
| Dermatitis                             |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                      | 0              | 0              | 0                |
| Dry skin                               |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 12 / 81 (14.81%) |
| occurrences (all)                      | 0              | 0              | 12               |
| Eczema                                 |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 2 / 81 (2.47%)   |
| occurrences (all)                      | 0              | 0              | 2                |
| Erythema                               |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                      | 0              | 0              | 0                |
| Pain of skin                           |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                      | 0              | 0              | 0                |
| Papule                                 |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 81 (0.00%)   |
| occurrences (all)                      | 0              | 0              | 0                |
| Photosensitivity reac                  |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 20 / 81 (24.69%) |
| occurrences (all)                      | 0              | 0              | 21               |
| Pruritus                               |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 16 / 81 (19.75%) |
| occurrences (all)                      | 0              | 0              | 17               |
| Rash                                   |                |                |                  |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 21 / 81 (25.93%) |
| occurrences (all)                      | 0              | 0              | 25               |
| Rash papulosquamous                    |                |                |                  |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 81 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Arthralgia                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 4 / 81 (4.94%)      |
| occurrences (all)                                | 0                   | 0                   | 4                   |
| Back pain  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 3 / 81 (3.70%)      |
| occurrences (all)                                | 0                   | 0                   | 3                   |
| Muscle spasms                                    |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 4 / 81 (4.94%)      |
| occurrences (all)                                | 0                   | 0                   | 4                   |
| Myalgia  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 1 / 81 (1.23%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Pain in extremity                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 2 / 81 (2.47%)      |
| occurrences (all)                                | 0                   | 0                   | 2                   |
| Infections and infestations                      |                     |                     |                     |
| Nasopharyngitis                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 4 / 81 (4.94%)      |
| occurrences (all)                                | 0                   | 0                   | 4                   |
| Urinary tract infecti                            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 1 / 81 (1.23%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Metabolism and nutrition disorders               |                     |                     |                     |
| Decreased appetite                               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 17 (0.00%)      | 4 / 81 (4.94%)      |
| occurrences (all)                                | 0                   | 0                   | 4                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| <b>Non-serious adverse events</b>                     | P2:TID_28wks     | P2:TID_40wks     | P2:BID_28wks     |
| Total subjects affected by non-serious adverse events |                  |                  |                  |
| subjects affected / exposed                           | 71 / 80 (88.75%) | 74 / 77 (96.10%) | 73 / 78 (93.59%) |
| General disorders and administration site conditions  |                  |                  |                  |
| Asthenia  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 28 / 80 (35.00%) | 25 / 77 (32.47%) | 21 / 78 (26.92%) |
| occurrences (all)                               | 29               | 25               | 21               |
| Chest pain                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 80 (0.00%)   | 0 / 77 (0.00%)   | 1 / 78 (1.28%)   |
| occurrences (all)                               | 0                | 0                | 1                |
| Chills  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 80 (2.50%)   | 3 / 77 (3.90%)   | 2 / 78 (2.56%)   |
| occurrences (all)                               | 2                | 3                | 2                |
| Fatigue   |                  |                  |                  |
| subjects affected / exposed                     | 14 / 80 (17.50%) | 22 / 77 (28.57%) | 21 / 78 (26.92%) |
| occurrences (all)                               | 15               | 23               | 22               |
| Influenza like illness                          |                  |                  |                  |
| subjects affected / exposed                     | 6 / 80 (7.50%)   | 5 / 77 (6.49%)   | 5 / 78 (6.41%)   |
| occurrences (all)                               | 7                | 6                | 5                |
| Irritability                                    |                  |                  |                  |
| subjects affected / exposed                     | 6 / 80 (7.50%)   | 4 / 77 (5.19%)   | 2 / 78 (2.56%)   |
| occurrences (all)                               | 6                | 4                | 2                |
| Oedema peripheral                               |                  |                  |                  |
| subjects affected / exposed                     | 2 / 80 (2.50%)   | 0 / 77 (0.00%)   | 0 / 78 (0.00%)   |
| occurrences (all)                               | 2                | 0                | 0                |
| Pyrexia   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 80 (5.00%)   | 4 / 77 (5.19%)   | 4 / 78 (5.13%)   |
| occurrences (all)                               | 4                | 6                | 4                |
| Respiratory, thoracic and mediastinal disorders |                  |                  |                  |
| Cough   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 80 (5.00%)   | 10 / 77 (12.99%) | 9 / 78 (11.54%)  |
| occurrences (all)                               | 4                | 11               | 9                |
| Dyspnoea  |                  |                  |                  |
| subjects affected / exposed                     | 8 / 80 (10.00%)  | 10 / 77 (12.99%) | 4 / 78 (5.13%)   |
| occurrences (all)                               | 9                | 11               | 4                |
| Epistaxis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 80 (1.25%)   | 4 / 77 (5.19%)   | 1 / 78 (1.28%)   |
| occurrences (all)                               | 2                | 5                | 1                |
| Psychiatric disorders                           |                  |                  |                  |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 4 / 80 (5.00%)<br>4    | 7 / 77 (9.09%)<br>7    | 4 / 78 (5.13%)<br>4    |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)  | 2 / 80 (2.50%)<br>2    | 5 / 77 (6.49%)<br>5    | 2 / 78 (2.56%)<br>2    |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 10 / 80 (12.50%)<br>10 | 5 / 77 (6.49%)<br>5    | 5 / 78 (6.41%)<br>5    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 8 / 80 (10.00%)<br>8   | 12 / 77 (15.58%)<br>12 | 7 / 78 (8.97%)<br>7    |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)  | 4 / 80 (5.00%)<br>4    | 7 / 77 (9.09%)<br>7    | 4 / 78 (5.13%)<br>4    |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 80 (7.50%)<br>6    | 11 / 77 (14.29%)<br>12 | 8 / 78 (10.26%)<br>8   |
| Injury, poisoning and procedural complications<br>Sunburn<br>subjects affected / exposed<br>occurrences (all) | 4 / 80 (5.00%)<br>4    | 9 / 77 (11.69%)<br>11  | 6 / 78 (7.69%)<br>7    |
| Nervous system disorders<br>Disturbance in attent<br>subjects affected / exposed<br>occurrences (all)         | 4 / 80 (5.00%)<br>4    | 4 / 77 (5.19%)<br>4    | 3 / 78 (3.85%)<br>3    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 3 / 80 (3.75%)<br>3    | 5 / 77 (6.49%)<br>5    | 3 / 78 (3.85%)<br>3    |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 80 (5.00%)<br>4    | 5 / 77 (6.49%)<br>5    | 2 / 78 (2.56%)<br>2    |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 8 / 80 (10.00%)<br>9   | 15 / 77 (19.48%)<br>18 | 11 / 78 (14.10%)<br>12 |

|  |                       |                        |                     |
|--|-----------------------|------------------------|---------------------|
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 80 (1.25%)<br>1   | 1 / 77 (1.30%)<br>1    | 2 / 78 (2.56%)<br>2 |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)   | 1 / 80 (1.25%)<br>1   | 2 / 77 (2.60%)<br>2    | 1 / 78 (1.28%)<br>1 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                       | 9 / 80 (11.25%)<br>10 | 6 / 77 (7.79%)<br>7    | 4 / 78 (5.13%)<br>4 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)   | 2 / 80 (2.50%)<br>2   | 0 / 77 (0.00%)<br>0    | 0 / 78 (0.00%)<br>0 |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 2 / 80 (2.50%)<br>2   | 5 / 77 (6.49%)<br>5    | 6 / 78 (7.69%)<br>6 |
| Tremor<br>subjects affected / exposed<br>occurrences (all)   | 1 / 80 (1.25%)<br>1   | 1 / 77 (1.30%)<br>1    | 1 / 78 (1.28%)<br>1 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 9 / 80 (11.25%)<br>10 | 10 / 77 (12.99%)<br>12 | 7 / 78 (8.97%)<br>7 |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)            | 0 / 80 (0.00%)<br>0   | 0 / 77 (0.00%)<br>0    | 0 / 78 (0.00%)<br>0 |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 80 (0.00%)<br>0   | 3 / 77 (3.90%)<br>3    | 1 / 78 (1.28%)<br>1 |
| Ocular icterus<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 80 (0.00%)<br>0   | 3 / 77 (3.90%)<br>3    | 5 / 78 (6.41%)<br>5 |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 80 (1.25%)<br>1   | 1 / 77 (1.30%)<br>1    | 6 / 78 (7.69%)<br>7 |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| Abdominal distension        |                  |                  |                  |
| subjects affected / exposed | 3 / 80 (3.75%)   | 7 / 77 (9.09%)   | 4 / 78 (5.13%)   |
| occurrences (all)           | 3                | 7                | 4                |
| Abdominal pain              |                  |                  |                  |
| subjects affected / exposed | 7 / 80 (8.75%)   | 6 / 77 (7.79%)   | 12 / 78 (15.38%) |
| occurrences (all)           | 7                | 6                | 13               |
| Abdominal pain upper        |                  |                  |                  |
| subjects affected / exposed | 15 / 80 (18.75%) | 12 / 77 (15.58%) | 2 / 78 (2.56%)   |
| occurrences (all)           | 15               | 13               | 2                |
| Constipation                |                  |                  |                  |
| subjects affected / exposed | 1 / 80 (1.25%)   | 6 / 77 (7.79%)   | 3 / 78 (3.85%)   |
| occurrences (all)           | 1                | 7                | 3                |
| Diarrhoea                   |                  |                  |                  |
| subjects affected / exposed | 33 / 80 (41.25%) | 36 / 77 (46.75%) | 29 / 78 (37.18%) |
| occurrences (all)           | 44               | 49               | 39               |
| Dry mouth                   |                  |                  |                  |
| subjects affected / exposed | 0 / 80 (0.00%)   | 4 / 77 (5.19%)   | 0 / 78 (0.00%)   |
| occurrences (all)           | 0                | 5                | 0                |
| Dyspepsia                   |                  |                  |                  |
| subjects affected / exposed | 5 / 80 (6.25%)   | 8 / 77 (10.39%)  | 14 / 78 (17.95%) |
| occurrences (all)           | 5                | 8                | 16               |
| Flatulence                  |                  |                  |                  |
| subjects affected / exposed | 5 / 80 (6.25%)   | 4 / 77 (5.19%)   | 4 / 78 (5.13%)   |
| occurrences (all)           | 5                | 4                | 4                |
| Gastrooesophageal ref       |                  |                  |                  |
| subjects affected / exposed | 4 / 80 (5.00%)   | 2 / 77 (2.60%)   | 2 / 78 (2.56%)   |
| occurrences (all)           | 4                | 2                | 2                |
| Hypoaesthesia oral          |                  |                  |                  |
| subjects affected / exposed | 1 / 80 (1.25%)   | 0 / 77 (0.00%)   | 0 / 78 (0.00%)   |
| occurrences (all)           | 1                | 0                | 0                |
| Lip dry                     |                  |                  |                  |
| subjects affected / exposed | 2 / 80 (2.50%)   | 1 / 77 (1.30%)   | 1 / 78 (1.28%)   |
| occurrences (all)           | 2                | 1                | 1                |
| Nausea                      |                  |                  |                  |
| subjects affected / exposed | 43 / 80 (53.75%) | 41 / 77 (53.25%) | 39 / 78 (50.00%) |
| occurrences (all)           | 48               | 51               | 47               |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)              | 29 / 80 (36.25%)<br>43 | 23 / 77 (29.87%)<br>38 | 20 / 78 (25.64%)<br>29 |
| Hepatobiliary disorders   |                        |                        |                        |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 80 (2.50%)<br>2    | 3 / 77 (3.90%)<br>3    | 0 / 78 (0.00%)<br>0    |
| Jaundice<br>subjects affected / exposed<br>occurrences (all)              | 22 / 80 (27.50%)<br>22 | 15 / 77 (19.48%)<br>16 | 16 / 78 (20.51%)<br>16 |
| Skin and subcutaneous tissue disorders                                    |                        |                        |                        |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 80 (8.75%)<br>7    | 2 / 77 (2.60%)<br>2    | 7 / 78 (8.97%)<br>7    |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)            | 1 / 80 (1.25%)<br>1    | 0 / 77 (0.00%)<br>0    | 0 / 78 (0.00%)<br>0    |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)              | 12 / 80 (15.00%)<br>12 | 11 / 77 (14.29%)<br>11 | 18 / 78 (23.08%)<br>18 |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                | 3 / 80 (3.75%)<br>3    | 2 / 77 (2.60%)<br>3    | 4 / 78 (5.13%)<br>4    |
| Erythema<br>subjects affected / exposed<br>occurrences (all)              | 1 / 80 (1.25%)<br>2    | 1 / 77 (1.30%)<br>2    | 2 / 78 (2.56%)<br>4    |
| Pain of skin<br>subjects affected / exposed<br>occurrences (all)          | 0 / 80 (0.00%)<br>0    | 0 / 77 (0.00%)<br>0    | 0 / 78 (0.00%)<br>0    |
| Papule<br>subjects affected / exposed<br>occurrences (all)                | 0 / 80 (0.00%)<br>0    | 0 / 77 (0.00%)<br>0    | 1 / 78 (1.28%)<br>1    |
| Photosensitivity reac<br>subjects affected / exposed<br>occurrences (all) | 23 / 80 (28.75%)<br>25 | 23 / 77 (29.87%)<br>25 | 19 / 78 (24.36%)<br>21 |
| Pruritus  |                        |                        |                        |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                          | 24 / 80 (30.00%)<br>27 | 31 / 77 (40.26%)<br>39 | 23 / 78 (29.49%)<br>24 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                  | 11 / 80 (13.75%)<br>13 | 28 / 77 (36.36%)<br>39 | 15 / 78 (19.23%)<br>19 |
| Rash papulosquamous<br>subjects affected / exposed<br>occurrences (all)   | 0 / 80 (0.00%)<br>0    | 0 / 77 (0.00%)<br>0    | 0 / 78 (0.00%)<br>0    |
| Musculoskeletal and connective tissue disorders                           |                        |                        |                        |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)            | 5 / 80 (6.25%)<br>5    | 4 / 77 (5.19%)<br>5    | 4 / 78 (5.13%)<br>4    |
| Back pain<br>subjects affected / exposed<br>occurrences (all)             | 3 / 80 (3.75%)<br>3    | 1 / 77 (1.30%)<br>1    | 6 / 78 (7.69%)<br>7    |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)         | 1 / 80 (1.25%)<br>1    | 6 / 77 (7.79%)<br>7    | 3 / 78 (3.85%)<br>3    |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)               | 4 / 80 (5.00%)<br>4    | 4 / 77 (5.19%)<br>4    | 3 / 78 (3.85%)<br>3    |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)     | 1 / 80 (1.25%)<br>1    | 2 / 77 (2.60%)<br>2    | 3 / 78 (3.85%)<br>4    |
| Infections and infestations   |                        |                        |                        |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)       | 8 / 80 (10.00%)<br>9   | 7 / 77 (9.09%)<br>8    | 6 / 78 (7.69%)<br>7    |
| Urinary tract infecti<br>subjects affected / exposed<br>occurrences (all) | 2 / 80 (2.50%)<br>2    | 0 / 77 (0.00%)<br>0    | 2 / 78 (2.56%)<br>2    |
| Metabolism and nutrition disorders  |                        |                        |                        |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)    | 15 / 80 (18.75%)<br>15 | 10 / 77 (12.99%)<br>10 | 8 / 78 (10.26%)<br>8   |

| <b>Non-serious adverse events</b>                     | P3:BID600_16wks  | P2:NRBV_28wks    | P3:BID800_24wks   |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                   |
| subjects affected / exposed                           | 30 / 32 (93.75%) | 43 / 46 (93.48%) | 26 / 26 (100.00%) |
| General disorders and administration site conditions  |                  |                  |                   |
| Asthenia  |                  |                  |                   |
| subjects affected / exposed                           | 7 / 32 (21.88%)  | 7 / 46 (15.22%)  | 4 / 26 (15.38%)   |
| occurrences (all)                                     | 7                | 7                | 4                 |
| Chest pain  |                  |                  |                   |
| subjects affected / exposed                           | 2 / 32 (6.25%)   | 0 / 46 (0.00%)   | 0 / 26 (0.00%)    |
| occurrences (all)                                     | 2                | 0                | 0                 |
| Chills  |                  |                  |                   |
| subjects affected / exposed                           | 1 / 32 (3.13%)   | 2 / 46 (4.35%)   | 1 / 26 (3.85%)    |
| occurrences (all)                                     | 1                | 2                | 1                 |
| Fatigue   |                  |                  |                   |
| subjects affected / exposed                           | 9 / 32 (28.13%)  | 7 / 46 (15.22%)  | 9 / 26 (34.62%)   |
| occurrences (all)                                     | 9                | 7                | 9                 |
| Influenza like illness                                |                  |                  |                   |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 2 / 46 (4.35%)   | 0 / 26 (0.00%)    |
| occurrences (all)                                     | 0                | 2                | 0                 |
| Irritability  |                  |                  |                   |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 1 / 46 (2.17%)   | 1 / 26 (3.85%)    |
| occurrences (all)                                     | 0                | 1                | 1                 |
| Oedema peripheral                                     |                  |                  |                   |
| subjects affected / exposed                           | 2 / 32 (6.25%)   | 0 / 46 (0.00%)   | 0 / 26 (0.00%)    |
| occurrences (all)                                     | 2                | 0                | 0                 |
| Pyrexia   |                  |                  |                   |
| subjects affected / exposed                           | 1 / 32 (3.13%)   | 1 / 46 (2.17%)   | 2 / 26 (7.69%)    |
| occurrences (all)                                     | 1                | 1                | 2                 |
| Respiratory, thoracic and mediastinal disorders       |                  |                  |                   |
| Cough   |                  |                  |                   |
| subjects affected / exposed                           | 2 / 32 (6.25%)   | 2 / 46 (4.35%)   | 2 / 26 (7.69%)    |
| occurrences (all)                                     | 2                | 2                | 2                 |
| Dyspnoea  |                  |                  |                   |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 0 / 46 (0.00%)   | 1 / 26 (3.85%)    |
| occurrences (all)                                     | 0                | 0                | 1                 |
| Epistaxis   |                  |                  |                   |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 0 / 46 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |
| Psychiatric disorders                            |                     |                     |                     |
| Anxiety  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 32 (6.25%)      | 0 / 46 (0.00%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 2                   | 0                   | 2                   |
| Depressed mood                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 0 / 46 (0.00%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Depression                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 1 / 46 (2.17%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 0                   | 1                   | 2                   |
| Insomnia   |                     |                     |                     |
| subjects affected / exposed                      | 4 / 32 (12.50%)     | 2 / 46 (4.35%)      | 3 / 26 (11.54%)     |
| occurrences (all)                                | 4                   | 2                   | 3                   |
| Sleep disorder                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 2 / 46 (4.35%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 0                   | 2                   | 1                   |
| Investigations                                   |                     |                     |                     |
| Weight decreased                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 4 / 46 (8.70%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 0                   | 4                   | 2                   |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Sunburn  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 8 / 46 (17.39%)     | 2 / 26 (7.69%)      |
| occurrences (all)                                | 1                   | 9                   | 2                   |
| Nervous system disorders                         |                     |                     |                     |
| Disturbance in attent                            |                     |                     |                     |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 3 / 46 (6.52%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 1                   | 3                   | 1                   |
| Dizziness  |                     |                     |                     |
| subjects affected / exposed                      | 5 / 32 (15.63%)     | 1 / 46 (2.17%)      | 1 / 26 (3.85%)      |
| occurrences (all)                                | 5                   | 1                   | 1                   |
| Dysgeusia  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 2 / 46 (4.35%)      | 2 / 26 (7.69%)      |
| occurrences (all)                                | 0                   | 2                   | 2                   |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| Headache                             |                 |                 |                 |
| subjects affected / exposed          | 4 / 32 (12.50%) | 7 / 46 (15.22%) | 3 / 26 (11.54%) |
| occurrences (all)                    | 4               | 7               | 3               |
| Hypoaesthesia                        |                 |                 |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 46 (0.00%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Lethargy                             |                 |                 |                 |
| subjects affected / exposed          | 2 / 32 (6.25%)  | 1 / 46 (2.17%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 2               | 1               | 0               |
| Paraesthesia                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 5 / 46 (10.87%) | 3 / 26 (11.54%) |
| occurrences (all)                    | 0               | 5               | 3               |
| Somnolence                           |                 |                 |                 |
| subjects affected / exposed          | 1 / 32 (3.13%)  | 0 / 46 (0.00%)  | 4 / 26 (15.38%) |
| occurrences (all)                    | 1               | 0               | 4               |
| Syncope                              |                 |                 |                 |
| subjects affected / exposed          | 0 / 32 (0.00%)  | 0 / 46 (0.00%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 0               | 0               | 0               |
| Tremor                               |                 |                 |                 |
| subjects affected / exposed          | 2 / 32 (6.25%)  | 1 / 46 (2.17%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 2               | 1               | 0               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 8 / 32 (25.00%) | 0 / 46 (0.00%)  | 3 / 26 (11.54%) |
| occurrences (all)                    | 8               | 0               | 3               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Tinnitus                             |                 |                 |                 |
| subjects affected / exposed          | 2 / 32 (6.25%)  | 0 / 46 (0.00%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Eye disorders                        |                 |                 |                 |
| Dry eye                              |                 |                 |                 |
| subjects affected / exposed          | 2 / 32 (6.25%)  | 0 / 46 (0.00%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Ocular icterus                       |                 |                 |                 |
| subjects affected / exposed          | 2 / 32 (6.25%)  | 0 / 46 (0.00%)  | 2 / 26 (7.69%)  |
| occurrences (all)                    | 2               | 0               | 2               |
| Gastrointestinal disorders           |                 |                 |                 |

|                             |                 |                  |                 |
|-----------------------------|-----------------|------------------|-----------------|
| Abdominal discomfort        |                 |                  |                 |
| subjects affected / exposed | 4 / 32 (12.50%) | 0 / 46 (0.00%)   | 2 / 26 (7.69%)  |
| occurrences (all)           | 4               | 0                | 2               |
| Abdominal distension        |                 |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 3 / 46 (6.52%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 1               | 3                | 1               |
| Abdominal pain              |                 |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 8 / 46 (17.39%)  | 3 / 26 (11.54%) |
| occurrences (all)           | 0               | 8                | 3               |
| Abdominal pain upper        |                 |                  |                 |
| subjects affected / exposed | 3 / 32 (9.38%)  | 2 / 46 (4.35%)   | 5 / 26 (19.23%) |
| occurrences (all)           | 3               | 2                | 5               |
| Constipation                |                 |                  |                 |
| subjects affected / exposed | 4 / 32 (12.50%) | 1 / 46 (2.17%)   | 4 / 26 (15.38%) |
| occurrences (all)           | 4               | 1                | 4               |
| Diarrhoea                   |                 |                  |                 |
| subjects affected / exposed | 7 / 32 (21.88%) | 12 / 46 (26.09%) | 9 / 26 (34.62%) |
| occurrences (all)           | 7               | 12               | 9               |
| Dry mouth                   |                 |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 46 (0.00%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 0               | 0                | 0               |
| Dyspepsia                   |                 |                  |                 |
| subjects affected / exposed | 6 / 32 (18.75%) | 4 / 46 (8.70%)   | 4 / 26 (15.38%) |
| occurrences (all)           | 6               | 4                | 4               |
| Flatulence                  |                 |                  |                 |
| subjects affected / exposed | 2 / 32 (6.25%)  | 2 / 46 (4.35%)   | 1 / 26 (3.85%)  |
| occurrences (all)           | 2               | 2                | 1               |
| Gastrooesophageal ref       |                 |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 46 (0.00%)   | 2 / 26 (7.69%)  |
| occurrences (all)           | 1               | 0                | 2               |
| Hypoaesthesia oral          |                 |                  |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 46 (2.17%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 1               | 1                | 0               |
| Lip dry                     |                 |                  |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 4 / 46 (8.70%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 0               | 4                | 0               |

|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| Nausea<br>subjects affected / exposed<br>occurrences (all)              | 18 / 32 (56.25%)<br>18 | 26 / 46 (56.52%)<br>28 | 16 / 26 (61.54%)<br>16 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)            | 11 / 32 (34.38%)<br>11 | 13 / 46 (28.26%)<br>16 | 6 / 26 (23.08%)<br>6   |
| Hepatobiliary disorders   |                        |                        |                        |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all) | 3 / 32 (9.38%)<br>3    | 0 / 46 (0.00%)<br>0    | 0 / 26 (0.00%)<br>0    |
| Jaundice<br>subjects affected / exposed<br>occurrences (all)            | 6 / 32 (18.75%)<br>6   | 2 / 46 (4.35%)<br>2    | 5 / 26 (19.23%)<br>5   |
| Skin and subcutaneous tissue disorders                                  |                        |                        |                        |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)            | 1 / 32 (3.13%)<br>1    | 4 / 46 (8.70%)<br>4    | 2 / 26 (7.69%)<br>2    |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0    | 0 / 46 (0.00%)<br>0    | 0 / 26 (0.00%)<br>0    |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)            | 3 / 32 (9.38%)<br>3    | 7 / 46 (15.22%)<br>7   | 2 / 26 (7.69%)<br>2    |
| Eczema<br>subjects affected / exposed<br>occurrences (all)              | 0 / 32 (0.00%)<br>0    | 3 / 46 (6.52%)<br>3    | 1 / 26 (3.85%)<br>1    |
| Erythema<br>subjects affected / exposed<br>occurrences (all)            | 1 / 32 (3.13%)<br>1    | 0 / 46 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1    |
| Pain of skin<br>subjects affected / exposed<br>occurrences (all)        | 0 / 32 (0.00%)<br>0    | 0 / 46 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1    |
| Papule<br>subjects affected / exposed<br>occurrences (all)              | 2 / 32 (6.25%)<br>2    | 0 / 46 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1    |
| Photosensitivity reac   |                        |                        |                        |

|   |                      |                        |                      |
|---|----------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                          | 4 / 32 (12.50%)<br>4 | 11 / 46 (23.91%)<br>11 | 3 / 26 (11.54%)<br>3 |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)              | 7 / 32 (21.88%)<br>7 | 14 / 46 (30.43%)<br>14 | 6 / 26 (23.08%)<br>6 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 32 (0.00%)<br>0  | 13 / 46 (28.26%)<br>15 | 9 / 26 (34.62%)<br>9 |
| Rash papulosquamous<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>2  | 0 / 46 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1  |
| Musculoskeletal and connective tissue disorders                           |                      |                        |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 32 (0.00%)<br>0  | 3 / 46 (6.52%)<br>3    | 1 / 26 (3.85%)<br>1  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 32 (3.13%)<br>1  | 0 / 46 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)         | 1 / 32 (3.13%)<br>1  | 1 / 46 (2.17%)<br>1    | 2 / 26 (7.69%)<br>2  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)               | 2 / 32 (6.25%)<br>2  | 1 / 46 (2.17%)<br>1    | 1 / 26 (3.85%)<br>1  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)     | 1 / 32 (3.13%)<br>1  | 1 / 46 (2.17%)<br>1    | 2 / 26 (7.69%)<br>2  |
| Infections and infestations   |                      |                        |                      |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)       | 2 / 32 (6.25%)<br>2  | 6 / 46 (13.04%)<br>6   | 0 / 26 (0.00%)<br>0  |
| Urinary tract infecti<br>subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>2  | 1 / 46 (2.17%)<br>1    | 0 / 26 (0.00%)<br>0  |
| Metabolism and nutrition disorders  |                      |                        |                      |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 3 / 32 (9.38%)<br>3 | 0 / 46 (0.00%)<br>0 | 0 / 26 (0.00%)<br>0 |
|--|---------------------|---------------------|---------------------|

| <b>Non-serious adverse events</b>  | P4:BID600_16wks      | P3:TID600_24wks        | P4:BID600_24wks     |
|--|----------------------|------------------------|---------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 1 / 1 (100.00%)      | 25 / 25 (100.00%)      | 2 / 2 (100.00%)     |
| General disorders and administration site conditions                                 |                      |                        |                     |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 1 (0.00%)<br>0   | 1 / 25 (4.00%)<br>1    | 0 / 2 (0.00%)<br>0  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 1 (0.00%)<br>0   | 1 / 25 (4.00%)<br>1    | 1 / 2 (50.00%)<br>1 |
| Chills<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 1 (0.00%)<br>0   | 0 / 25 (0.00%)<br>0    | 0 / 2 (0.00%)<br>0  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 1 (100.00%)<br>1 | 10 / 25 (40.00%)<br>10 | 0 / 2 (0.00%)<br>0  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)           | 0 / 1 (0.00%)<br>0   | 0 / 25 (0.00%)<br>0    | 0 / 2 (0.00%)<br>0  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 1 (0.00%)<br>0   | 2 / 25 (8.00%)<br>2    | 0 / 2 (0.00%)<br>0  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                | 0 / 1 (0.00%)<br>0   | 0 / 25 (0.00%)<br>0    | 0 / 2 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 1 (0.00%)<br>0   | 0 / 25 (0.00%)<br>0    | 0 / 2 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders                                      |                      |                        |                     |
| Cough<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 1 (0.00%)<br>0   | 2 / 25 (8.00%)<br>2    | 0 / 2 (0.00%)<br>0  |

|   |                    |                      |                     |
|---|--------------------|----------------------|---------------------|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)              | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 1 / 2 (50.00%)<br>1 |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  |
| Psychiatric disorders   |                    |                      |                     |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)               | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 1 / 2 (50.00%)<br>1 |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)        | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  |
| Depression<br>subjects affected / exposed<br>occurrences (all)            | 0 / 1 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  | 1 / 2 (50.00%)<br>1 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 1 (0.00%)<br>0 | 5 / 25 (20.00%)<br>5 | 0 / 2 (0.00%)<br>0  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)        | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  |
| Investigations  |                    |                      |                     |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 1 (0.00%)<br>0 | 2 / 25 (8.00%)<br>2  | 0 / 2 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                            |                    |                      |                     |
| Sunburn<br>subjects affected / exposed<br>occurrences (all)               | 0 / 1 (0.00%)<br>0 | 4 / 25 (16.00%)<br>4 | 0 / 2 (0.00%)<br>0  |
| Nervous system disorders  |                    |                      |                     |
| Disturbance in attent<br>subjects affected / exposed<br>occurrences (all) | 0 / 1 (0.00%)<br>0 | 0 / 25 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  |
| Dizziness   |                    |                      |                     |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 1 (0.00%)   | 3 / 25 (12.00%) | 1 / 2 (50.00%)  |
| occurrences (all)                    | 0               | 3               | 1               |
| Dysgeusia                            |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 0               | 0               |
| Headache                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 2 / 25 (8.00%)  | 2 / 2 (100.00%) |
| occurrences (all)                    | 0               | 2               | 2               |
| Hypoaesthesia                        |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 3 / 25 (12.00%) | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 3               | 0               |
| Lethargy                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 0               | 0               |
| Paraesthesia                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 2 / 25 (8.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 2               | 0               |
| Somnolence                           |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 0               | 0               |
| Syncope                              |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 0               | 0               |
| Tremor                               |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 1 / 25 (4.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 1               | 0               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 1 / 1 (100.00%) | 2 / 25 (8.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 1               | 2               | 0               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Tinnitus                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 1 (0.00%)   | 0 / 25 (0.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                    | 0               | 0               | 0               |
| Eye disorders                        |                 |                 |                 |

|                             |               |                 |                |
|-----------------------------|---------------|-----------------|----------------|
| Dry eye                     |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 25 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Ocular icterus              |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 25 (4.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Gastrointestinal disorders  |               |                 |                |
| Abdominal discomfort        |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 25 (8.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 2               | 0              |
| Abdominal distension        |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 25 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Abdominal pain              |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 25 (12.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 3               | 0              |
| Abdominal pain upper        |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 25 (8.00%)  | 1 / 2 (50.00%) |
| occurrences (all)           | 0             | 2               | 1              |
| Constipation                |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 25 (4.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Diarrhoea                   |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 9 / 25 (36.00%) | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 9               | 0              |
| Dry mouth                   |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 25 (0.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 0               | 0              |
| Dyspepsia                   |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 25 (4.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Flatulence                  |               |                 |                |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 25 (4.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)           | 0             | 1               | 0              |
| Gastrooesophageal ref       |               |                 |                |

|  |                 |                  |                |
|--|-----------------|------------------|----------------|
| subjects affected / exposed            | 0 / 1 (0.00%)   | 2 / 25 (8.00%)   | 1 / 2 (50.00%) |
| occurrences (all)                      | 0               | 2                | 1              |
| Hypoaesthesia oral                     |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 2 / 25 (8.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 2                | 0              |
| Lip dry                                |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 1 / 25 (4.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 1                | 0              |
| Nausea                                 |                 |                  |                |
| subjects affected / exposed            | 1 / 1 (100.00%) | 18 / 25 (72.00%) | 1 / 2 (50.00%) |
| occurrences (all)                      | 1               | 18               | 1              |
| Vomiting                               |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 5 / 25 (20.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 5                | 0              |
| Hepatobiliary disorders                |                 |                  |                |
| Hyperbilirubinaemia                    |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 0 / 25 (0.00%)   | 1 / 2 (50.00%) |
| occurrences (all)                      | 0               | 0                | 1              |
| Jaundice                               |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 4 / 25 (16.00%)  | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 4                | 0              |
| Skin and subcutaneous tissue disorders |                 |                  |                |
| Alopecia                               |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 0 / 25 (0.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 0                | 0              |
| Dermatitis                             |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 2 / 25 (8.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 2                | 0              |
| Dry skin                               |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 2 / 25 (8.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 2                | 0              |
| Eczema                                 |                 |                  |                |
| subjects affected / exposed            | 0 / 1 (0.00%)   | 1 / 25 (4.00%)   | 0 / 2 (0.00%)  |
| occurrences (all)                      | 0               | 1                | 0              |
| Erythema                               |                 |                  |                |

|   |               |                  |                 |
|---|---------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 1 (0.00%) | 3 / 25 (12.00%)  | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 5                | 0               |
| Pain of skin                                    |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 2 / 25 (8.00%)   | 1 / 2 (50.00%)  |
| occurrences (all)                               | 0             | 2                | 1               |
| Papule  |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 0                | 0               |
| Photosensitivity reac                           |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 8 / 25 (32.00%)  | 1 / 2 (50.00%)  |
| occurrences (all)                               | 0             | 8                | 1               |
| Pruritus  |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 7 / 25 (28.00%)  | 2 / 2 (100.00%) |
| occurrences (all)                               | 0             | 7                | 2               |
| Rash  |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 10 / 25 (40.00%) | 2 / 2 (100.00%) |
| occurrences (all)                               | 0             | 10               | 2               |
| Rash papulosquamous                             |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 0                | 0               |
| Musculoskeletal and connective tissue disorders |               |                  |                 |
| Arthralgia                                      |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 0                | 0               |
| Back pain                                       |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 1                | 0               |
| Muscle spasms                                   |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 1 / 25 (4.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 1                | 0               |
| Myalgia   |               |                  |                 |
| subjects affected / exposed                     | 0 / 1 (0.00%) | 0 / 25 (0.00%)   | 0 / 2 (0.00%)   |
| occurrences (all)                               | 0             | 0                | 0               |
| Pain in extremity                               |               |                  |                 |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 1 (0.00%)<br>0 | 1 / 25 (4.00%)<br>1 | 0 / 2 (0.00%)<br>0 |
| Infections and infestations                      |                    |                     |                    |
| Nasopharyngitis                                  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 1 (0.00%)      | 0 / 25 (0.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Urinary tract infecti                            |                    |                     |                    |
| subjects affected / exposed                      | 0 / 1 (0.00%)      | 1 / 25 (4.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Metabolism and nutrition disorders               |                    |                     |                    |
| Decreased appetite                               |                    |                     |                    |
| subjects affected / exposed                      | 0 / 1 (0.00%)      | 1 / 25 (4.00%)      | 0 / 2 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 23 April 2010   | Protocol Amendment 1, dated 23 Apr 2010, was implemented before patient enrolment began, in order to clarify: 1. That the aims and design of Part 1 of the 1241.21 clinical trial is typical of a Phase Ib study (drug-drug interaction, short term safety and on-treatment activity in a small cohort of patients), while Part 2 will extend treatment duration and establish proof of concept (sustained virological response), thus representing a phase II study. The trial phase was changed from II to Ib/II in title page and synopsis. 2. The time-points when targeted physical exams took place. 3. How the eCRF pages were to be completed in case of early end of treatment of a patient. 4. The time-point of the End of Observation in case of viral relapse and to add a time point for End of Observation visit. 5. Which assessments was part of the end of treatment (EOT) visit for patients who have their EOT visit at Week 24. 6. How PK sample for DBV and its metabolites were collected and analysed.  |
| 05 October 2010 | Protocol amendment 2, dated 05 Oct 2010, was implemented in order to increase patient safety. HCV RNA related stopping rules were modified and are no longer based on 'lower limit of quantification' (<25 IU/ml) but on 'lower limit of detection' (approximately 10 IU/ml) according to FDA Draft Guidance for Developing new HCV Treatments from Sep 2010. Changes to planned analysis in Part 1: Changes to the planned analyses from the protocol concerned sustained virological response (SVR12) which was not determined as secondary efficacy endpoint as stated in the CTP. Comparison to historical data was performed with trials 1220.2 (monotherapy with FDV) and trial 1241.7 (triple therapy with DBV). Data from trials 1241.2, 1220.5, and 1220.40 were not used for historical comparison; these trials were written up in protocol Section 3.2 for completeness, but in the end they did not provide data that were directly comparable with those of the present trial. The final analysis contained no model search for response, as there were almost no cases in which no SVR occurred. Changes in Part 2: Global protocol amendments in Part 2. In the course of Part 2, 4 amendments to the CTP were issued (global protocol amendments 3 to 6). All of these amendments required approval by the IEC and CA.   |
| 20 October 2010 | Protocol amendment 3, dated 20 Oct 2010 were implemented due to the excellent antiviral response rates and good tolerability and safety observed in Part 1. 1. The sample size per treatment arm was increased from n = 30 to n = 80 to support a full Phase IIb trial design. This was planned to accelerate the clinical development of FDV/DBV combination therapy. 2. Re-randomisation was deleted in the new Part 2 design to simplify the design. 3. The DBV 600 mg BID dose was introduced: Based on the observed dose-dependent difference in tolerability over 4 weeks in Part 1 with very robust antiviral effect in both dose groups, investigation of a second dose that was lower than 600 mg TID was justified for long-term treatment in Part 2. 4. Treatment durations of 16, 28, and 40 weeks were tested. 5. Patients with cirrhosis Child A were allowed to participate in Part 2, based on safety, pharmacokinetics and efficacy data from cirrhotic patients in the Phase Ib/II trials 1220.2 (FDV+SOC for 4 weeks), 1220.40 (FDV+SOC for 12-24 weeks) and 1241.2 (DBV monotherapy for 5 days). 6. Furthermore Protocol Amendment 3 was implemented based on the recently published Food and Drug Administration (FDA). 7. Patients who achieved SVR were followed for 144 weeks after EOT. Patients who discontinued early on investigational treatment were followed for at least 48 weeks. Genotyping of IL28B, was included as a stratifying factor. As an association of the IL28B genotype with spontaneous cure from acute HCV infection or response to PegIFN therapy was reported, it was important to understand the impact of the IL28B genotype on the response to PegIFN-sparing direct-acting antiviral combinations and, therefore, IL28B genotype was considered in the analysis of efficacy data. 9. Additional follow-up visits were added to ensure that HCV RNA was measured for all patients (incl. those that discontinued prematurely) at 12 weeks and at 24 weeks after EOT. |

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| 04 February 2011 | Protocol amendment 4, dated 4 Feb 2011, was issued to stop recruitment to treatment arm NRBV, due to evidence presented for other direct acting antiviral agents raising concerns about an increased risk of virological breakthrough with RBV-free treatment regimens.  |
| 18 April 2011    | Protocol amendment 5, dated 18 Apr 2011, included: 1. Further drugs which were not allowed to be used or were to be avoided concomitantly. 2. A new version of rash management plan. 3. Clarification of the DBV dose reduction. 4. Recommendations for symptomatic treatment of gastrointestinal (GI) AEs. 5. The use of urine instead of serum pregnancy tests. 6. Correction of storage conditions for FDV. 7. The need to confirm virological breakthrough with a second measurement was omitted for patients with plasma HCV RNA $\geq 1000$ IU/mL in the initial measurement of breakthrough. As HCV RNA generally rebounds rapidly during virological breakthrough, and low viral load (VL) level is associated with a better sustained viral response to PegIFN/RBV therapy, the aim is to switch patients to SOC treatment as soon as possible after the detection of virological breakthrough. 8. The achievement of an undetectable HCV RNA level at Week 4 was added as a secondary efficacy endpoint. 9. The time windows for later protocol visits were shortened, to ensure that the amount of dispensed medication be sufficient to cover the periods between clinical visits.   |
| 14 July 2011     | Protocol amendment 6, dated 14 Jul 2011, was implemented for the following reasons: 1. Exclusion criterion 25 (HbA1c $>8.5\%$ ) was adapted. 2. A confirmed definition for virological relapse was provided. 3. Prompt treatment initiation with PegIFN and RBV was required in patients with confirmed virological relapse. 4. The assignment of AEs to treatment phases was made clearer. Changes in conduct of Part 2. Enrolment in the ribavirin-free arm (NRBV 28wks group) was stopped on 03 Feb 2011 on request of the FDA after 49 patients were randomised, following the observation from other studies that breakthrough was more common in IFN-free regimens that did not contain ribavirin. Changes to planned analysis in Part 2: Prior to the internal unblinding of the data and the signature of the TSAP for Part 2, the primary endpoint was changed from SVR24 (plasma HCV RNA level not detectable at 24 weeks after completion of all therapy) to SVR12. SVR24 was defined as secondary endpoint. Other additional analyses not specified in the CTP or TSAP (Part 2) include: 5. Analysis of PPV of SVR4 to SVR24, SVR12 to SVR24, and SVR24 to SVR48 (using available data) were also calculated for the VES. 6. The predictive value (positive and negative) of earlier endpoints for the occurrence of later endpoints was investigated from the observed data using the VES population. 7. The assessments of the incidence, prevalence, and duration of rash, photosensitivity, nausea, vomiting, and diarrhoea. Time windows used in these analyses differ from those specified in the minutes of the final blinded report planning meeting (BRPM) (September 10, 2012) in order to display the timing of the episodes of these AEs more clearly. 8. Efficacy and safety tabulations by cirrhosis (yes/no) 9.8.3.1 Global protocol amendments in Part 3. In the course of Part 3, 3 global protocol amendments to the CTP were issued (amendment 7, 8, and 9). All of these amendments required approval by the IEC and CA. |
| 30 December 2011 | Protocol amendment 7, dated 30 Dec 2011, implemented Part 3 to the trial protocol. This resulted in a number of changes throughout the protocol, among them: 1. Changes to the protocol title. 2. Addition of the treatment groups for Part 3. 3. New endpoints for Part 3. 4. New criteria for PK. 5. New futility rules. 6. A new definition for lack of antiviral activity. 7. Changes in inclusion and exclusion criteria. 8. Addition of new skin and GI management plans.  |
| 16 May 2012      | Protocol amendment 8, dated 16 May 2012 included some additional updates and adjustments: 1. Changes to inclusion and exclusion criteria. 2. The primary endpoint was changed to be SVR12 (plasma HCV RNA undetectable 12 weeks after end of all therapy). 3. Accordingly, SVR4 was used as a secondary endpoint. 4. Intensity of all adverse events was to be assessed according to the DAIDS (Division of AIDS) grading system of the US National Institute of Allergy and Infectious Diseases. 5. Bayer Trugene® Hepatitis C virus genotyping assay was to be used, when a GT-1 subtype could not be determined using the iNNO-LiPA HCV 2.0 genotyping assay. 6. Added one interim analysis to obtain Week 4 on-treatment results in treatment group BID 600 mg 16wks.  |

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| 01 August 2012   | <p>Protocol amendment 9, dated 01 August 2012 implemented: 1. The requirement to confirm virological breakthrough, if the VL was &lt;1000 IU/mL, was deleted for the 24wks groups as these patients were at higher risk for virological failure. 2. Inclusion criterion No. 7 was changed to require two non hormonal methods for contraception as interaction of the two trial drugs with oral contraceptives may lead to reduced efficacy of these. Changes in conduct of Part 3: In Part 3, the following changes were made in the conduct of the trial: The requirement to confirm virological breakthrough, if the VL was &lt;1000 IU/mL was deleted for treatment groups BID 800 mg 24wks and TID 600 mg 24wks. This was done because in an interim analysis the patients in these groups appeared to be at higher risk for virological failure. Part 3, patients in the BID 24wks group (Group 9; FDV 120 mg QD + DBV 800 mg BID + RBV) and the TID 24wks group (Group 10; FDV 120 mg QD + DBV 600 mg TID + RBV) were at greater risk to experience virological failure with emergent resistance to both direct-acting antivirals. Although all patients in these 2 arms were among the more difficult to treat, i.e. GT-1a with unfavourable IL28B non-CC genotype, the DMC recommended to stop further randomisation into the BID 800 mg 24wks and TID 600 mg 24wks groups. Due to this, the BID 800 mg 24wks and TID 600 mg 24wks groups consisted of 26 and 25 patients, respectively, instead of the 30 patients planned per group. Changes to planned analysis in Part 3: AEs occurring up to 28 days after last administration of trial medication were attributed to the trial period instead of the 30 days stated in the CTP. Changes in Part 4: Global protocol amendments in Part 4. In the course of Part 4 of this trial, 4 global protocol amendments to the CTP were issued. These amendments required approval by the IEC and CA.</p> |
| 17 December 2012 | <p>Protocol amendment 10, dated 17 Dec 2012, added Part 4 to the CTP. In this part, patients with chronic HCV GT-1b infection and previous non-response to combination treatment with PegIFN and RBV were enrolled. The major changes introduced by protocol amendment 10 were: 1. Change of the number of recruited patients: 30 additional patients were to be enrolled. 2. Changes to inclusion criterion 2 and 3. Addition of treatment groups for Part 4. Clarification that an Interactive Voice Response System (IVRS) was not used in Part 4 of this trial. 5. Low density lipoprotein (LDL) was deleted from the list of substrates to be analysed, as it had been listed by mistake.</p>  |
| 21 June 2013     | <p>Protocol amendment 11, dated 21 Jun 2013, included the following changes: 1. Change of PK-sample collection method: PK-samples which are collected outside of the intensive PK-sampling in Part 4 were not to be collected at any time during the visit days but in fasting condition and prior to the intake of study medication. 2. Update of lists of restricted medications (Appendices 10.3 and 10.4 of the CTP). The most current medications list was to be included in the ISF Section 11 'Safety Information'. 3. Addition of Appendix 10.5 in the CTP: List of comedications that should be used with caution as the levels of these drugs might decrease in studies with the combination of FDV and DBV. The most current medications list was to be included in the ISF Section 11 'Safety Information'. 4. Adjustment of the inclusion criterion 3, Part 4. 5. Updated frequency of ECG measurements. 6. Updated benefit-risk section with no change in the benefit-risk relationship. 7. Information was added that skin reactions of moderate or higher severity was to be adjudicated by an external panel of dermatology specialists. 8. Inclusion of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) into the definition of Potentially Life-Threatening (Grade IV) skin events. 9. Virology samples for resistance testing were no longer shipped to the BI facility in Laval, Canada but to Janssen Diagnostics in Belgium.</p>  |
| 29 October 2013  | <p>Protocol amendment 12, dated 29 Oct 2013, implemented changes in the benefit-risk assessment and the criteria for removal of patients: 1. Benefit-risk assessment: Potential risk of agranulocytosis/neutropenia were added, as cases of Grade IV neutropenia were recently observed. 2. Removal of individual patients: Added that treatment was to be discontinued if absolute neutrophil count was <math>\leq 500</math> cell/mm<sup>3</sup> to ensure treatment discontinuation in case of life-threatening neutropenia.</p>   |

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| 14 March 2014 | Protocol amendment 13, dated 14 Mar 2014, introduced the following changes due to the termination of the developmental programme for DBV and FDV by the sponsor: 1. Flow Chart 8 for Part 4: The follow-up period in Part 4 was shortened to 24 weeks after EOT; only 3 patients were randomised in Part 4 of this trial by the time of DBV development termination. The long term follow-up in Part 4 was not needed. 2. Interim Analysis: The interim analysis was not needed. Changes in conduct of Part 4: Enrolment in Part 4 of trial 1241.21 was stopped on 17 January 2014 as the sponsor Boehringer Ingelheim decided to discontinue the developmental programmes of DBV and FDV. All pending marketing applications for FDV were withdrawn and further HCV drug development was discontinued. The decision was taken as there is no longer an unmet medical need for the FDV interferon-based regimen. Changes to planned analysis in Part 4: In Part 4 of this trial, only 3 patients with previous 'null-response' to HCV therapy were entered, because Part 4 had been terminated early. Therefore, no formal analysis of efficacy was performed. Safety and efficacy data for these patients are described based on listings. The TSAP for this final CTR that defines analyses for Parts 2 to 4, mentions SVR24 as a secondary endpoint for both, Parts 2 and 3. However, SVR24 was defined as a secondary only for Part 2 of this trial; for Part 3 it was defined as a further (tertiary) endpoint. |
|---------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date            | Interruption  | Restart date |
|-----------------|---|--------------|
| 17 January 2014 | As trial 1241.21 was terminated early and in Part 4 only 3 patients were entered, no formal analysis of efficacy data was performed. For part 4, only descriptive statistics of HCV RNA viral load are presented. | -            |

Notes:

## Limitations and caveats

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

There were only 3 patients entered in part 4 of the trial, therefore no formal analyses of efficacy data were performed. Long term follow-up: Part 1: 168 Days, Part2: 144 Weeks, Part3: 96 Weeks, Part4: 24 Weeks.

Notes: