Clinical trial results:
A Phase 3 Study Evaluating the Safety and Efficacy of Lambda/Ribavirin/Daclatasvir in Subjects with Chronic HCV Infection and Underlying Hemophilia Who are Treatment Naive or are Prior Relapsers to Peginterferon Alfa-2a/Ribavirin

Summary

EudraCT number	2012-003463-22
Trial protocol	ES IT NL FR RO
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	23 April 2016
First version publication date	23 April 2016

Trial information

Trial identification

Sponsor protocol code	AI452-030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01741545
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium,
Public contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy and safety of peginterferon lambda-1a (pegIFNλ-1a referred to as Lambda) in combination with the direct-acting antiviral agent daclatasvir (DCV) and ribavirin (RBV) in hemophilia subjects with genotype (GT)-1b, -2, -3, or -4 chronic hepatitis C virus (HCV) infection.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	71
EEA total number of subjects	47

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)	69
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 centres in 8 countries.

Pre-assignment

Screening details:

A total of 71 subjects were enrolled, of which 51 subjects were randomised and treated.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding was performed as the study was open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A (Treatment period)

Arm description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Arm type	Experimental
Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered DCV 60 mg orally twice daily.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Ribasphere
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 ribavirin 200-mg tablets were administered twice daily for a total dose of 800 mg.

Investigational medicinal product name	Peginterferon lambda-1a
Investigational medicinal product code	BMS-914143
Other name	Lambda
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were administered 180 µg pegIFNα-2a subcutaneously.

Arm title	Cohort B (Treatment period)

Arm description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based

on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Arm type	Experimental
Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052-05
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered DCV 60 mg orally twice daily.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Ribasphere
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered ribavirin 200-mg tablets for a total daily dose stratified on body weight (<75kg=1000mg or>=75kg=1200 mg).

Investigational medicinal product name	Peginterferon lambda-1a
Investigational medicinal product code	BMS-914143
Other name	Lambda
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were administered 180 µg pegIFNα-2a subcutaneously.

Number of subjects in period 1[1]	Cohort A (Treatment period)	Cohort B (Treatment period)
Started	12	39
Completed	11	35
Not completed	1	4
Adverse event, non-fatal	1	3
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as out of 71 subjects only 51 were randomised and received treatment in the study.

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding was performed as the study was open-label study.

Arms

Are arms mutually exclusive?	Yes

Arm title	Cohort A (Follow-up period)

Arm description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Cohort B (Follow-up period)

Arm description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing >=75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Cohort A (Follow-up period)	Cohort B (Follow-up period)
Started	11	35
Completed	11	37
Not completed	1	2
Consent withdrawn by subject	1	1
Other reason	-	1
Joined	1	4
Rejoined for follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (Treatment period)
Reporting group description:	
Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.	
Reporting group title	Cohort B (Treatment period)
Reporting group description:	
Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.	

Reporting group values	Cohort A (Treatment period)	Cohort B (Treatment period)	Total
Number of subjects	12	39	51
Age categorical Units: Subjects			
21 - <65 years	12	38	50
>=65 years	0	1	1
Age continuous Units: years			
arithmetic mean	42.8	45.2	
standard deviation	± 9.94	± 12.04	-
Gender categorical Units: Subjects			
Male	12	39	51
HCV Genotype Units: Subjects			
Genotype 1A	0	0	0
Genotype 1B	0	39	39
Genotype 2	2	0	2
Genotype 3	10	0	10
Genotype 4	0	0	0

End points

End points reporting groups

Reporting group title	Cohort A (Treatment period)

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Reporting group title	Cohort B (Treatment period)

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/Ribavirin/Daclatasvir. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Reporting group title	Cohort A (Follow-up period)

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Reporting group title	Cohort B (Follow-up period)

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. Subjects were administered daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing >=75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Subject analysis set title	Cohort A (Treatment and Follow-up periods)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. During treatment period subjects received daclatasvir 60 mg orally, once daily; pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, orally, twice daily (a total 800 mg per day) for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Subject analysis set title	Cohort B (Treatment and Follow-up periods)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were followed up for 24 weeks who received treatment with Lambda/RBV/DCV. During treatment period subjects received daclatasvir 60 mg orally, once daily, pegIFNλ-1a 180 µg subcutaneous injection, once weekly and ribavirin tablets, twice daily, orally, based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing >=75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Primary: Percentage of Subjects Who Achieve Sustained Virologic Response (SVR12) at Follow-Up Week 12

End point title	Percentage of Subjects Who Achieve Sustained Virologic Response (SVR12) at Follow-Up Week 12[1]

End point description:

SVR12 was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target detected or target not detected at follow-up Week 12. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Primary

End point timeframe:

Follow-up Week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Cohort A (Follow-up period)	Cohort B (Follow-up period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	91.7 (61.5 to 99.8)	89.7 (75.8 to 97.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rapid Virologic Response (RVR)

End point title	Percentage of Subjects With Rapid Virologic Response (RVR)

End point description:

RVR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at Week 4. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

Week 4

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	91.7 (61.5 to 99.8)	76.9 (60.7 to 88.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects With Complete Early Virologic Response (cEVR)

End point title	Percentage of subjects With Complete Early Virologic Response (cEVR)

End point description:

cEVR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at Week 12. The analysis was performed in modified intent to treat population defined as

subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

Week 12

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	91.7 (61.5 to 99.8)	92.3 (79.1 to 98.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of the Treatment Response (EOTR)

End point title	Percentage of Subjects With End of the Treatment Response (EOTR)

End point description:

EOTR was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at end of treatment. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

End of the treatment (Week 24)

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	100 (73.5 to 100)	100 (91 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-Up Week 24 (SVR24)

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-Up Week 24 (SVR24)

End point description:

SVR24 was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target detected or target not detected at follow-up week 24. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

Follow-up Week 24 Follow-up

End point values	Cohort A (Follow-up period)	Cohort B (Follow-up period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	66.7 (34.9 to 90.1)	30.8 (17 to 47.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Cytopenic Abnormalities On-Treatment

End point title	Percentage of Subjects With Treatment-Emergent Cytopenic Abnormalities On-Treatment

End point description:

Cytopenic abnormalities were defined as anemia as defined by Hb <10 g/dL, and/or neutropenia as defined by ANC <750 mm^3, and/or thrombocytopenia as defined by platelets <50,000 mm^3. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

After Day 1 to end of treatment

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)	0 (0 to 26.5)	0 (0 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Flu-Like Symptoms and Musculoskeletal Symptoms On-Treatment

End point title	Percentage of Subjects With Flu-Like Symptoms and Musculoskeletal Symptoms On-Treatment

End point description:

Flu-like symptoms were defined as pyrexia or chills or pain. Musculoskeletal symptoms were defined as arthralgia or myalgia or back pain. The analysis was performed in modified intent to treat population defined as subjects meeting the response criteria over all treated subjects.

End point type	Secondary

End point timeframe:

Day 1 to end of treatment

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Percentage of subjects				
number (confidence interval 95%)				
Flu-like symptoms	8.3 (0.2 to 38.5)	12.8 (4.3 to 27.4)		
Musculoskeletal symptoms	0 (0 to 26.5)	15.4 (5.9 to 30.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), AEs Leading to Discontinuation, Dose Reductions, And Who Died

End point title	Percentage of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), AEs Leading to Discontinuation, Dose Reductions, And Who Died

End point description:

AE=any new untoward medical event or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event. Treatment-related SAE=possibly, probably, or certainly related to study drug. The analysis was performed on all treated subjects.

End point type	Secondary

End point timeframe:

From Day 1 to end of follow-up (maximum of 60 weeks for Cohort A and 72 weeks for Cohort B)

End point values	Cohort A (Treatment and Follow-up periods)	Cohort B (Treatment and Follow-up periods)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	39		
Units: Subjects				
AEs on treatment	10	38		
SAEs	0	4		
Death	0	0		
AE leading to discontinuation	1	3		
Dose reduction - Lambda	0	1		
Dose reduction - RBV	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

End point title	Number of Subjects With Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

End point description:

Laboratory abnormalities were determined and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. International Normalized Ratio (INR): >2.0*Upper limit of normal (ULN); Alanine aminotransferase (ALT) : >5*ULN; Aspartate aminotransferase (AST): >5*ULN; Prothrombin Time (PT): >1.50*ULN; Bilirubin (Total): >2.5*ULN; Triglycerides (fasting): >750 mg/dL. The analysis was performed on all treated subjects.

End point type	Secondary

End point timeframe:

After Day 1 to end of treatment

End point values	Cohort A (Treatment period)	Cohort B (Treatment period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	39		
Units: Subjects				
INR	0	1		
ALT	2	1		
AST	0	2		
PT	0	1		
Bilirubin	2	7		
Triglycerides	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After Day 1 to end of treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Cohort A (Treatment period)

Reporting group description:

Subjects with HCV GT-2 or GT-3 infection (Cohort A) were to be treated with Lambda/RBV/DCV. Subjects were administered with once daily DCV 60 mg orally, once weekly pegIFNλ-1a 180 µg SC injection and twice daily RBV a total 800 mg per day for 12 weeks treatment, 12 weeks and a maximum of 12 weeks, respectively.

Reporting group title	Cohort B (Treatment period)

Reporting group description:

Subjects with HCV GT-1b or GT-4 infection (Cohort B) were to be treated with Lambda/RBV/DCV. Subjects were administered with once daily DCV 60 mg orally, once weekly pegIFNλ-1a 180 µg SC injection and twice daily RBV based on weight (subjects weighing <75 kg = 1000 mg and subjects weighing ≥75 kg = 1200 mg per day) for 12 weeks treatment, 24 weeks and a maximum of 24 weeks, respectively.

Serious adverse events	Cohort A (Treatment period)	Cohort B (Treatment period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 12 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 12 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A (Treatment period)	Cohort B (Treatment period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	36 / 39 (92.31%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	12 / 39 (30.77%)	
occurrences (all)	0	13	
Fatigue			
subjects affected / exposed	3 / 12 (25.00%)	9 / 39 (23.08%)	
occurrences (all)	3	9	
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	5 / 39 (12.82%)	
occurrences (all)	1	6	
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			

subjects affected / exposed	3 / 12 (25.00%)	13 / 39 (33.33%)	
occurrences (all)	3	16	
Sleep disorder			
subjects affected / exposed	1 / 12 (8.33%)	5 / 39 (12.82%)	
occurrences (all)	1	5	
Affect lability			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Anger			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Irritability			
subjects affected / exposed	2 / 12 (16.67%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Initial insomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 12 (16.67%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 39 (2.56%)	
occurrences (all)	1	3	

Blood bicarbonate decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	7 / 39 (17.95%)	
occurrences (all)	1	14	
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Disturbance in attention			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	8 / 39 (20.51%)	
occurrences (all)	3	9	
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	6 / 39 (15.38%)	
occurrences (all)	0	6	
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 39 (5.13%)	
occurrences (all)	1	2	

Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	7 / 39 (17.95%)	
occurrences (all)	1	7	
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	4 / 39 (10.26%)	
occurrences (all)	0	5	
Rash			
subjects affected / exposed	1 / 12 (8.33%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	2 / 12 (16.67%)	4 / 39 (10.26%)	
occurrences (all)	2	4	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 39 (10.26%)	
occurrences (all)	0	4	
Haemarthrosis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	5 / 39 (12.82%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	Removed GT-1a subjects from being eligible to participate in the trial.
19 July 2013	Updated to exclude cirrhotic subjects who have evidence of preexisting portal hypertension.
24 October 2013	Updated to include severe hemophiliacs, change in Medical Monitor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported