Clinical trial results:
Long-Term Follow-Up of Subjects in a Phase 1, 2, or 3 Clinical Trial in Which Boceprevir or Narlaprevir was Administered for the Treatment of Chronic Hepatitis C

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

Summary

EudraCT number	2006-006529-25
Trial protocol	FR DE ES IT NL PT
Global end of trial date	13 October 2014

Results information

Result version number	v1 (current)
This version publication date	30 January 2016
First version publication date	30 January 2016

Trial information

Trial identification

Sponsor protocol code	P05063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00689390
WHO universal trial number (UTN)	-
Other trial identifiers	MK-3034-021: Merck Registration Number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	13 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2014
Global end of trial reached?	Yes
Global end of trial date	13 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Study P05063 is a 3-year long-term follow-up (LTFU) study in participants previously treated with boceprevir (BOC) or narlaprevir (NAR) in a Phase 1, 2, or 3 clinical study. Participants will be followed for up to 3.5 years after the end of their participation in the treatment protocol to document maintenance of the antiviral response (for sustained responders) and to characterize the long-term safety after use of this therapeutic regimen. LTFU procedures include collection of plasma samples for measuring Hepatitis C Virus ribonucleic acid (HCV-RNA) by polymerase chain reaction (PCR) and HCV sequence analysis. No drug therapy will be administered as part of this study.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2007
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	Argentina: 24
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 91
Country: Number of subjects enrolled	France: 146
Country: Number of subjects enrolled	Germany: 103
Country: Number of subjects enrolled	Italy: 102
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	United States: 1369
Country: Number of subjects enrolled	Portugal: 5
Worldwide total number of subjects	1954
EEA total number of subjects	467

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)	1871
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 9 boceprevir studies (P03523 [NCT00423670], P03659 [NCT00160251], P04487 [No NCT], P05101 [NCT00708500], P05216 [NCT00705432], P05411 [NCT00959699], P05514 [NCT00910624], P05685 [NCT00845065], and P06086 [NCT01023035]) and 1 narlaprevir study (P05104 [NCT00797745]).

Pre-assignment

Screening details:

1954 participants enrolled in this long-term follow-up (LTFU) study, with 1907 participants from 9 boceprevir studies and 47 participants from 1 narlaprevir study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Participants from Boceprevir Studies

Arm description:

Participants who previously participated in treatment studies in which boceprevir was administered were subsequently enrolled in Part 1 of the current follow-up study P05063 (NCT00689390). Participants may have received boceprevir or control peginterferon plus ribavirin (PR) in the previous treatment study. No treatment was administered in the current follow-up study.

Arm type	Follow-up
Investigational medicinal product name	Boceprevir
Investigational medicinal product code	
Other name	VICTRELIS®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In previous treatment studies, boceprevir was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

Investigational medicinal product name	Peginterferon alfa-2b
Investigational medicinal product code	
Other name	PEG-Intron®, SCH 054031
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In previous treatment studies, peginterferon alfa-2b was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

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

Dosage and administration details:

In previous treatment studies, ribavirin was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

Arm title	Participants from Narlaprevir Studies

Arm description:

Participants who previously participated in treatment studies in which narlaprevir was administered were subsequently enrolled in Part 2 of the current follow-up study P05063 (NCT00689390). Participants may have received narlaprevir or control PR in the previous treatment study. No treatment was administered in the current follow-up study.

Arm type	Follow-up
Investigational medicinal product name	Narlaprevir
Investigational medicinal product code	
Other name	SCH 900518, MK-8515
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In previous treatment studies, narlaprevir was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

Investigational medicinal product name	Peginterferon alfa-2b
Investigational medicinal product code	
Other name	PEG-Intron®, SCH 054031
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In previous treatment studies, peginterferon alfa-2b was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

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

Dosage and administration details:

In previous treatment studies, ribavirin was administered as specified by the protocol. No treatment was administered in the current follow-up study (P05063, NCT00689390, 2006-006529-25).

Number of subjects in period 1	Participants from Boceprevir Studies	Participants from Narlaprevir Studies
Started	1907	47
Completed	1481	37
Not completed	426	10
Adverse event, serious fatal	14	-
Consent withdrawn by subject	117	3
Administrative	37	-
Adverse event, non-fatal	5	-
Did Not Meet Protocol Eligibility	1	-
Non-Compliance With Protocol	21	-
Lost to follow-up	179	7
Withdrew Consent-Retreatment Opportunity	52	-

Baseline characteristics

Reporting groups	
Reporting group title	Participants from Boceprevir Studies
Reporting group description:	
Participants who previously participated in treatment studies in which boceprevir was administered were subsequently enrolled in Part 1 of the current follow-up study P05063 (NCT00689390). Participants may have received boceprevir or control peginterferon plus ribavirin (PR) in the previous treatment study. No treatment was administered in the current follow-up study.	
Reporting group title	Participants from Narlaprevir Studies
Reporting group description:	
Participants who previously participated in treatment studies in which narlaprevir was administered were subsequently enrolled in Part 2 of the current follow-up study P05063 (NCT00689390). Participants may have received narlaprevir or control PR in the previous treatment study. No treatment was administered in the current follow-up study.	

Reporting group values	Participants from Boceprevir Studies	Participants from Narlaprevir Studies	Total
Number of subjects	1907	47	1954
Age categorical Units: Subjects			
<40 years	173	5	178
40 to <65 years	1651	42	1693
≥65 years	83	0	83
Gender, Male/Female Units: participants			
Female	785	19	804
Male	1122	28	1150

End points reporting groups

Reporting group title	Participants from Boceprevir Studies

Reporting group description:

Participants who previously participated in treatment studies in which boceprevir was administered were subsequently enrolled in Part 1 of the current follow-up study P05063 (NCT00689390). Participants may have received boceprevir or control peginterferon plus ribavirin (PR) in the previous treatment study. No treatment was administered in the current follow-up study.

Reporting group title	Participants from Narlaprevir Studies

Reporting group description:

Participants who previously participated in treatment studies in which narlaprevir was administered were subsequently enrolled in Part 2 of the current follow-up study P05063 (NCT00689390). Participants may have received narlaprevir or control PR in the previous treatment study. No treatment was administered in the current follow-up study.

Subject analysis set title	Previous SVR on Boceprevir + PR
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who previously received boceprevir plus PR in treatment studies and achieved sustained virologic response (SVR). No treatment was administered in the current follow-up study.

Subject analysis set title	Previous SVR on Narlaprevir + PR
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who previously received narlaprevir plus PR in treatment studies and achieved SVR. No treatment was administered in the current follow-up study.

Subject analysis set title	Previous SVR on PR Only
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who previously received PR only in boceprevir or narlaprevir treatment studies and achieved SVR. No treatment was administered in the current follow-up study

Subject analysis set title	Participants from Boceprevir Studies with TE-RAVs
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who previously participated in treatment studies in which boceprevir was administered were subsequently enrolled in Part 1 of the current follow-up study P05063 (NCT00689390). Participants may have received boceprevir or control peginterferon plus ribavirin (PR) in the previous treatment study. No treatment was administered in the current follow-up study.

Subject analysis set title	Participants from Narlaprevir Studies with TE-RAVs
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who previously participated in treatment studies in which narlaprevir was administered were subsequently enrolled in Part 2 of the current follow-up study P05063 (NCT00689390). Participants may have received narlaprevir or control PR in the previous treatment study. No treatment was administered in the current follow-up study.

Primary: Number of participants with relapse during the LTFU among sustained responders from previous treatment studies with boceprevir or narlaprevir (Durability of virologic response)

End point title	Number of participants with relapse during the LTFU among sustained responders from previous treatment studies with boceprevir or narlaprevir (Durability of virologic response)[1]

End point description:

Durability of response was assessed by the number of participants who relapsed during the LTFU among those that had achieved sustained virologic response (SVR) by 24 weeks after treatment with boceprevir or narlaprevir in a previous Phase 1, 2, or 3 treatment study. In the current LTFU, participants were classified based on the last Hepatitis C Virus ribonucleic acid (HCV-RNA) result available at the time of the data cut-off date as follows: A participant was classified as a sustained virologic responder at a given

time point if serum HCV-RNA was undetectable at that time point and there had not been a positive HCV-RNA since the participant was determined to have achieved SVR in the previous study. A participant was classified as a relapser if they were a sustained virologic responder in the previous treatment study and became serum HCV-RNA positive with no subsequent negative results during LTFU.

End point type	Primary

End point timeframe:

From End Of Treatment (EOT) date in the previous treatment study to the first date of a positive HCV RNA result for relapsers or the last contact date for non-relapsers in the LTFU (up to 3.5 years)

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 statistics were reported for this endpoint. No statistical analyses were performed.

End point values	Previous SVR on Boceprevir + PR	Previous SVR on Narlaprevir + PR	Previous SVR on PR Only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1116[2]	40[3]	144[4]	
Units: participants	8	0	1	

Notes:

[2] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

[3] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

[4] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

Statistical analyses

No statistical analyses for this end point

Primary: Kaplan-Meier exposure-adjusted relapse rate

End point title	Kaplan-Meier exposure-adjusted relapse rate[5]

End point description:

The distribution of time to relapse was summarized using Kaplan-Meier estimates for all participants who were sustained responders at 24 weeks post-treatment in the previous study. Exposure Adjusted Relapse Rate = 1000 × (number of relapses) / (Total exposure time in years). Total exposure time in years = [(total number of days from last day of treatment to the last follow-up day for all subjects who did not relapse) + (total number of days from last day of treatment to the day of relapse for those who relapsed)] / 365.25 days [for 1 year].

End point type	Primary

End point timeframe:

From EOT date in the previous treatment study to the first date of a positive HCV RNA result for relapsers or the last contact date for non-relapsers in the LTFU (up to 3.5 years)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported for this endpoint. No statistical analyses were performed.

End point values	Previous SVR on Boceprevir + PR	Previous SVR on Narlaprevir + PR	Previous SVR on PR Only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1116[6]	40[7]	144[8]	
Units: relapses per 1,000 person-years				
number (not applicable)	2.3	0	2.2	

Notes:

[6] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

[7] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

[8] - All sustained responders at 24 weeks post-treatment in the previous study with available data.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with HCV Treatment-Emergent Resistance Associated Variants (TE-RAVs) of NS3/4A protease loci

End point title	Number of participants with HCV Treatment-Emergent Resistance Associated Variants (TE-RAVs) of NS3/4A protease loci[9]

End point description:

Plasma samples of all participants receiving at least one dose of study medication in a previous treatment protocol were evaluated by population sequencing and analyzed to detect amino acid variants in the NS3/4A protease known to be associated with reduced susceptibility to boceprevir and narlaprevir. RAVs in the NS3/4A protease gene were evaluated at 12 loci (V36, Q41, F43, T54, V55, V107, R155, A156, V158, D168, I/V170 and M175) on the basis of in vitro studies. A TE-RAV was defined as a RAV not present at baseline and that had not returned to wild type (WT) while the participant was still on treatment. The number of participants with TE-RAVS detected at the EOT in the previous treatment study are reported below, followed by those participants with TE-RAVS that returned to WT during the LTFU (among those with detected TE-RAVS).

Participants could have had more than one TE-RAV. All TE-RAVs were observed in participants in the boceprevir studies.

End point type	Primary

End point timeframe:

From EOT in the previous treatment study to the last available date in the LTFU (up to 3.5 years)

Notes:

[9] - 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 statistics were reported for this endpoint. No statistical analyses were performed.

End point values	Participants from Boceprevir Studies with TE-RAVs	Participants from Narlaprevir Studies with TE-RAVs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	308[10]	0[11]		
Units: participants				
V36A TE-RAVs detected	6			
__V36A TE-RAVs returned to WT (out of 6)	6			
V36G TE-RAVs detected	1			
__V36G TE-RAVs returned to WT (out of 1)	1			
V36L TE-RAVs detected	9			
__V36L TE-RAVs returned to WT (out of 9)	8			
V36M TE-RAVs detected	142			
__V36M TE-RAVs returned to WT (out of 142)	135			
F43C TE-RAVs detected	3			

__F43C TE-RAVs returned to WT (out of 3)	3			
T54A TE-RAVs detected	40			
__T54A TE-RAVs returned to WT (out of 40)	40			
T54C TE-RAVs detected	2			
__T54C TE-RAVs returned to WT (out of 2)	2			
T54S TE-RAVs detected	143			
__T54S TE-RAVs returned to WT (out of 143)	104			
V55A TE-RAVs detected	5			
__V55A TE-RAVs returned to WT (out of 5)	3			
V107I TE-RAVs detected	3			
__V107I TE-RAVs returned to WT (out of 3)	2			
R155K TE-RAVs detected	183			
__R155K TE-RAVs returned to WT (out of 183)	154			
R155T TE-RAVs detected	22			
__R155T TE-RAVs returned to WT (out of 22)	20			
A156S TE-RAVs detected	37			
__A156S TE-RAVs returned to WT (out of 37)	35			
A156T TE-RAVs detected	4			
__A156T TE-RAVs returned to WT (out of 4)	4			
V158I TE-RAVs detected	18			
__V158I TE-RAVs returned to WT (out of 16)	16			
V158M TE-RAVs detected	1			
__V158M TE-RAVs returned to WT (out of 1)	1			
D168N TE-RAVs detected	12			
__D168N TE-RAVs returned to WT (out of 12)	11			
I170T TE-RAVs detected	3			
__I170T TE-RAVs returned to WT (out of 3)	3			
V170A TE-RAVs detected	27			
__V170A TE-RAVs returned to WT (out of 27)	24			
M175L TE-RAVs detected	5			
__M175L TE-RAVs returned to WT (out of 5)	2			

Notes:

[10] - Participants with TE-RAVs receiving ≥1 dose of study drug in a previous boceprevir clinical study.

[11] - No participants in this treatment group had a TE-RAV.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with serious adverse events (SAEs) reported during the LTFU

End point title	Number of participants with serious adverse events (SAEs) reported during the LTFU[12]

End point description:

Long-term safety was assessed based on the SAEs reported during the LTFU period. An SAE was any adverse drug or biologic or device experience occurring at any dose that resulted in any of the following outcomes: death, life-threatening AE, persistent or significant disability/incapacity, required in-patient hospitalization or prolongs hospitalization, congenital anomaly or birth defect. Important medical events that did not result in any of these outcomes could still be considered SAEs if they jeopardized the participant and/or required medical/surgical intervention, based on appropriate medical judgment. Grade 4 laboratory abnormalities and out of normal range liver function tests that were not accompanied by clinical manifestations were NOT considered SAEs.

End point type	Primary

End point timeframe:

From enrollment in the LTFU study to the last available date in the LTFU study (up to 3 years)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported for this endpoint. No statistical analyses were performed.

End point values	Participants from Boceprevir Studies	Participants from Narlaprevir Studies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1907[13]	47[14]		
Units: participants	136	2		

Notes:

[13] - All enrolled participants were included in safety analyses.

[14] - All enrolled participants were included in safety analyses.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants that discontinued the LTFU due to SAEs

End point title	Number of participants that discontinued the LTFU due to

End point description:

An SAE was any adverse drug or biologic or device experience occurring at any dose that resulted in any of the following outcomes: death, life-threatening AE, persistent or significant disability/incapacity, required in-patient hospitalization or prolongs hospitalization, congenital anomaly or birth defect. Important medical events that did not result in any of these outcomes could still be considered SAEs if they jeopardized the participant and/or required medical/surgical intervention, based on appropriate medical judgment. Grade 4 laboratory abnormalities and out of normal range liver function tests that were not accompanied by clinical manifestations were NOT considered SAEs.

End point type	Primary

End point timeframe:

From enrollment in the LTFU study to the last available date in the LTFU study (up to 3 years)

Notes:

[15] - 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 statistics were reported for this endpoint. No statistical analyses were performed.

End point values	Participants from Boceprevir Studies	Participants from Narlaprevir Studies		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1907[16]	47[17]		
Units: participants	19	0		

Notes:

[16] - All enrolled participants were included in safety analyses.

[17] - All enrolled participants were included in safety analyses.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From enrollment in the LTFU study to the last available date in the LTFU study (up to 3 years)

Adverse event reporting additional description:

As specified in the protocol, only serious adverse events (SAEs) were collected. Other Adverse Events were not monitored and not collected, thus no participants were at risk for these events. All enrolled participants were included in safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Participants from Narlaprevir Studies

Reporting group description:

Participants who previously participated in treatment studies in which narlaprevir was administered were subsequently enrolled in Part 2 of the current follow-up study P05063 (NCT00689390, 2006-006529-25). Participants may have received narlaprevir or control PR in the previous treatment study. No treatment was administered in the current follow-up study.

Reporting group title	Participants from Boceprevir Studies

Reporting group description:

Participants who previously participated in treatment studies in which boceprevir was administered were subsequently enrolled in Part 1 of the current follow-up study P05063 (NCT00689390, 2006-006529-25). Participants may have received boceprevir or control peginterferon plus ribavirin (PR) in theprevious treatment study. No treatment was administered in the current follow-up study.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As specified in the protocol, long-term safety was assessed based on the SAEs reported during the long-term follow-up period. No non-serious AEs were collected or reported on this study.

Serious adverse events	Participants from Narlaprevir Studies	Participants from Boceprevir Studies	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 47 (4.26%)	136 / 1907 (7.13%)	
number of deaths (all causes)	0	14	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma Benign			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Cancer Stage 0			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Neoplasm			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchioloalveolar Carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diffuse Large B-Cell Lymphoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatocellular Carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	9 / 1907 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Adenocarcinoma			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Adenocarcinoma Stage IV			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Liver			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate Cancer			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cell Carcinoma			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary Gland Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Head And Neck			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Thrombosis			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary Artery Bypass			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger Amputation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Arthroplasty			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee Arthroplasty			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Transplant			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder Arthroplasty			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Valvuloplasty Cardiac			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 47 (0.00%)	4 / 1907 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterovaginal Prolapse			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Fibrosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed Suicide			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional State			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ankle Fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot Fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Scapula Fracture			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab Wound			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound Complication			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Endocardial Fibroelastosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Huntington's Disease			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina Unstable			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 47 (0.00%)	3 / 1907 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary Failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary Artery Disease			
subjects affected / exposed	0 / 47 (0.00%)	3 / 1907 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			

subjects affected / exposed	0 / 47 (0.00%)	9 / 1907 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Arachnoid Cyst			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension Headache			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Corneal Oedema			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Fistula			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	1 / 47 (2.13%)	0 / 1907 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular Perforation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 1907 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial Eventration			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Varices Haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Palatal Disorder			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices Oesophageal			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 47 (0.00%)	5 / 1907 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Cirrhosis			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Calculus Ureteric			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical Spinal Stenosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	0 / 47 (0.00%)	5 / 1907 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute Hepatitis B			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis Perforated			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Simplex Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	5 / 1907 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative Wound Infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	3 / 1907 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 47 (0.00%)	2 / 1907 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Diabetic Complication			

subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Acidosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 1907 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Participants from Narlaprevir Studies	Participants from Boceprevir Studies	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 1907 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2009	General amendment 1 (AM1) included changes to allow for the inclusion of participants who previously participated in boceprevir AND narlaprevir clinical studies, including Phase 1 studies and participants who received peginterferon alfa-2a as part of their therapeutic regimen. Changes included revisions to the protocol title, number of study sites, overall duration, background, rationale, primary objectives, statistical methods, and the addition of new methods for pharmacogenetic sampling and IL-28 genotype.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 July 2014	The study was terminated due to satisfaction of postmarketing commitments.	-

Notes:

Limitations and caveats

None reported