Clinical trial results:
A Multicenter, Open-Label, Phase 2b Pilot Study to Evaluate the Efficacy and Safety of Quadruple Therapy (VX-222, Telaprevir, Peginterferon-Alfa-2 and Ribavirin) in Subjects With Genotype 1 Chronic Hepatitis C With Compensated Cirrhosis

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-004150-26
Trial protocol	DE GB PL
Global end of trial date	06 February 2014

Results information

Result version number	v2 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Address EudraCT system related issues identified through full data set Quality check review

Trial information

Trial identification

Sponsor protocol code	VX11-222-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01516918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.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	27 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antiviral efficacy of a quadruple drug regimen (VX-222, telaprevir, pegylated interferon [Peg IFN], and ribavirin [RBV]) in subjects with Genotype 1 chronic hepatitis C (CHC), with compensated cirrhosis, who are treatment naïve or were non-responders (partial or null) or relapsers to previous Peg IFN/RBV therapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	92
EEA total number of subjects	31

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)	85
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at a total of 35 sites in the US (24 sites), Canada (1 site), Germany (6 sites), Poland (2 sites), and United Kingdom (2 sites).

Pre-assignment

Screening details:

A total of 92 subjects were enrolled in the quadruple regimen and received at least 1 dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Quadruple Regimen - All Subjects

Arm description:

All subjects received active study drugs (quadruple regimen: VX-222, telaprevir,Peg-IFN, and RBV) for a fixed treatment duration of 24 weeks.

Arm type	Experimental
Investigational medicinal product name	VX-222
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 milligram (mg) twice daily in fed state.

Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	Incivek, VX-950, Incivo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1125 mg twice daily in fed state.

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

Dosage and administration details:

1000 mg per day for subjects weighing less than (<) 75 kilogram (kg) and 1200 mg per day for subjects weighing greater than equal to (>=)75 kg, divided in 2 doses.

Investigational medicinal product name	Pegylated Interferon-Alfa-2a
Investigational medicinal product code	
Other name	Pegasys, Peg-IFN-alfa-2a
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 micrograms (mcg) once weekly.

Number of subjects in period 1	Quadruple Regimen - All Subjects
Started	92
Completed	77
Not completed	15
Other Non-Compliance	1
Death	1
Study Terminated by Sponsor	8
Adverse Events	3
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	92	92	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	55.6		
standard deviation	± 7.98	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	63	63	

Subject analysis sets

Subject analysis set title	Treatment Naive
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with Genotype 1 CHC, with compensated cirrhosis, who were treatment naïve.

Subject analysis set title	Prior Nonresponder
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior nonresponders (that is, who received prior HCV treatment with Peg-IFN/RBV and experienced partial response [had >=2-log drop in HCV RNA at Week 12 of previous therapy but never achieved undetectable HCV RNA levels while on treatment] or who experienced null response (that is had <2-log decline in HCV RNA at Week 12 of therapy].

Subject analysis set title	Prior Relapser
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior relapsers (that is, received prior HCV treatment with Peg-IFN/RBV, had undetectable HCV RNA at the end of treatment, but who subsequently had detectable HCV RNA).

Reporting group values	Treatment Naive	Prior Nonresponder	Prior Relapser
Number of subjects	9	76	7
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.6	55.2	62.6
standard deviation	± 5.98	± 8.11	± 5.41

Gender categorical Units: Subjects			
Female	4	24	1
Male	5	52	6

End points

End points reporting groups

Reporting group title	Quadruple Regimen - All Subjects
Reporting group description:	
All subjects received active study drugs (quadruple regimen: VX-222, telaprevir,Peg-IFN, and RBV) for a fixed treatment duration of 24 weeks.	
Subject analysis set title	Treatment Naive
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were treatment naïve.	
Subject analysis set title	Prior Nonresponder
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior nonresponders (that is, who received prior HCV treatment with Peg-IFN/RBV and experienced partial response [had >=2-log drop in HCV RNA at Week 12 of previous therapy but never achieved undetectable HCV RNA levels while on treatment] or who experienced null response (that is had <2-log decline in HCV RNA at Week 12 of therapy].	
Subject analysis set title	Prior Relapser
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior relapsers (that is, received prior HCV treatment with Peg-IFN/RBV, had undetectable HCV RNA at the end of treatment, but who subsequently had detectable HCV RNA).	

Primary: Percentage of Subjects With Sustained Viral Response 12 Weeks After Last Planned Dose of Study Drug (SVR12)

End point title	Percentage of Subjects With Sustained Viral Response 12 Weeks After Last Planned Dose of Study Drug (SVR12)[1]
End point description:	
SVR12 was defined as Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) Levels below (<) the lower limit of quantification (LLOQ) at 12 weeks after last planned dose of study drug. The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The lower limit of quantification was 25 international units per milliliter (IU/mL). Full analysis set included all subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
12 weeks after last planned dose of study drug (Week 36)	

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: No inferential statistics were planned for this study.

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (29.9 to 92.5)	69.7 (58.1 to 79.8)	100 (59 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Safety set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	Quadruple Regimen - All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (not applicable)				
Subjects with any AEs	98.9			
Subjects with SAEs	15.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Viral Response 24 Weeks After Last Planned Dose of Study Drug (SVR 24)

End point title	Percentage of Subjects With Sustained Viral Response 24 Weeks After Last Planned Dose of Study Drug (SVR 24)

End point description:

SVR24 was defined as HCV RNA Levels < LLOQ at 24 weeks after last planned dose of study drug. The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The LLOQ was 25 IU/mL. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

24 weeks after last planned dose of study drug (Week 48)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (29.9 to 92.5)	67.1 (55.4 to 77.5)	100 (59 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HCV RNA Level <LLOQ at Planned End of Treatment (EOT)

End point title	Percentage of Subjects With HCV RNA Level <LLOQ at Planned End of Treatment (EOT)

End point description:

The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The LLOQ was 25 IU/mL. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

EOT (Week 24)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (confidence interval 95%)	100 (66.4 to 100)	82.9 (72.5 to 90.6)	100 (59 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Undetectable HCV RNA at Week, 2, 4, 8, 12, and 24

End point title	Percentage of Subjects with Undetectable HCV RNA at Week, 2, 4, 8, 12, and 24

End point description:

The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The limit of detection was 10 IU/mL. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 2, 4, 8, 12 and 24

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (not applicable)				
Week 2	0	21.1	28.6	
Week 4	77.8	72.4	85.7	
Week 8	100	85.5	100	
Week 12	100	84.2	100	
Week 24	100	72.4	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With On Treatment Virologic Failure

End point title	Percentage of Subjects With On Treatment Virologic Failure

End point description:

On treatment virologic failure was defined as meeting any futility rule or completing assigned treatment duration and having detectable HCV RNA at EOT. The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The LLOQ was 25 IU/mL. Futility rules: 1) HCV RNA levels >1000 IU/mL on Weeks 4 through 12; and 2) HCV RNA levels >LLOQ (repeated within 2 weeks to confirm detectability) after Week 12 through EOT (up to Week 24). Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to EOT (Week 24)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (not applicable)	0	7.9	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Relapse

End point title	Percentage of Subjects With Relapse

End point description:

Relapse was defined as having HCV RNA level <LLOQ at EOT followed by HCV RNA level >=LLOQ during follow-up. The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The LLOQ was 25 IU/mL. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to 24 weeks after last planned dose (up to Week 48)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	76	7	
Units: percentage of subjects				
number (not applicable)	33.3	15.9	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with SVR12 by IL-28B Genotype

End point title	Percentage of Subjects with SVR12 by IL-28B Genotype

End point description:

SVR12 was defined as HCV RNA Levels <LLOQ at 12 weeks after last planned dose of study drug. The plasma HCV RNA level was measured using Roche TaqMan HCV RNA assay. The LLOQ was 25 IU/mL. Data for this endpoint was not collected as the endpoint was omitted as per the ICH Harmonized Tripartite Guideline "Structure and Content of Clinical Study Reports: E3" and FDA Guidance Document "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications.

End point type	Secondary

End point timeframe:

12 weeks after last planned dose of study drug (Week 36)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - The endpoint was omitted as specified in endpoint description.

[3] - The endpoint was omitted as specified in endpoint description.

[4] - The endpoint was omitted as specified in endpoint description.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Telaprevir Resistant HCV Variant at Non-Structural Viral Protein 3-4A (NS3-4A) Region

End point title	Number of Participants With Telaprevir Resistant HCV Variant at Non-Structural Viral Protein 3-4A (NS3-4A) Region

End point description:

Sequence analysis of the HCV NS3-4A region was to be performed to monitor telaprevir-resistant variants. HCV RNA was isolated from the plasma, amplified by reverse transcription-polymerase chain reaction (RT-PCR), and sequenced (sequencing assay limit of detection HCV RNA >=1000 IU/mL). Data for this endpoint was not collected as the endpoint was omitted as per the ICH Harmonized Tripartite Guideline "Structure and Content of Clinical Study Reports: E3" and FDA Guidance Document "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications.

End point type	Secondary

End point timeframe:

up to 24 weeks after last planned dose (up to Week 48)

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: subjects				

Notes:

[5] - The endpoint was omitted, as specified in endpoint description.

[6] - The endpoint was omitted, as specified in endpoint description.

[7] - The endpoint was omitted, as specified in endpoint description.

Statistical analyses

No statistical analyses for this end point

Secondary: VX-222, Telaprevir, and RBV Plasma Concentrations And Peg-IFN Serum Concentration

End point title	VX-222, Telaprevir, and RBV Plasma Concentrations And Peg-IFN Serum Concentration

End point description:

Data for this endpoint was not collected as the endpoint was omitted as per the ICH Harmonized Tripartite Guideline "Structure and Content of Clinical Study Reports: E3" and FDA Guidance Document "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications.

End point type	Secondary

End point timeframe:

A single blood sample at Day 1 (pre-dose), Week 2, and 8; 3 blood samples at Week 1, 4, and 12

End point values	Treatment Naive	Prior Nonresponder	Prior Relapser	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[8] - The endpoint was omitted, as specified in endpoint description.

[9] - The endpoint was omitted, as specified in endpoint description.

[10] - The endpoint was omitted, as specified in endpoint description.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Treatment Naive
Reporting group description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were treatment naïve.	
Reporting group title	Prior Relapser
Reporting group description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior relapsers (that is, received prior HCV treatment with Peg-IFN/RBV, had undetectable HCV RNA at the end of treatment, but who subsequently had detectable HCV RNA).	
Reporting group title	Prior Nonresponder
Reporting group description:	
Subjects with Genotype 1 CHC, with compensated cirrhosis, who were prior nonresponders (that is, who received prior HCV treatment with Peg-IFN/RBV and experienced partial response [had >=2-log drop in HCV RNA at Week 12 of previous therapy but never achieved undetectable HCV RNA levels while on treatment] or who experienced null response (that is had <2-log decline in HCV RNA at Week 12 of therapy].	

Serious adverse events	Treatment Naive	Prior Relapser	Prior Nonresponder
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	13 / 76 (17.11%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Lipase increased			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
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			
Acetabulum fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Vocal cord leukoplakia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment Naive	Prior Relapser	Prior Nonresponder
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	7 / 7 (100.00%)	75 / 76 (98.68%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Raynaud's phenomenon			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Venous thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	5 / 9 (55.56%)	6 / 7 (85.71%)	37 / 76 (48.68%)
occurrences (all)	5	6	42
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	3 / 7 (42.86%)	21 / 76 (27.63%)
occurrences (all)	2	4	24
Chills			
subjects affected / exposed	1 / 9 (11.11%)	3 / 7 (42.86%)	12 / 76 (15.79%)
occurrences (all)	1	3	13
Influenza like illness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	15 / 76 (19.74%)
occurrences (all)	1	0	17
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	14 / 76 (18.42%)
occurrences (all)	0	1	17
Irritability			
subjects affected / exposed	2 / 9 (22.22%)	2 / 7 (28.57%)	5 / 76 (6.58%)
occurrences (all)	2	2	5
Pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	4 / 76 (5.26%)
occurrences (all)	1	2	4
Injection site erythema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	4
Malaise			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	1 / 76 (1.32%)
occurrences (all)	1	2	1
Injection site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences (all)	0	1	1
Feeling abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2

Local swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Temperature intolerance			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Early satiety			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injection site discolouration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injection site irritation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injection site pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Sluggishness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Genital rash			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Genital tract inflammation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 9 (33.33%)	2 / 7 (28.57%)	17 / 76 (22.37%)
occurrences (all)	3	2	17
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 7 (28.57%)	12 / 76 (15.79%)
occurrences (all)	0	3	13
Dyspnoea exertional			
subjects affected / exposed	0 / 9 (0.00%)	2 / 7 (28.57%)	12 / 76 (15.79%)
occurrences (all)	0	2	12
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	5
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	5
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Nasal dryness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences (all)	0	1	1
Dry throat			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Increased upper airway secretion			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Nasal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Tachypnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	14 / 76 (18.42%)
occurrences (all)	1	2	15
Depression			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	4 / 76 (5.26%)
occurrences (all)	2	2	4
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	4 / 76 (5.26%)
occurrences (all)	1	1	4
Depressed mood			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	5 / 76 (6.58%)
occurrences (all)	0	1	5

Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Anger			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Mood altered			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Abnormal dreams			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	2
Frustration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Impatience			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Initial insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Libido decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Loss of libido			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Mood swings			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1

Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	3 / 76 (3.95%)
occurrences (all)	1	1	4
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	3 / 76 (3.95%)
occurrences (all)	0	1	3
Blood uric acid increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Haemoglobin decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	5
Liver palpable subcostal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences (all)	0	1	1
Weight increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Blood albumin decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Blood pressure systolic increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Chest X-ray abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Pancreatic enzymes increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Laceration			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Lip injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Procedural site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Cardiovascular insufficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 9 (44.44%)	1 / 7 (14.29%)	23 / 76 (30.26%)
occurrences (all)	4	1	26
Dizziness			

subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	6 / 76 (7.89%)
occurrences (all)	2	4	7
Dysgeusia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	8 / 76 (10.53%)
occurrences (all)	1	0	10
Memory impairment			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	2 / 76 (2.63%)
occurrences (all)	1	1	2
Disturbance in attention			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Migraine			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Sinus headache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Ageusia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Burning sensation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hyperaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Resting tremor			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	2
Restless legs syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 9 (44.44%)	3 / 7 (42.86%)	26 / 76 (34.21%)
occurrences (all)	5	3	29
Neutropenia			
subjects affected / exposed	3 / 9 (33.33%)	0 / 7 (0.00%)	14 / 76 (18.42%)
occurrences (all)	5	0	21
Thrombocytopenia			
subjects affected / exposed	4 / 9 (44.44%)	0 / 7 (0.00%)	11 / 76 (14.47%)
occurrences (all)	4	0	15
Leukopenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	3
Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Vertigo			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	5
Dry eye			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	4
Chalazion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Conjunctivitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Eye inflammation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Keratitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Lenticular opacities			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Uveitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Vitreous degeneration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	5 / 9 (55.56%)	4 / 7 (57.14%)	36 / 76 (47.37%)
occurrences (all)	6	6	42
Nausea			
subjects affected / exposed	4 / 9 (44.44%)	4 / 7 (57.14%)	31 / 76 (40.79%)
occurrences (all)	5	5	31
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	3 / 7 (42.86%)	19 / 76 (25.00%)
occurrences (all)	1	4	23
Anorectal discomfort			
subjects affected / exposed	4 / 9 (44.44%)	1 / 7 (14.29%)	13 / 76 (17.11%)
occurrences (all)	4	1	14
Anal pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	16 / 76 (21.05%)
occurrences (all)	1	0	18
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	6 / 76 (7.89%)
occurrences (all)	0	0	7
Dry mouth			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	5
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	4 / 76 (5.26%)
occurrences (all)	0	1	4
Frequent bowel movements			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	4
Haemorrhoids			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	5
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	4
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	2	0	3
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	4
Proctalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	3 / 76 (3.95%)
occurrences (all)	0	1	3
Abdominal discomfort			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences (all)	1	1	1
Cheilitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Toothache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	2
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Rectal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	2
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Abdominal rigidity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Defaecation urgency			

subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Faeces pale			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gastric ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gingival inflammation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Oral discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Oral mucosal erythema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tongue coated			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hepatobiliary disorders			

Hyperbilirubinaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	5
Jaundice			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Cholelithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 9 (33.33%)	3 / 7 (42.86%)	25 / 76 (32.89%)
occurrences (all)	5	4	32
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	23 / 76 (30.26%)
occurrences (all)	1	2	24
Dry skin			
subjects affected / exposed	3 / 9 (33.33%)	0 / 7 (0.00%)	12 / 76 (15.79%)
occurrences (all)	3	0	12
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	9 / 76 (11.84%)
occurrences (all)	0	0	10
Pruritus generalised			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	1	0	4
Skin lesion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	2	0	3
Eczema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	5
Rash pruritic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	2 / 76 (2.63%)
occurrences (all)	0	2	2
Acne			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Petechiae			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Photosensitivity reaction			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Neurodermatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Rash erythematous			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Skin exfoliation			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	3	0	1
Leukocyturia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 7 (14.29%)	14 / 76 (18.42%)
occurrences (all)	2	1	15
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	13 / 76 (17.11%)
occurrences (all)	2	2	14
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	5
Joint swelling			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	1 / 76 (1.32%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Joint warmth			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	4
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	3 / 76 (3.95%)
occurrences (all)	2	1	3
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	3
Otitis externa			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Abdominal abscess			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0

Anal abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Eczema infected			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gingival abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Gingival infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Injection site infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1

Pharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Subcutaneous abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Vaginitis bacterial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	3 / 7 (42.86%)	15 / 76 (19.74%)
occurrences (all)	1	3	15
Hyperuricaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	6
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	4
Hypokalaemia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	0	4
Fluid retention			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hyperlipidaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 7 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2012	Updated inclusion exclusion criteria.
10 April 2012	Updated inclusion exclusion criteria.
05 June 2012	This amendment involved modifying the study design, such that all subjects newly-enrolled under this version of the protocol received VX-222 combined with telaprevir, Peg-IFN, and RBV, for a total treatment duration of 24 weeks (all active drug). In addition, the response-guided treatment requirements were removed from the quadruple regimen, as current thought has shifted to making regimens as simple as possible for ease of compliance, and a quadruple regimen of 24 weeks is predicted to be as effective as a 48-week regimen. No further enrollment to be made into the VX-222-placebo, telaprevir, Peg-IFN, and RBV regimen, as this arm was no longer considered to be required for this Phase 2b pilot study, and its removal allowed all newly-enrolled subjects to receive a simplified, shortened duration regimen of active VX-222 combined with telaprevir, Peg-IFN and RBV for 24 weeks in this difficult-to-treat population. Title was modified to reflect the new study design for ongoing enrollment. Because the aforementioned changes result in this study now being an open-label study, safety monitoring by an independent data monitoring committee (DMC) is no longer necessary. Vertex personnel monitored for safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported