Clinical trial results:
A multicenter, randomized, double-blind, placebocontrolled, parallel-group phase II study on efficacy and safety of DEB025 combined with pegIFNalpha2a and ribavirin in chronic hepatitis C genotype 1 relapsers and non-responders to previous pegIFN plus ribavirin treatment

Summary

EudraCT number	2010-020033-14
Trial protocol	GB HU DE FR ES BE IT PL
Global end of trial date	09 May 2013

Results information

Result version number	v1 (current)
This version publication date	29 September 2016
First version publication date	29 September 2016

Trial information

Trial identification

Sponsor protocol code	CDEB025A2210

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01183169
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,

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	09 May 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that in chronic hepatitis C G1 patients with previous non-response to pegIFN/RBV or with previous relapse after pegIFN/RBV treatment:
• triple therapy with DEB025 600 mg BID (loading dose) / 600 mg QD plus pegIFNα2a/RBV leads to a superior cEVR (by Limit of Quantification [LOQ] i.e. HCV RNA < 25 IU/mL) rate as compared to pegIFNα2a/RBV AND/OR
• triple therapy with DEB025 600 mg BID (loading dose) / 800 mg QD plus pegIFNα2a/RBV leads to a superior cEVR rate (by LOQ) as compared to pegIFNα2a/RBV AND/OR
• triple therapy with DEB025 400 mg BID plus pegIFNα2a/RBV leads to a superior cEVR rate (by LOQ) as compared to pegIFNα2a/RBV

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Romania: 76
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	United States: 59
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Taiwan: 80
Country: Number of subjects enrolled	Turkey: 30

Worldwide total number of subjects	459
EEA total number of subjects	261

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)	444
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was planned to enroll 344 patients. A total of 459 patients were randomized and included in the Full Analysis Set (FAS).

Period 1

Period 1 title	Initial treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

At Visit 2 (baseline visit) all eligible patients were randomized via Interactive Response Technology (IRT) to one of the four treatment arms. In order to blind all treatment arms, the placebo-treated patients of arm C were split into two sub-arms of (C1 and C2) in 1:1 ratio.

Arms

Are arms mutually exclusive?	No
Arm title	Arm A: DEB025 600 mg QD

Arm description:

DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks

Arm type	Experimental
Investigational medicinal product name	DEB025
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

Arm title	Arm B: DEB 800 QD

Arm description:

DEB025 800 mg QD with PEG and RBV for up to 48 weeks.

Arm type	Experimental

Investigational medicinal product name	DEB025
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

Arm title	Arm C1- Placebo QD

Arm description:

Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV.
Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status.

Arm type	Placebo
Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

Investigational medicinal product name	Placebo to DEB025
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Placebo soft gel capsules administered orally

Arm title	Arm C2- Placebo BID
Arm description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV.	
Arm type	Placebo
Investigational medicinal product name	Placebo to DEB025
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details:	
Placebo soft gel capsules administered orally	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details:	
RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.	
Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
PEG 180 µg administered via subcutaneous (s.c.) injection once weekly	
Arm title	Arm D DEB 400 BID
Arm description:	
DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks	
Arm type	Experimental
Investigational medicinal product name	DEB025
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details:	
DEB025 was supplied as 200 mg soft gel capsules.	
Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
PEG 180 µg administered via subcutaneous (s.c.) injection once weekly	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details:	
RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day)	

administered orally in a divided daily dose.

Arm title	Arm C- Placebo

Arm description:

Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV.
Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status.

Arm type	Placebo
Investigational medicinal product name	Placebo to DEB025
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Placebo soft gel capsules administered orally

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

Number of subjects in period 1	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm C1- Placebo QD
Started	121	115	59
Completed	72	78	18
Not completed	49	37	41
Abnormal laboratory value(s)	-	2	1
Consent withdrawn by subject	7	5	1
Disease progression	1	-	-
Adverse event, non-fatal	12	9	3
Unsatisfactory therapeutic effect	25	20	1

Administrative problems	2	-	-
Non-compliance	1	-	-
Protocol deviation	1	1	-
Switch to DEB025	-	-	35

Number of subjects in period 1	Arm C2- Placebo BID	Arm D DEB 400 BID	Arm C- Placebo
Started	55	109	114
Completed	17	77	35
Not completed	38	32	79
Abnormal laboratory value(s)	1	1	2
Consent withdrawn by subject	2	9	3
Disease progression	-	-	-
Adverse event, non-fatal	2	18	5
Unsatisfactory therapeutic effect	3	3	4
Administrative problems	-	1	-
Non-compliance	-	-	-
Protocol deviation	-	-	-
Switch to DEB025	30	-	65

Period 2

Period 2 title	After week 16 switch to DEB025
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Arm C1-A

Arm description:

Placebo to DEB 600 QD

Arm type	Experimental
Investigational medicinal product name	DEB025
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection

Routes of administration	Subcutaneous use
Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.	
Arm title	Arm C2-A
Arm description: Placebo to DEB 400 BID	
Arm type	Experimental
Investigational medicinal product name	DEB025
Investigational medicinal product code	
Other name	Alisporivir
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details: DEB025 was supplied as 200 mg soft gel capsules.	
Investigational medicinal product name	Peginterferon alfa-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Copegus®
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.	

Number of subjects in period 2	Arm C1-A	Arm C2-A
Started	35	30
Completed	12	13
Not completed	23	17
Abnormal laboratory value(s)	-	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	3	3
Unsatisfactory therapeutic effect	17	9
Administrative problems	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: DEB025 600 mg QD
Reporting group description:	
DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks	
Reporting group title	Arm B: DEB 800 QD
Reporting group description:	
DEB025 800 mg QD with PEG and RBV for up to 48 weeks.	
Reporting group title	Arm C1- Placebo QD
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status.	
Reporting group title	Arm C2- Placebo BID
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV.	
Reporting group title	Arm D DEB 400 BID
Reporting group description:	
DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks	
Reporting group title	Arm C- Placebo
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status.	

Reporting group values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm C1- Placebo QD
Number of subjects	121	115	59
Age categorical Units: Subjects			
Adults (18-64 years)	118	111	57
From 65-84 years	3	4	2
Age continuous Units: years			
arithmetic mean	50.2	50.9	51.5
standard deviation	± 9.24	± 10.11	± 8.99
Gender categorical Units: Subjects			
Female	58	47	19
Male	63	68	40

Reporting group values	Arm C2- Placebo BID	Arm D DEB 400 BID	Arm C- Placebo
Number of subjects	55	109	114

Age categorical Units: Subjects			
Adults (18-64 years)	55	103	112
From 65-84 years	0	6	2
Age continuous Units: years			
arithmetic mean	49.4	51	50.5
standard deviation	± 11.91	± 9.68	± 10.5
Gender categorical Units: Subjects			
Female	17	40	36
Male	38	69	78

Reporting group values	Total		
Number of subjects	459		
Age categorical Units: Subjects			
Adults (18-64 years)	444		
From 65-84 years	15		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	181		
Male	278		

End points

End points reporting groups

Reporting group title	Arm A: DEB025 600 mg QD
Reporting group description:	
DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks	
Reporting group title	Arm B: DEB 800 QD
Reporting group description:	
DEB025 800 mg QD with PEG and RBV for up to 48 weeks.	
Reporting group title	Arm C1- Placebo QD
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status.	
Reporting group title	Arm C2- Placebo BID
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV.	
Reporting group title	Arm D DEB 400 BID
Reporting group description:	
DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks	
Reporting group title	Arm C- Placebo
Reporting group description:	
Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status.	
Reporting group title	Arm C1-A
Reporting group description:	
Placebo to DEB 600 QD	
Reporting group title	Arm C2-A
Reporting group description:	
Placebo to DEB 400 BID	

Primary: Percentage of Participants With Complete Early Viral Response (cEVR)-LOQ

End point title	Percentage of Participants With Complete Early Viral Response (cEVR)-LOQ[1]
End point description:	
cEVR-LOQ was defined as serum HCV RNA below the limit of quantification (< LOQ; i.e., 25 IU/mL) after 12 weeks of treatment. Post-switch groups were assessed 12 weeks after the switch.	
End point type	Primary
End point timeframe:	
12 weeks	

Notes:

[1] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C1-A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[2]	108[3]	109[4]	33[5]
Units: percent				
number (not applicable)	48.2	61.1	74.3	45.5

Notes:

[2] - Full Analysis Set (FAS): all patients to whom study treatment had been assigned
[3] - FAS
[4] - FAS
[5] - FAS

End point values	Arm C2-A	Arm C- Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[6]	110[7]		
Units: percent				
number (not applicable)	80	35.5		

Notes:

[6] - FAS
[7] - FAS

Statistical analyses

Statistical analysis title	Arm A: Comparison with Arm C (Placebo)
Comparison groups	Arm A: DEB025 600 mg QD v Arm C- Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0131
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.082
upper limit	1.951

Statistical analysis title	Arm B: Comparison with Arm C (Placebo)
Comparison groups	Arm B: DEB 800 QD v Arm C- Placebo

Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.358
upper limit	2.325

Statistical analysis title	Arm D: Comparison with Arm C (Placebo)
Comparison groups	Arm C- Placebo v Arm D DEB 400 BID
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.656
upper limit	2.889

Secondary: Percentage of participants who achieved sustained virologic response (SVR) 12 weeks post treatment

End point title	Percentage of participants who achieved sustained virologic response (SVR) 12 weeks post treatment[8]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

Notes:

[8] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C1-A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[9]	108[10]	109	33[11]
Units: percent				
number (not applicable)	42.7	51.9	65.1	18.2

Notes:

[9] - FAS

[10] - FAS

[11] - FAS

End point values	Arm C2-A	Arm C- Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[12]	110[13]		
Units: percent				
number (not applicable)	53.3	14.5		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

Statistical analysis title	Arm A: Comparison with Arm C (Placebo)
Comparison groups	Arm A: DEB025 600 mg QD v Arm C- Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.917
upper limit	5.063

Statistical analysis title	Arm B: Comparison with Arm C (Placebo)
Comparison groups	Arm C- Placebo v Arm B: DEB 800 QD
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	3.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.31
upper limit	5.963

Statistical analysis title	Arm D: Comparison with Arm C (Placebo)
Comparison groups	Arm C- Placebo v Arm D DEB 400 BID
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Hochberg
Parameter estimate	Cochran-Mantel-Haenszel test
Point estimate	4.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.799
upper limit	7.41

Secondary: Percentage of participants who achieved virologic response by level of quantification (LOQ)

End point title	Percentage of participants who achieved virologic response by level of quantification (LOQ)[14]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

Notes:

[14] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[15]	108[16]	109[17]	110[18]
Units: percent				
number (not applicable)				
RVR (rapid virologic response)	20.9	25	41.3	7.3
cEVR (complete early virologic response)	48.2	61.1	74.3	35.5

EDTR (end of DEB025-treatment virologic response)	72.7	77.8	87.2	33.6
ETR (end of treatment virologic response)	68.2	74.1	82.6	33.6
SVR4 (sustained virologic response 4 weeks)	50	57.4	69.7	21.8
SVR12 (sustained virologic response 12 weeks)	42.7	51.9	65.1	14.5
SVR24 (sustained virologic response 24 weeks)	41.8	51.9	65.1	14.5

Notes:

[15] - FAS

[16] - FAS

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by response status to previous treatment

End point title	Percentage of participants who achieved virologic response by LOQ by response status to previous treatment[19]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[20]	108[21]	109[22]	110[23]
Units: percent				
number (not applicable)				
Relapser - cEVR	64.6	77.6	77.1	57.4
Relapser - EDTR	85.4	83.7	85.4	59.3
Relapser - ETR	87.5	83.7	85.4	59.3
Relapser - SVR12	60.4	63.3	64.6	25.9
Relapser - SVR24	58.3	65.3	64.6	25.9
Non-responder - cEVR	35.5	47.35	72.1	14.3
Non-responder - EDTR	62.9	72.9	88.5	8.9
Non-responder - ETR	53.2	66.1	80.3	8.9
Non-responder - SVR12	29	42.4	65.6	3.6
Non-responder - SVR24	29	40.7	65.6	3.6
Null non-responder - cEVR	33.3	40.5	70.6	11.1
Null non-responder - EDTR	60.4	70.3	82.4	8.3
Null non-responder - ETR	50	64.9	73.5	8.3

Null non-responder - SVR12	22.9	40.5	67.6	2.8
Null non-responder - SVR24	22.9	37.8	67.6	2.8
Partial non-responder / unspecified – cEVR	42.9	59.1	74.1	20
Partial non-responder / unspecified – EDTR	71.4	77.3	96.3	10
Partial non-responder / unspecified – ETR	64.3	68.2	88.9	10
Partial non-responder / unspecified – SVR12	50	45.5	63	5
Partial non-responder / unspecified – SVR24	50	45.5	63	5

Notes:

[20] - FAS: n= 48, 62, 48, 14

[21] - FAS: n = 49, 59, 37, 22

[22] - FAS: n = 48, 61, 34, 27

[23] - FAS: n = 54, 56, 36, 20

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by IL28B polymorphism

End point title	Percentage of participants who achieved virologic response by LOQ by IL28B polymorphism[24]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

Notes:

[24] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[25]	108[26]	109[27]	110[28]
Units: percent				
number (not applicable)				
CC - cEVR	71.4	90.5	85	60.9
CC - EDTR	81	95.2	100	65.2
CC - ETR	81	95.2	100	65.2
CC - SVR12	66.7	85.7	65	26.1
CC - SVR24	66.7	81	65	26.1
CT/TT - cEVR	42.7	54	71.9	28.7
CT/TT - EDTR	70.8	73.6	84.3	25.3
CT/TT - ETR	65.2	69	78.7	25.3
CT/TT - SVR12	37.1	43.7	65.2	11.5
CT/TT - SVR24	36	44.8	65.2	11.5

Notes:

[25] - FAS: n = 21, 89

[26] - FAS: n = 21, 87

[27] - FAS: n = 20, 89

[28] - FAS: n = 23, 87

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by cirrhosis or transition to cirrhosis

End point title	Percentage of participants who achieved virologic response by LOQ by cirrhosis or transition to cirrhosis[29]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

Notes:

[29] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[30]	108[31]	109[32]	110[33]
Units: percent				
number (not applicable)				
Cirrhosis or transition to cirrhosis - cEVR	40.7	57.1	60.9	20.7
Cirrhosis or transition to cirrhosis - EDTR	70.4	68.6	73.9	17.2
Cirrhosis or transition to cirrhosis - ETR	55.6	65.7	69.6	17.2
Cirrhosis or transition to cirrhosis - SVR12	33.3	40	52.2	0
Cirrhosis or transition to cirrhosis - SVR24	33.3	40	52.2	0
No cirrhosis or transition to cirrhosis - cEVR	51.2	64.3	78	39.2
No cirrhosis or transition to cirrhosis - EDTR	74.4	81.4	91.5	38
No cirrhosis or transition to cirrhosis - ETR	73.2	78.6	86.6	38
No cirrhosis or transition to cirrhosis - SVR12	46.3	58.6	68.3	20.3
No cirrhosis or transition to cirrhosis - SVR24	45.1	58.6	68.3	20.3

Notes:

[30] - FAS: n= 27, 82

[31] - FAS: n= 35, 70

[32] - FAS: n= 23, 82

[33] - FAS: n= 29, 79

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by HCV genotype 1 subtype

End point title	Percentage of participants who achieved virologic response by LOQ by HCV genotype 1 subtype[34]

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

End point type	Secondary

End point timeframe:

12 weeks post treatment

Notes:

[34] - 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: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

End point values	Arm A: DEB025 600 mg QD	Arm B: DEB 800 QD	Arm D DEB 400 BID	Arm C- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110[35]	108[36]	109[37]	110[38]
Units: percent				
number (not applicable)				
1a - cEVR	50	63	66.7	32.3
1a - EDTR	73.3	74.1	86.1	35.5
1a - ETR	73.3	66.7	77.8	35.5
1a - SVR12	46.7	59.3	55.6	12.9
1a - SVR24	46.7	59.3	55.6	12.9
1b - cEVR	47.5	60.5	78.1	36.7
1b - EDTR	72.5	79	87.7	32.9
1b - ETR	66.3	76.5	84.9	32.9
1b - SVR12	41.3	49.4	69.9	15.2
1b - SVR24	40	49.4	69.9	15.2

Notes:

[35] - FAS: n= 30, 80

[36] - FAS: n= 27, 81

[37] - FAS: n= 36, 73

[38] - FAS: n= 31, 79

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Arm A DEB 600 QD
Reporting group description: Arm A DEB 600 QD	
Reporting group title	Arm B DEB 800 QD
Reporting group description: Arm B DEB 800 QD	
Reporting group title	Arm C1 Placebo QD
Reporting group description: Arm C1 Placebo QD	
Reporting group title	Arm C2 Placebo BID
Reporting group description: Arm C2 Placebo BID	
Reporting group title	Arm C Placebo
Reporting group description: Arm C Placebo	
Reporting group title	Arm D DEB 400 BID
Reporting group description: Arm D DEB 400 BID	
Reporting group title	Total
Reporting group description: Total	

Serious adverse events	Arm A DEB 600 QD	Arm B DEB 800 QD	Arm C1 Placebo QD
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 120 (5.83%)	11 / 115 (9.57%)	5 / 59 (8.47%)
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)			
Malignant melanoma			

subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage I			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 120 (0.83%)	1 / 115 (0.87%)	0 / 59 (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
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Chest pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Pneumonitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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 distress			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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			
Disorientation			

subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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			
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Loss of consciousness			

subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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 / 120 (0.00%)	2 / 115 (1.74%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Diarrhoea			

subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Vomiting			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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 acute			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Cholelithiasis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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			

Psoriasis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Rash erythematous			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 120 (0.00%)	2 / 115 (1.74%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis viral			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Cystitis			

subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Ear infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Hepatitis C			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Orchitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Peritonitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 115 (0.87%)	0 / 59 (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
Pneumonia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 120 (0.83%)	0 / 115 (0.00%)	0 / 59 (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
Metabolism and nutrition disorders			
Hyperamylasaemia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipasaemia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 115 (0.00%)	0 / 59 (0.00%)
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	Arm C2 Placebo BID	Arm C Placebo	Arm D DEB 400 BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)	6 / 114 (5.26%)	18 / 108 (16.67%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	0 / 108 (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
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 distress			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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			
Supraventricular tachycardia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
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			
Dizziness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 55 (1.82%)	1 / 114 (0.88%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	0 / 108 (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
Neutropenia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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 erythematous			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	0 / 108 (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			
Renal failure			

subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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			
Appendicitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis viral			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Orchitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	3 / 108 (2.78%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	0 / 108 (0.00%)
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			
Hyperamylasaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipasaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 457 (9.19%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer stage I			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 457 (0.88%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	4 / 457 (0.88%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Drug interaction			

subjects affected / exposed	1 / 457 (0.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 457 (0.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 457 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 457 (0.44%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Endometriosis				
subjects affected / exposed	1 / 457 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 457 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 457 (0.44%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			

subjects affected / exposed	2 / 457 (0.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	2 / 457 (0.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 457 (0.66%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	3 / 457 (0.66%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholecystitis acute			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash erythematous			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 457 (0.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis viral			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis C			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orchitis			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			

subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 457 (0.88%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperamylasaemia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperlipasaemia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 457 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A DEB 600 QD	Arm B DEB 800 QD	Arm C1 Placebo QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 120 (96.67%)	108 / 115 (93.91%)	54 / 59 (91.53%)
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 120 (17.50%)	22 / 115 (19.13%)	0 / 59 (0.00%)
occurrences (all)	21	24	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 120 (15.83%)	30 / 115 (26.09%)	9 / 59 (15.25%)
occurrences (all)	19	31	11
Chest pain			
subjects affected / exposed	3 / 120 (2.50%)	4 / 115 (3.48%)	1 / 59 (1.69%)
occurrences (all)	3	4	1
Chills			
subjects affected / exposed	14 / 120 (11.67%)	13 / 115 (11.30%)	6 / 59 (10.17%)
occurrences (all)	19	15	7
Fatigue			
subjects affected / exposed	47 / 120 (39.17%)	45 / 115 (39.13%)	21 / 59 (35.59%)
occurrences (all)	53	48	23
Influenza like illness			
subjects affected / exposed	13 / 120 (10.83%)	10 / 115 (8.70%)	15 / 59 (25.42%)
occurrences (all)	18	11	18
Injection site erythema			
subjects affected / exposed	8 / 120 (6.67%)	11 / 115 (9.57%)	5 / 59 (8.47%)
occurrences (all)	8	13	5
Injection site rash			
subjects affected / exposed	1 / 120 (0.83%)	1 / 115 (0.87%)	4 / 59 (6.78%)
occurrences (all)	1	1	4
Irritability			
subjects affected / exposed	8 / 120 (6.67%)	7 / 115 (6.09%)	3 / 59 (5.08%)
occurrences (all)	8	7	3
Malaise			
subjects affected / exposed	9 / 120 (7.50%)	8 / 115 (6.96%)	1 / 59 (1.69%)
occurrences (all)	14	8	2
Pyrexia			

subjects affected / exposed	32 / 120 (26.67%)	34 / 115 (29.57%)	16 / 59 (27.12%)
occurrences (all)	48	48	20
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 120 (31.67%)	29 / 115 (25.22%)	17 / 59 (28.81%)
occurrences (all)	43	33	19
Dyspnoea			
subjects affected / exposed	21 / 120 (17.50%)	8 / 115 (6.96%)	6 / 59 (10.17%)
occurrences (all)	21	8	6
Dyspnoea exertional			
subjects affected / exposed	6 / 120 (5.00%)	9 / 115 (7.83%)	3 / 59 (5.08%)
occurrences (all)	9	11	3
Epistaxis			
subjects affected / exposed	5 / 120 (4.17%)	3 / 115 (2.61%)	3 / 59 (5.08%)
occurrences (all)	6	4	3
Oropharyngeal pain			
subjects affected / exposed	9 / 120 (7.50%)	8 / 115 (6.96%)	5 / 59 (8.47%)
occurrences (all)	11	9	6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 120 (15.83%)	8 / 115 (6.96%)	3 / 59 (5.08%)
occurrences (all)	19	8	3
Depression			
subjects affected / exposed	22 / 120 (18.33%)	14 / 115 (12.17%)	8 / 59 (13.56%)
occurrences (all)	24	14	10
Insomnia			
subjects affected / exposed	35 / 120 (29.17%)	24 / 115 (20.87%)	10 / 59 (16.95%)
occurrences (all)	45	25	10
Nervousness			
subjects affected / exposed	1 / 120 (0.83%)	1 / 115 (0.87%)	2 / 59 (3.39%)
occurrences (all)	1	1	2
Restlessness			
subjects affected / exposed	7 / 120 (5.83%)	4 / 115 (3.48%)	1 / 59 (1.69%)
occurrences (all)	10	5	1
Sleep disorder			

subjects affected / exposed	2 / 120 (1.67%)	4 / 115 (3.48%)	3 / 59 (5.08%)
occurrences (all)	2	4	3
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 120 (5.00%)	1 / 115 (0.87%)	0 / 59 (0.00%)
occurrences (all)	9	1	0
Lipase increased			
subjects affected / exposed	2 / 120 (1.67%)	1 / 115 (0.87%)	4 / 59 (6.78%)
occurrences (all)	3	1	4
Total bile acids increased			
subjects affected / exposed	5 / 120 (4.17%)	3 / 115 (2.61%)	1 / 59 (1.69%)
occurrences (all)	7	4	1
Weight decreased			
subjects affected / exposed	9 / 120 (7.50%)	9 / 115 (7.83%)	2 / 59 (3.39%)
occurrences (all)	10	9	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	11 / 120 (9.17%)	7 / 115 (6.09%)	3 / 59 (5.08%)
occurrences (all)	12	7	3
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	9 / 120 (7.50%)	10 / 115 (8.70%)	3 / 59 (5.08%)
occurrences (all)	10	10	3
Dizziness			
subjects affected / exposed	20 / 120 (16.67%)	22 / 115 (19.13%)	10 / 59 (16.95%)
occurrences (all)	27	30	12
Dysgeusia			
subjects affected / exposed	5 / 120 (4.17%)	7 / 115 (6.09%)	3 / 59 (5.08%)
occurrences (all)	5	7	3
Headache			
subjects affected / exposed	59 / 120 (49.17%)	47 / 115 (40.87%)	23 / 59 (38.98%)
occurrences (all)	92	69	30
Hypoaesthesia			
subjects affected / exposed	6 / 120 (5.00%)	2 / 115 (1.74%)	1 / 59 (1.69%)
occurrences (all)	7	2	1
Memory impairment			

subjects affected / exposed	5 / 120 (4.17%)	4 / 115 (3.48%)	2 / 59 (3.39%)
occurrences (all)	5	4	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 120 (40.83%)	41 / 115 (35.65%)	17 / 59 (28.81%)
occurrences (all)	79	63	24
Leukopenia			
subjects affected / exposed	17 / 120 (14.17%)	13 / 115 (11.30%)	7 / 59 (11.86%)
occurrences (all)	33	27	14
Lymphopenia			
subjects affected / exposed	5 / 120 (4.17%)	2 / 115 (1.74%)	3 / 59 (5.08%)
occurrences (all)	5	4	5
Neutropenia			
subjects affected / exposed	49 / 120 (40.83%)	40 / 115 (34.78%)	15 / 59 (25.42%)
occurrences (all)	88	72	25
Thrombocytopenia			
subjects affected / exposed	24 / 120 (20.00%)	19 / 115 (16.52%)	3 / 59 (5.08%)
occurrences (all)	39	28	4
Eye disorders			
Dry eye			
subjects affected / exposed	7 / 120 (5.83%)	7 / 115 (6.09%)	2 / 59 (3.39%)
occurrences (all)	7	7	2
Ocular icterus			
subjects affected / exposed	5 / 120 (4.17%)	8 / 115 (6.96%)	1 / 59 (1.69%)
occurrences (all)	8	13	1
Vision blurred			
subjects affected / exposed	4 / 120 (3.33%)	8 / 115 (6.96%)	1 / 59 (1.69%)
occurrences (all)	4	10	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 120 (1.67%)	5 / 115 (4.35%)	0 / 59 (0.00%)
occurrences (all)	3	6	0
Abdominal pain			
subjects affected / exposed	9 / 120 (7.50%)	7 / 115 (6.09%)	6 / 59 (10.17%)
occurrences (all)	9	9	6
Abdominal pain upper			

subjects affected / exposed	15 / 120 (12.50%)	8 / 115 (6.96%)	5 / 59 (8.47%)
occurrences (all)	15	9	5
Aphthous stomatitis			
subjects affected / exposed	6 / 120 (5.00%)	3 / 115 (2.61%)	3 / 59 (5.08%)
occurrences (all)	6	5	4
Cheilitis			
subjects affected / exposed	1 / 120 (0.83%)	6 / 115 (5.22%)	1 / 59 (1.69%)
occurrences (all)	1	7	1
Constipation			
subjects affected / exposed	10 / 120 (8.33%)	7 / 115 (6.09%)	1 / 59 (1.69%)
occurrences (all)	11	7	1
Diarrhoea			
subjects affected / exposed	19 / 120 (15.83%)	18 / 115 (15.65%)	8 / 59 (13.56%)
occurrences (all)	27	18	8
Dry mouth			
subjects affected / exposed	15 / 120 (12.50%)	10 / 115 (8.70%)	5 / 59 (8.47%)
occurrences (all)	17	11	5
Dyspepsia			
subjects affected / exposed	15 / 120 (12.50%)	4 / 115 (3.48%)	5 / 59 (8.47%)
occurrences (all)	18	4	6
Mouth ulceration			
subjects affected / exposed	7 / 120 (5.83%)	10 / 115 (8.70%)	2 / 59 (3.39%)
occurrences (all)	16	11	2
Nausea			
subjects affected / exposed	46 / 120 (38.33%)	35 / 115 (30.43%)	17 / 59 (28.81%)
occurrences (all)	57	55	22
Toothache			
subjects affected / exposed	3 / 120 (2.50%)	3 / 115 (2.61%)	3 / 59 (5.08%)
occurrences (all)	3	4	3
Vomiting			
subjects affected / exposed	19 / 120 (15.83%)	18 / 115 (15.65%)	4 / 59 (6.78%)
occurrences (all)	39	27	5
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	19 / 120 (15.83%)	14 / 115 (12.17%)	2 / 59 (3.39%)
occurrences (all)	25	16	2

Jaundice			
subjects affected / exposed	14 / 120 (11.67%)	11 / 115 (9.57%)	3 / 59 (5.08%)
occurrences (all)	17	12	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 120 (18.33%)	23 / 115 (20.00%)	6 / 59 (10.17%)
occurrences (all)	22	23	6
Dermatitis			
subjects affected / exposed	3 / 120 (2.50%)	2 / 115 (1.74%)	3 / 59 (5.08%)
occurrences (all)	4	2	3
Dry skin			
subjects affected / exposed	15 / 120 (12.50%)	16 / 115 (13.91%)	8 / 59 (13.56%)
occurrences (all)	20	17	8
Erythema			
subjects affected / exposed	6 / 120 (5.00%)	7 / 115 (6.09%)	0 / 59 (0.00%)
occurrences (all)	6	7	0
Hyperhidrosis			
subjects affected / exposed	2 / 120 (1.67%)	1 / 115 (0.87%)	4 / 59 (6.78%)
occurrences (all)	3	1	4
Pruritus			
subjects affected / exposed	36 / 120 (30.00%)	30 / 115 (26.09%)	20 / 59 (33.90%)
occurrences (all)	52	42	24
Rash			
subjects affected / exposed	23 / 120 (19.17%)	22 / 115 (19.13%)	14 / 59 (23.73%)
occurrences (all)	29	29	16
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	7 / 120 (5.83%)	6 / 115 (5.22%)	0 / 59 (0.00%)
occurrences (all)	7	7	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 120 (15.83%)	19 / 115 (16.52%)	7 / 59 (11.86%)
occurrences (all)	21	21	7
Back pain			
subjects affected / exposed	20 / 120 (16.67%)	5 / 115 (4.35%)	4 / 59 (6.78%)
occurrences (all)	24	5	4

Muscle spasms			
subjects affected / exposed	14 / 120 (11.67%)	12 / 115 (10.43%)	3 / 59 (5.08%)
occurrences (all)	15	14	4
Myalgia			
subjects affected / exposed	23 / 120 (19.17%)	21 / 115 (18.26%)	15 / 59 (25.42%)
occurrences (all)	29	28	16
Neck pain			
subjects affected / exposed	4 / 120 (3.33%)	1 / 115 (0.87%)	3 / 59 (5.08%)
occurrences (all)	4	1	3
Osteopenia			
subjects affected / exposed	5 / 120 (4.17%)	6 / 115 (5.22%)	0 / 59 (0.00%)
occurrences (all)	5	6	0
Pain in extremity			
subjects affected / exposed	7 / 120 (5.83%)	5 / 115 (4.35%)	2 / 59 (3.39%)
occurrences (all)	8	5	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 120 (5.00%)	5 / 115 (4.35%)	1 / 59 (1.69%)
occurrences (all)	7	5	1
Oral herpes			
subjects affected / exposed	4 / 120 (3.33%)	7 / 115 (6.09%)	2 / 59 (3.39%)
occurrences (all)	4	7	2
Pharyngitis			
subjects affected / exposed	4 / 120 (3.33%)	3 / 115 (2.61%)	2 / 59 (3.39%)
occurrences (all)	4	6	2
Upper respiratory tract infection			
subjects affected / exposed	12 / 120 (10.00%)	5 / 115 (4.35%)	2 / 59 (3.39%)
occurrences (all)	17	5	3
Urinary tract infection			
subjects affected / exposed	7 / 120 (5.83%)	2 / 115 (1.74%)	3 / 59 (5.08%)
occurrences (all)	9	2	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 120 (25.83%)	23 / 115 (20.00%)	8 / 59 (13.56%)
occurrences (all)	35	26	9
Hypertriglyceridaemia			

subjects affected / exposed	16 / 120 (13.33%)	21 / 115 (18.26%)	2 / 59 (3.39%)
occurrences (all)	19	22	2

Non-serious adverse events	Arm C2 Placebo BID	Arm C Placebo	Arm D DEB 400 BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 55 (90.91%)	104 / 114 (91.23%)	106 / 108 (98.15%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 55 (3.64%)	2 / 114 (1.75%)	28 / 108 (25.93%)
occurrences (all)	2	2	31
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 55 (21.82%)	21 / 114 (18.42%)	17 / 108 (15.74%)
occurrences (all)	13	24	18
Chest pain			
subjects affected / exposed	4 / 55 (7.27%)	5 / 114 (4.39%)	4 / 108 (3.70%)
occurrences (all)	4	5	4
Chills			
subjects affected / exposed	3 / 55 (5.45%)	9 / 114 (7.89%)	14 / 108 (12.96%)
occurrences (all)	4	11	18
Fatigue			
subjects affected / exposed	20 / 55 (36.36%)	41 / 114 (35.96%)	45 / 108 (41.67%)
occurrences (all)	24	47	50
Influenza like illness			
subjects affected / exposed	6 / 55 (10.91%)	21 / 114 (18.42%)	11 / 108 (10.19%)
occurrences (all)	6	24	14
Injection site erythema			
subjects affected / exposed	3 / 55 (5.45%)	8 / 114 (7.02%)	3 / 108 (2.78%)
occurrences (all)	3	8	4
Injection site rash			
subjects affected / exposed	1 / 55 (1.82%)	5 / 114 (4.39%)	0 / 108 (0.00%)
occurrences (all)	1	5	0
Irritability			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	6 / 108 (5.56%)
occurrences (all)	2	5	6
Malaise			

subjects affected / exposed	2 / 55 (3.64%)	3 / 114 (2.63%)	9 / 108 (8.33%)
occurrences (all)	4	6	12
Pyrexia			
subjects affected / exposed	16 / 55 (29.09%)	32 / 114 (28.07%)	28 / 108 (25.93%)
occurrences (all)	49	69	48
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 55 (21.82%)	29 / 114 (25.44%)	16 / 108 (14.81%)
occurrences (all)	13	32	18
Dyspnoea			
subjects affected / exposed	4 / 55 (7.27%)	10 / 114 (8.77%)	16 / 108 (14.81%)
occurrences (all)	4	10	17
Dyspnoea exertional			
subjects affected / exposed	4 / 55 (7.27%)	7 / 114 (6.14%)	8 / 108 (7.41%)
occurrences (all)	5	8	8
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)	3 / 114 (2.63%)	10 / 108 (9.26%)
occurrences (all)	0	3	13
Oropharyngeal pain			
subjects affected / exposed	3 / 55 (5.45%)	8 / 114 (7.02%)	8 / 108 (7.41%)
occurrences (all)	3	9	8
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 55 (5.45%)	6 / 114 (5.26%)	11 / 108 (10.19%)
occurrences (all)	3	6	12
Depression			
subjects affected / exposed	4 / 55 (7.27%)	12 / 114 (10.53%)	13 / 108 (12.04%)
occurrences (all)	4	14	14
Insomnia			
subjects affected / exposed	15 / 55 (27.27%)	25 / 114 (21.93%)	17 / 108 (15.74%)
occurrences (all)	19	29	22
Nervousness			
subjects affected / exposed	4 / 55 (7.27%)	6 / 114 (5.26%)	2 / 108 (1.85%)
occurrences (all)	4	6	2
Restlessness			

subjects affected / exposed	2 / 55 (3.64%)	3 / 114 (2.63%)	1 / 108 (0.93%)
occurrences (all)	2	3	1
Sleep disorder			
subjects affected / exposed	0 / 55 (0.00%)	3 / 114 (2.63%)	2 / 108 (1.85%)
occurrences (all)	0	3	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 55 (1.82%)	1 / 114 (0.88%)	3 / 108 (2.78%)
occurrences (all)	1	1	3
Lipase increased			
subjects affected / exposed	1 / 55 (1.82%)	5 / 114 (4.39%)	5 / 108 (4.63%)
occurrences (all)	2	6	6
Total bile acids increased			
subjects affected / exposed	1 / 55 (1.82%)	2 / 114 (1.75%)	8 / 108 (7.41%)
occurrences (all)	2	3	17
Weight decreased			
subjects affected / exposed	2 / 55 (3.64%)	4 / 114 (3.51%)	9 / 108 (8.33%)
occurrences (all)	2	4	10
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 55 (1.82%)	4 / 114 (3.51%)	2 / 108 (1.85%)
occurrences (all)	1	4	2
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	3 / 55 (5.45%)	6 / 114 (5.26%)	4 / 108 (3.70%)
occurrences (all)	3	6	5
Dizziness			
subjects affected / exposed	4 / 55 (7.27%)	14 / 114 (12.28%)	15 / 108 (13.89%)
occurrences (all)	5	17	18
Dysgeusia			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	9 / 108 (8.33%)
occurrences (all)	2	5	10
Headache			
subjects affected / exposed	18 / 55 (32.73%)	41 / 114 (35.96%)	38 / 108 (35.19%)
occurrences (all)	23	53	53
Hypoaesthesia			

subjects affected / exposed	1 / 55 (1.82%)	2 / 114 (1.75%)	2 / 108 (1.85%)
occurrences (all)	1	2	2
Memory impairment			
subjects affected / exposed	3 / 55 (5.45%)	5 / 114 (4.39%)	3 / 108 (2.78%)
occurrences (all)	3	5	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 55 (18.18%)	27 / 114 (23.68%)	51 / 108 (47.22%)
occurrences (all)	17	41	87
Leukopenia			
subjects affected / exposed	5 / 55 (9.09%)	12 / 114 (10.53%)	20 / 108 (18.52%)
occurrences (all)	5	19	50
Lymphopenia			
subjects affected / exposed	0 / 55 (0.00%)	3 / 114 (2.63%)	8 / 108 (7.41%)
occurrences (all)	0	5	21
Neutropenia			
subjects affected / exposed	12 / 55 (21.82%)	27 / 114 (23.68%)	46 / 108 (42.59%)
occurrences (all)	19	44	97
Thrombocytopenia			
subjects affected / exposed	1 / 55 (1.82%)	4 / 114 (3.51%)	28 / 108 (25.93%)
occurrences (all)	3	7	45
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 55 (0.00%)	2 / 114 (1.75%)	3 / 108 (2.78%)
occurrences (all)	0	2	3
Ocular icterus			
subjects affected / exposed	2 / 55 (3.64%)	3 / 114 (2.63%)	14 / 108 (12.96%)
occurrences (all)	4	5	18
Vision blurred			
subjects affected / exposed	0 / 55 (0.00%)	1 / 114 (0.88%)	3 / 108 (2.78%)
occurrences (all)	0	1	6
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 55 (1.82%)	1 / 114 (0.88%)	7 / 108 (6.48%)
occurrences (all)	1	1	8
Abdominal pain			

subjects affected / exposed	3 / 55 (5.45%)	9 / 114 (7.89%)	6 / 108 (5.56%)
occurrences (all)	3	9	6
Abdominal pain upper			
subjects affected / exposed	4 / 55 (7.27%)	9 / 114 (7.89%)	13 / 108 (12.04%)
occurrences (all)	5	10	15
Aphthous stomatitis			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	6 / 108 (5.56%)
occurrences (all)	2	6	9
Cheilitis			
subjects affected / exposed	1 / 55 (1.82%)	2 / 114 (1.75%)	3 / 108 (2.78%)
occurrences (all)	1	2	3
Constipation			
subjects affected / exposed	3 / 55 (5.45%)	4 / 114 (3.51%)	15 / 108 (13.89%)
occurrences (all)	3	4	16
Diarrhoea			
subjects affected / exposed	6 / 55 (10.91%)	14 / 114 (12.28%)	10 / 108 (9.26%)
occurrences (all)	7	15	13
Dry mouth			
subjects affected / exposed	6 / 55 (10.91%)	11 / 114 (9.65%)	10 / 108 (9.26%)
occurrences (all)	9	14	10
Dyspepsia			
subjects affected / exposed	2 / 55 (3.64%)	7 / 114 (6.14%)	15 / 108 (13.89%)
occurrences (all)	2	8	17
Mouth ulceration			
subjects affected / exposed	5 / 55 (9.09%)	7 / 114 (6.14%)	3 / 108 (2.78%)
occurrences (all)	5	7	3
Nausea			
subjects affected / exposed	12 / 55 (21.82%)	29 / 114 (25.44%)	51 / 108 (47.22%)
occurrences (all)	12	34	59
Toothache			
subjects affected / exposed	1 / 55 (1.82%)	4 / 114 (3.51%)	2 / 108 (1.85%)
occurrences (all)	2	5	2
Vomiting			
subjects affected / exposed	5 / 55 (9.09%)	9 / 114 (7.89%)	19 / 108 (17.59%)
occurrences (all)	7	12	32
Hepatobiliary disorders			

Hyperbilirubinaemia			
subjects affected / exposed	0 / 55 (0.00%)	2 / 114 (1.75%)	36 / 108 (33.33%)
occurrences (all)	0	2	56
Jaundice			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	18 / 108 (16.67%)
occurrences (all)	2	6	19
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 55 (9.09%)	11 / 114 (9.65%)	19 / 108 (17.59%)
occurrences (all)	5	11	19
Dermatitis			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	0 / 108 (0.00%)
occurrences (all)	4	7	0
Dry skin			
subjects affected / exposed	9 / 55 (16.36%)	17 / 114 (14.91%)	16 / 108 (14.81%)
occurrences (all)	9	17	16
Erythema			
subjects affected / exposed	0 / 55 (0.00%)	0 / 114 (0.00%)	5 / 108 (4.63%)
occurrences (all)	0	0	5
Hyperhidrosis			
subjects affected / exposed	2 / 55 (3.64%)	6 / 114 (5.26%)	3 / 108 (2.78%)
occurrences (all)	3	7	3
Pruritus			
subjects affected / exposed	12 / 55 (21.82%)	32 / 114 (28.07%)	32 / 108 (29.63%)
occurrences (all)	14	38	39
Rash			
subjects affected / exposed	6 / 55 (10.91%)	20 / 114 (17.54%)	17 / 108 (15.74%)
occurrences (all)	6	22	20
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 55 (5.45%)	3 / 114 (2.63%)	14 / 108 (12.96%)
occurrences (all)	3	3	15
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 55 (10.91%)	13 / 114 (11.40%)	9 / 108 (8.33%)
occurrences (all)	9	16	9

Back pain			
subjects affected / exposed	5 / 55 (9.09%)	9 / 114 (7.89%)	10 / 108 (9.26%)
occurrences (all)	5	9	15
Muscle spasms			
subjects affected / exposed	3 / 55 (5.45%)	6 / 114 (5.26%)	17 / 108 (15.74%)
occurrences (all)	4	8	24
Myalgia			
subjects affected / exposed	11 / 55 (20.00%)	26 / 114 (22.81%)	18 / 108 (16.67%)
occurrences (all)	16	32	20
Neck pain			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	3 / 108 (2.78%)
occurrences (all)	3	6	3
Osteopenia			
subjects affected / exposed	2 / 55 (3.64%)	2 / 114 (1.75%)	6 / 108 (5.56%)
occurrences (all)	2	2	6
Pain in extremity			
subjects affected / exposed	1 / 55 (1.82%)	3 / 114 (2.63%)	5 / 108 (4.63%)
occurrences (all)	2	4	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 55 (5.45%)	4 / 114 (3.51%)	4 / 108 (3.70%)
occurrences (all)	3	4	7
Oral herpes			
subjects affected / exposed	0 / 55 (0.00%)	2 / 114 (1.75%)	3 / 108 (2.78%)
occurrences (all)	0	2	3
Pharyngitis			
subjects affected / exposed	1 / 55 (1.82%)	3 / 114 (2.63%)	6 / 108 (5.56%)
occurrences (all)	1	3	6
Upper respiratory tract infection			
subjects affected / exposed	4 / 55 (7.27%)	6 / 114 (5.26%)	6 / 108 (5.56%)
occurrences (all)	4	7	6
Urinary tract infection			
subjects affected / exposed	2 / 55 (3.64%)	5 / 114 (4.39%)	9 / 108 (8.33%)
occurrences (all)	2	5	10
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	8 / 55 (14.55%)	16 / 114 (14.04%)	26 / 108 (24.07%)
occurrences (all)	8	17	26
Hypertriglyceridaemia			
subjects affected / exposed	2 / 55 (3.64%)	4 / 114 (3.51%)	18 / 108 (16.67%)
occurrences (all)	2	4	23

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	434 / 457 (94.97%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	73 / 457 (15.97%)		
occurrences (all)	78		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	87 / 457 (19.04%)		
occurrences (all)	92		
Chest pain			
subjects affected / exposed	16 / 457 (3.50%)		
occurrences (all)	16		
Chills			
subjects affected / exposed	50 / 457 (10.94%)		
occurrences (all)	63		
Fatigue			
subjects affected / exposed	178 / 457 (38.95%)		
occurrences (all)	198		
Influenza like illness			
subjects affected / exposed	55 / 457 (12.04%)		
occurrences (all)	67		
Injection site erythema			
subjects affected / exposed	30 / 457 (6.56%)		
occurrences (all)	33		
Injection site rash			
subjects affected / exposed	7 / 457 (1.53%)		
occurrences (all)	7		
Irritability			

subjects affected / exposed	26 / 457 (5.69%)		
occurrences (all)	26		
Malaise			
subjects affected / exposed	29 / 457 (6.35%)		
occurrences (all)	40		
Pyrexia			
subjects affected / exposed	126 / 457 (27.57%)		
occurrences (all)	213		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	112 / 457 (24.51%)		
occurrences (all)	126		
Dyspnoea			
subjects affected / exposed	55 / 457 (12.04%)		
occurrences (all)	56		
Dyspnoea exertional			
subjects affected / exposed	30 / 457 (6.56%)		
occurrences (all)	36		
Epistaxis			
subjects affected / exposed	21 / 457 (4.60%)		
occurrences (all)	26		
Oropharyngeal pain			
subjects affected / exposed	33 / 457 (7.22%)		
occurrences (all)	37		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	44 / 457 (9.63%)		
occurrences (all)	45		
Depression			
subjects affected / exposed	61 / 457 (13.35%)		
occurrences (all)	66		
Insomnia			
subjects affected / exposed	101 / 457 (22.10%)		
occurrences (all)	121		
Nervousness			

subjects affected / exposed	10 / 457 (2.19%)		
occurrences (all)	10		
Restlessness			
subjects affected / exposed	15 / 457 (3.28%)		
occurrences (all)	19		
Sleep disorder			
subjects affected / exposed	11 / 457 (2.41%)		
occurrences (all)	11		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 457 (2.41%)		
occurrences (all)	14		
Lipase increased			
subjects affected / exposed	13 / 457 (2.84%)		
occurrences (all)	16		
Total bile acids increased			
subjects affected / exposed	18 / 457 (3.94%)		
occurrences (all)	31		
Weight decreased			
subjects affected / exposed	31 / 457 (6.78%)		
occurrences (all)	33		
Cardiac disorders			
Palpitations			
subjects affected / exposed	24 / 457 (5.25%)		
occurrences (all)	25		
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	29 / 457 (6.35%)		
occurrences (all)	31		
Dizziness			
subjects affected / exposed	71 / 457 (15.54%)		
occurrences (all)	92		
Dysgeusia			
subjects affected / exposed	26 / 457 (5.69%)		
occurrences (all)	27		
Headache			

subjects affected / exposed	185 / 457 (40.48%)		
occurrences (all)	267		
Hypoaesthesia			
subjects affected / exposed	12 / 457 (2.63%)		
occurrences (all)	13		
Memory impairment			
subjects affected / exposed	17 / 457 (3.72%)		
occurrences (all)	18		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	168 / 457 (36.76%)		
occurrences (all)	270		
Leukopenia			
subjects affected / exposed	62 / 457 (13.57%)		
occurrences (all)	129		
Lymphopenia			
subjects affected / exposed	18 / 457 (3.94%)		
occurrences (all)	35		
Neutropenia			
subjects affected / exposed	162 / 457 (35.45%)		
occurrences (all)	301		
Thrombocytopenia			
subjects affected / exposed	75 / 457 (16.41%)		
occurrences (all)	119		
Eye disorders			
Dry eye			
subjects affected / exposed	19 / 457 (4.16%)		
occurrences (all)	19		
Ocular icterus			
subjects affected / exposed	30 / 457 (6.56%)		
occurrences (all)	44		
Vision blurred			
subjects affected / exposed	16 / 457 (3.50%)		
occurrences (all)	21		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	15 / 457 (3.28%)			
occurrences (all)	18			
Abdominal pain				
subjects affected / exposed	31 / 457 (6.78%)			
occurrences (all)	33			
Abdominal pain upper				
subjects affected / exposed	45 / 457 (9.85%)			
occurrences (all)	49			
Aphthous stomatitis				
subjects affected / exposed	20 / 457 (4.38%)			
occurrences (all)	26			
Cheilitis				
subjects affected / exposed	12 / 457 (2.63%)			
occurrences (all)	13			
Constipation				
subjects affected / exposed	36 / 457 (7.88%)			
occurrences (all)	38			
Diarrhoea				
subjects affected / exposed	61 / 457 (13.35%)			
occurrences (all)	73			
Dry mouth				
subjects affected / exposed	46 / 457 (10.07%)			
occurrences (all)	52			
Dyspepsia				
subjects affected / exposed	41 / 457 (8.97%)			
occurrences (all)	47			
Mouth ulceration				
subjects affected / exposed	27 / 457 (5.91%)			
occurrences (all)	37			
Nausea				
subjects affected / exposed	161 / 457 (35.23%)			
occurrences (all)	205			
Toothache				
subjects affected / exposed	12 / 457 (2.63%)			
occurrences (all)	14			

Vomiting subjects affected / exposed occurrences (all)	65 / 457 (14.22%) 110		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) Jaundice subjects affected / exposed occurrences (all)	 71 / 457 (15.54%) 99 48 / 457 (10.50%) 54		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dermatitis subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 75 / 457 (16.41%) 75 10 / 457 (2.19%) 13 64 / 457 (14.00%) 70 18 / 457 (3.94%) 18 12 / 457 (2.63%) 14 130 / 457 (28.45%) 171 82 / 457 (17.94%) 100		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 30 / 457 (6.56%) 32		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	60 / 457 (13.13%)		
occurrences (all)	67		
Back pain			
subjects affected / exposed	44 / 457 (9.63%)		
occurrences (all)	53		
Muscle spasms			
subjects affected / exposed	49 / 457 (10.72%)		
occurrences (all)	61		
Myalgia			
subjects affected / exposed	88 / 457 (19.26%)		
occurrences (all)	109		
Neck pain			
subjects affected / exposed	13 / 457 (2.84%)		
occurrences (all)	14		
Osteopenia			
subjects affected / exposed	19 / 457 (4.16%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	20 / 457 (4.38%)		
occurrences (all)	22		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 457 (4.16%)		
occurrences (all)	23		
Oral herpes			
subjects affected / exposed	16 / 457 (3.50%)		
occurrences (all)	16		
Pharyngitis			
subjects affected / exposed	16 / 457 (3.50%)		
occurrences (all)	19		
Upper respiratory tract infection			
subjects affected / exposed	29 / 457 (6.35%)		
occurrences (all)	35		
Urinary tract infection			

subjects affected / exposed occurrences (all)	23 / 457 (5.03%) 26		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all)	 96 / 457 (21.01%) 104 59 / 457 (12.91%) 68		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2010	The amendment introduced the following change(s): • Exclusion criteria were changed to make sure women of child-bearing potential used highly effective contraception i.e. total abstinence, sterilization, male partner sterilization, or a combination of two specified methods. • A rationale for birth control to be used in this study was added • Substrates of cytochrome P450 3A for which a clinically important drug-drug interactions with DEB025 could not be excluded because it was not yet investigated (e.g., hormonal contraceptives, etc.) had been added to the list of prohibited treatment
14 December 2010	The amendment introduced the following change(s): • Changes were made to the protocol in the inclusion of HCV genotype 1 patients that have relapsed after pegIFNα2a/RBV treatment, as well as the addition of a further treatment arm to allow 400mg BID treatment with the study medication. • inconsistencies and typos in the original protocol were corrected.
26 April 2012	The amendment introduced the following change(s): • Patients on treatment with DEB025/placebo in combination with pegIFNα2a /RBV had already been requested to immediately discontinue DEB025/placebo treatment. These patients were asked to continue their treatment with the combination of pegIFNα2a and RBV and to continue in the study as scheduled in the protocol in order to achieve SVR. • All patients were to receive an addendum to the Informed Consent Form they have already signed. The addendum provided the most recent safety information and all patients were expected to sign that they have received and understood the addendum. Investigators were previously sent a safety alert to discontinue patients from DEB025/placebo with triglyceride levels above 350 mg/dL. This alert meanwhile became redundant due to the discontinuation of DEB025/placebo in all patients. However, since patients were still treated with pegIFNα2a, it was recommended that the management of triglyceride levels should follow the ATPIII guideline (NIH 2001). • According to the requirements of the study protocol, all patients who were still on study treatment by 18-Apr-2012, had responded to treatment and had reached a viral load for HCV RNA < 25 IU/mL. • To better understand the benefit-risk profile for the patients, a second Interim Analysis was to be performed on Week 24 data. • Furthermore, investigators were to be unblinded to the HCV RNA data i.e. they would have access to all HCV RNA data from their patients. • End-of-treatment assessments were to be performed at the next visit after DEB025/placebo discontinuation, including bone density X-ray assessments.
14 August 2012	This amendment was a follow-up to the urgent safety Amendment 3, i.e. the termination of the DEB025/placebo treatment in all patients as a result of the partial clinical hold. As planned at the time protocol Amendment 3 was issued, the protocol sections which were affected were fully updated after the impact of these safety measures had been assessed in detail.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

18 April 2012	Upon request from the US FDA, the study design was modified to immediately discontinue DEB025/placebo treatment in all patients (urgent safety measure). Patients remained on pegIFNα2a/RBV treatment.	-

Notes:

Limitations and caveats

None reported