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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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:

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.

Arm title	Part 3: 600mg DBV and 120mg FDV - 16w

Arm 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.

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 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:

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.

Arm title	Part 3: 800mg DBV and 120mg FDV - 24w

Arm 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.

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.

Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1[1]	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	-	-	-

Number of subjects in period 1[1]	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	-	-

Number of subjects in period 1[1]	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	-	-	-

Number of subjects in period 1[1]	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:

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:

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:

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:

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:

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:

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:

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:

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 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 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 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 Units: Participants			
Female	11	1	2
Male	14	0	0

Reporting group values	Total		
Number of subjects	480		
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			
standard deviation	-		

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

End points reporting groups

Reporting group title	Part 1: 400mg DBV and 120mg FDV - 4w

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	Part 1: 600mg DBV and 120mg FDV - 4w

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	Part 2: 600mg DBV and 120mg FDV - 16w

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	Part 2: 600mg DBV TID and 120mg FDV - 28w

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	Part 2: 600mg DBV and 120mg FDV - 40w

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	Part 2: 600mg DBV BID and 120mg FDV - 28w

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	Part 2: 600mg DBV and 120mg FDV, no RBV - 28w

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	Part 3: 600mg DBV and 120mg FDV - 16w

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	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)[1][2]

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[3]	17[4]		
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)[5][6]

End point description:

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:

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[7]	80[8]	77[9]	78[10]
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[11]			
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)[12][13]

End point description:

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:

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[14]	26[15]	25[16]	1[17]
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[18]			
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[19]

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[20]	17[21]		
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[22]

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

End point values	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[24]	17[25]	81[26]	80[27]
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[28]	78[29]	46[30]	
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[31]

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.

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[32]	80[33]	77[34]	78[35]
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

End point values	Part 2: 600mg DBV and 120mg FDV, no RBV - 28w			
Subject group type	Reporting group			
Number of subjects analysed	46[36]			
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[37]

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.

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[38]	26[39]	25[40]	1[41]
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.

End point values	Part 4: 600 mg DBV and 120mg FDV - 24w			
Subject group type	Reporting group			
Number of subjects analysed	2[42]			
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[43]

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.

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[44]	26[45]	25[46]	1[47]
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.

End point values	Part 4: 600 mg DBV and 120mg FDV - 24w			
Subject group type	Reporting group			
Number of subjects analysed	2[48]			
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 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.

Serious adverse events	P1:BI combi 400mg+RBV	P1:BI combi 600mg+RBV	P2:TID_16wks
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 infa			
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 l			
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 failu			
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 disea			

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

Serious adverse events	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
Injury, poisoning and procedural complications			
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
Cardiac disorders			
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 l			
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
Blood and lymphatic system disorders			
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
Eye disorders			
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
Gastrointestinal disorders			
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

Serious adverse events	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
Investigations			
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
Injury, poisoning and procedural complications			
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
Cardiac disorders			
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 l			
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

Serious adverse events	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 l			
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
Infections and infestations			
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
Gastroenteritis			
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
Herpes zoster			
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
Metabolism and nutrition disorders			
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 %

Non-serious adverse events	P1:BI combi 400mg+RBV	P1:BI combi 600mg+RBV	P2:TID_16wks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	76 / 81 (93.83%)
General disorders and administration site conditions			
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 illnes			
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	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	11 / 81 (13.58%)
occurrences (all)	0	0	11
Sleep disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	3 / 81 (3.70%)
occurrences (all)	0	0	3
Investigations			
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	8 / 81 (9.88%)
occurrences (all)	0	0	8
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	6 / 81 (7.41%)
occurrences (all)	0	0	6
Nervous system disorders			
Disturbance in attent			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	3 / 81 (3.70%)
occurrences (all)	0	0	3
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	4 / 81 (4.94%)
occurrences (all)	0	0	4
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	3 / 81 (3.70%)
occurrences (all)	0	0	3
Headache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	11 / 81 (13.58%)
occurrences (all)	0	0	12
Hypoaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	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	0 / 15 (0.00%)	0 / 17 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	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

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

Hypoaesthesia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	2 / 78 (2.56%)
occurrences (all)	1	1	2
Lethargy			
subjects affected / exposed	1 / 80 (1.25%)	2 / 77 (2.60%)	1 / 78 (1.28%)
occurrences (all)	1	2	1
Paraesthesia			
subjects affected / exposed	9 / 80 (11.25%)	6 / 77 (7.79%)	4 / 78 (5.13%)
occurrences (all)	10	7	4
Somnolence			
subjects affected / exposed	2 / 80 (2.50%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences (all)	2	0	0
Syncope			
subjects affected / exposed	2 / 80 (2.50%)	5 / 77 (6.49%)	6 / 78 (7.69%)
occurrences (all)	2	5	6
Tremor			
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 80 (11.25%)	10 / 77 (12.99%)	7 / 78 (8.97%)
occurrences (all)	10	12	7
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 80 (0.00%)	3 / 77 (3.90%)	1 / 78 (1.28%)
occurrences (all)	0	3	1
Ocular icterus			
subjects affected / exposed	0 / 80 (0.00%)	3 / 77 (3.90%)	5 / 78 (6.41%)
occurrences (all)	0	3	5
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	6 / 78 (7.69%)
occurrences (all)	1	1	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			
subjects affected / exposed	29 / 80 (36.25%)	23 / 77 (29.87%)	20 / 78 (25.64%)
occurrences (all)	43	38	29
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 80 (2.50%)	3 / 77 (3.90%)	0 / 78 (0.00%)
occurrences (all)	2	3	0
Jaundice			
subjects affected / exposed	22 / 80 (27.50%)	15 / 77 (19.48%)	16 / 78 (20.51%)
occurrences (all)	22	16	16
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 80 (8.75%)	2 / 77 (2.60%)	7 / 78 (8.97%)
occurrences (all)	7	2	7
Dermatitis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	12 / 80 (15.00%)	11 / 77 (14.29%)	18 / 78 (23.08%)
occurrences (all)	12	11	18
Eczema			
subjects affected / exposed	3 / 80 (3.75%)	2 / 77 (2.60%)	4 / 78 (5.13%)
occurrences (all)	3	3	4
Erythema			
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	2 / 78 (2.56%)
occurrences (all)	2	2	4
Pain of skin			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences (all)	0	0	1
Photosensitivity reac			
subjects affected / exposed	23 / 80 (28.75%)	23 / 77 (29.87%)	19 / 78 (24.36%)
occurrences (all)	25	25	21
Pruritus			

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

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

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

Decreased appetite			
subjects affected / exposed	3 / 32 (9.38%)	0 / 46 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0

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

Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 1 (0.00%)	2 / 25 (8.00%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 25 (20.00%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Sleep disorder			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 25 (8.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	0 / 1 (0.00%)	4 / 25 (16.00%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Nervous system disorders			
Disturbance in attent			
subjects affected / exposed	0 / 1 (0.00%)	0 / 25 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	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	0 / 1 (0.00%)	1 / 25 (4.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	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.

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 ≥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.

01 August 2012	Protocol amendment 9, dated 01 August 2012 implemented: 1. The requirement to confirm virological breakthrough, if the VL was <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 <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.
17 December 2012	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 enroled. 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.
21 June 2013	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.
29 October 2013	Protocol amendment 12, dated 29 Oct 2013, implemented changes in the benefit-risk assessement 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 ≤500 cell/mm3 to ensure treatment discontinuation in case of life-threatening neutropenia.

14 March 2014	Protocol amendment 13, dated 14 Mar 2014, introduced the following changes due to the termination of the developmental programme for DBVand 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: