Clinical trial results:
A Phase II Randomized Clinical Trial to Study the Efficacy and Safety of MK-5172 in Combination with Ribavirin (RBV) in Subjects with Chronic Hepatitis C Virus Infection

Summary

EudraCT number	2012-003340-72
Trial protocol	AT ES NO
Global end of trial date	12 March 2014

Results information

Result version number	v1
This version publication date	05 April 2016
First version publication date	01 March 2015

Trial information

Trial identification

Sponsor protocol code	5172-39

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01716156
WHO universal trial number (UTN)	-

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	12 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2014
Global end of trial reached?	Yes
Global end of trial date	12 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the efficacy of each treatment arm of grazoprevir (MK-5172) in combination with ribavarin (RBV) for 12 or 24 weeks as assessed by the percentage of participants achieving SVR12 (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as hepatitis C virus (HCV) ribonucleic acid (RNA) <25 IU/mL (either "target detectable but unquantifiable" [TD(u)] or "target not detected" [TND]) 12 weeks after the end of all study therapy.

2) To evaluate the safety and tolerability of grazoprevir in combination with RBV.

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.

The following additional measure defined for this individual study was in place for the protection of trial subjects: Peg-IFN (1.5 µg/kg/wk) + RBV (weight-based) was offered as rescue therapy to any participant who met the criteria for virologic failure and futility or discontinued study medications due to safety concerns that were not attributed to RBV. Participants had to start on rescue within 4 months from the time of discontinuing therapy or within 4 months of follow-up week 24 in case of relapse, if indicated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	26
EEA total number of subjects	0

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)	25
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 26 treatment-naive non-cirrhotic adult participants with HCV genotype 1 were recruited in Australia, Israel, and New Zealand.

Pre-assignment

Screening details:

Participants received grazoprevir + RBV for either 12 weeks or 24 weeks (participants in the 12-week arm with detectable HCV RNA at Treatment Week [TW] 4 received 12 additional weeks of study treatment). The allocation of participants to the 2 arms was stratified according to HCV GT1a vs. GT1b infection.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Grazoprevir 100 mg + RBV 12 Weeks

Arm description:

Participants with undetectable HCV RNA (TND) at Treatment Week (TW) 4 received Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Grazoprevir 100 mg tablet once daily by mouth for 12 or 24 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol™
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg capsules twice daily by mouth at a total daily dose of 800 mg/day to 1400 mg/day based on participant body weight on Day 1.

Arm title	Grazoprevir 100 mg + RBV 12 Weeks Extended

Arm description:

Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks. Participants with detectable HCV RNA at TW4 received received an additional 12 weeks of study therapy for a total of 24 weeks of treatment.

Arm type	Experimental

Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Grazoprevir 100 mg tablet once daily by mouth for 12 or 24 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol™
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg capsules twice daily by mouth at a total daily dose of 800 mg/day to 1400 mg/day based on participant body weight on Day 1.

Arm title	Grazoprevir 100 mg + RBV 24 Weeks

Arm description:

Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Grazoprevir
Investigational medicinal product code	
Other name	MK-5172
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Grazoprevir 100 mg tablet once daily by mouth for 12 or 24 weeks.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	Rebetol™
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

RBV 200 mg capsules twice daily by mouth at a total daily dose of 800 mg/day to 1400 mg/day based on participant body weight on Day 1.

Number of subjects in period 1	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks
Started	9	4	13
Completed	7	3	11
Not completed	2	1	2
Consent withdrawn by subject	-	1	2
Lost to follow-up	1	-	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Grazoprevir 100 mg + RBV 12 Weeks
Reporting group description:	
Participants with undetectable HCV RNA (TND) at Treatment Week (TW) 4 received Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 12 weeks.	
Reporting group title	Grazoprevir 100 mg + RBV 12 Weeks Extended
Reporting group description:	
Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks. Participants with detectable HCV RNA at TW4 received received an additional 12 weeks of study therapy for a total of 24 weeks of treatment.	
Reporting group title	Grazoprevir 100 mg + RBV 24 Weeks
Reporting group description:	
Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks.	

Reporting group values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks
Number of subjects	9	4	13
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	4	13
From 65-84 years	1	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	1	6
Male	7	3	7

Reporting group values	Total		
Number of subjects	26		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	25		
From 65-84 years	1		
85 years and over	0		
Gender categorical Units: Subjects			
Female	9		
Male	17		

End points

End points reporting groups

Reporting group title	Grazoprevir 100 mg + RBV 12 Weeks

Reporting group description:

Participants with undetectable HCV RNA (TND) at Treatment Week (TW) 4 received Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 12 weeks.

Reporting group title	Grazoprevir 100 mg + RBV 12 Weeks Extended

Reporting group description:

Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks. Participants with detectable HCV RNA at TW4 received received an additional 12 weeks of study therapy for a total of 24 weeks of treatment.

Reporting group title	Grazoprevir 100 mg + RBV 24 Weeks

Reporting group description:

Grazoprevir 100 mg tablet once per day by mouth for 12 weeks and RBV capsules twice per day by mouth at a total daily dose from 600 to 1400 mg based on participant weight for 24 weeks.

Subject analysis set title	Grazoprevir 100 mg + RBV: HCV GT1a
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This group consisted of all participants with HCV GT1a infection pooled across treatment arms.

Subject analysis set title	Grazoprevir 100 mg + RBV: HCV GT1b/c
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This group consisted of all participants with HCV GT1non-a infection, pooled across treatment arms.

Subject analysis set title	Grazoprevir 100 mg + RBV: Up to 12 Weeks
Subject analysis set type	Safety analysis

Subject analysis set description:

The All Patients as Treated (APaT) population included all randomized participants who received at least 1 dose of study therapy. The 12-week group consists of participants in the APaT who only received 12 weeks of treatment and not those originally assigned to 12 weeks that went on to receive 24 total weeks of treatment.

Subject analysis set title	Grazoprevir 100 mg + RBV: Beyond 12 Weeks
Subject analysis set type	Safety analysis

Subject analysis set description:

The APaT population included all randomized participants who received at least 1 dose of study therapy. The 24-week group consists of participants in the APaT who received 24 total weeks of treatment, regardless of original treatment regimen assignment.

Primary: Percentage of participants with undetectable HCV ribonucleic acid (RNA) 12 weeks after completing study therapy (SVR12)

End point title	Percentage of participants with undetectable HCV ribonucleic acid (RNA) 12 weeks after completing study therapy (SVR12)[1]

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR12 was defined as Hepatitis C Virus (HCV) ribonucleic acid (RNA) <25 IU/mL 12 weeks after the end of all study therapy.

End point type	Primary

End point timeframe:

Up to 36 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was conducted for this measure.

End point values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[2]	4[3]	10[4]	
Units: percentage of participants				
number (confidence interval 95%)	62.5 (24.5 to 91.5)	50 (6.8 to 93.2)	90 (55.5 to 99.7)	

Notes:

[2] - All randomized participants receiving ≥1 dose of study therapy and no important protocol deviations.
[3] - All randomized participants receiving ≥1 dose of study therapy and no important protocol deviations.
[4] - All randomized participants receiving ≥1 dose of study therapy and no important protocol deviations.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing an adverse event (AE)

End point title	Percentage of participants experiencing an adverse event

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. Data are presented according to actual treatment duration (12 weeks or 24 weeks) regardless of participants' initial arm assignment.

End point type	Primary

End point timeframe:

Fourteen days following last dose of study drug (up to 26 weeks).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was conducted for this measure.

End point values	Grazoprevir 100 mg + RBV: Up to 12 Weeks	Grazoprevir 100 mg + RBV: Beyond 12 Weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: percentage of participants				
number (not applicable)	72.7	86.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants discontinuing from study therapy due to AE(s)

End point title	Percentage of participants discontinuing from study therapy due to AE(s)[6]

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. Data are presented according to actual treatment duration (12 weeks or 24 weeks) regardless of participants' initial arm assignment.

End point type	Primary

End point timeframe:

Up to 24 weeks

Notes:

[6] - 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 formal hypothesis testing was conducted for this measure.

End point values	Grazoprevir 100 mg + RBV: Up to 12 Weeks	Grazoprevir 100 mg + RBV: Beyond 12 Weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	15		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with undetectable HCV RNA by time point

End point title	Percentage of participants with undetectable HCV RNA by time point

End point description:

HCV RNA levels in plasma were measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay on blood samples drawn from each participant at Week 2, Week 4, Week 12, and at end of treatment (End of Treatment Response). The assay has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. Undetectable HCV RNA was defined as below the limit of detection of 9.3 IU/mL.

End point type	Secondary

End point timeframe:

From Week 2 through end of treatment (up to 24 weeks)

End point values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	12[7]	
Units: percentage of participants				
number (confidence interval 95%)				
Week 2	50 (15.7 to 84.3)	0 (0 to 60.2)	41.7 (15.2 to 72.3)	
Week 4	100 (63.1 to 100)	0 (0 to 60.2)	81.8 (48.2 to 97.7)	
Week 12	100 (63.1 to 100)	75 (19.4 to 99.4)	81.8 (48.2 to 97.7)	
End of All Therapy	100 (63.1 to 100)	75 (19.4 to 99.4)	91.7 (61.5 to 99.8)	

Notes:

[7] - One participant did not have HCV RNA data available at Week 4 (n=11) and at Week 12 (n=11).

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with HCV RNA <25 IU/mL by time point

End point title	Percentage of participants with HCV RNA <25 IU/mL by time point

End point description:

HCV RNA levels in plasma were measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay on blood samples drawn from each participant at Week 2, Week 4, Week 12, and at end of treatment (End of Treatment Response). The assay has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. Undetectable HCV RNA was defined as below the limit of detection of 9.3 IU/mL.

End point type	Secondary

End point timeframe:

From Week 2 through end of treatment (up to 24 weeks).

End point values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	12[8]	
Units: percentage of participants				
number (confidence interval 95%)				
Week 2	100 (63.1 to 100)	75 (19.4 to 99.4)	100 (73.5 to 100)	
Week 4	100 (63.1 to 100)	100 (39.8 to 100)	100 (71.5 to 100)	
Week 12	100 (63.1 to 100)	75 (19.4 to 99.4)	90.9 (58.7 to 99.8)	
End of All Therapy	100 (63.1 to 100)	75 (19.4 to 99.4)	91.7 (61.5 to 99.8)	

Notes:

[8] - One participant did not have HCV RNA data available at Week 4 (n=11) and Week 12 (n=11).

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with sustained virologic response 4 weeks after ending study therapy (SVR4)

End point title	Percentage of participants with sustained virologic response 4 weeks after ending study therapy (SVR4)

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR4 was defined as HCV RNA <25 IU/mL 4 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	11	
Units: percentage of participants				
number (confidence interval 95%)	87.5 (47.3 to 99.7)	75 (19.4 to 99.4)	90.9 (58.7 to 99.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving sustained virologic response 24 weeks after the end of study therapy

End point title	Percentage of participants achieving sustained virologic response 24 weeks after the end of study therapy

End point description:

HCV RNA was measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay, which has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. SVR24 was defined as HCV RNA <25 IU/mL 24 weeks after the end of all study therapy.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Grazoprevir 100 mg + RBV 12 Weeks	Grazoprevir 100 mg + RBV 12 Weeks Extended	Grazoprevir 100 mg + RBV 24 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	10	
Units: percentage of participants				
number (confidence interval 95%)	62.5 (24.5 to 91.5)	50 (6.8 to 93.2)	80 (44.4 to 97.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achievement of first undetectable HCV RNA

End point title	Time to achievement of first undetectable HCV RNA

End point description:

The mean time (in days) to first achievement of undetectable HCV RNA was assessed using Kaplan-Meier plot and summary statistics. HCV RNA levels in plasma were measured using the Roche COBAS™ Taqman™ HCV Test, v2.0® assay on blood samples drawn from each participant at Week 2, Week 4, Week 12, and at end of treatment. The assay has a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. Undetectable HCV RNA was defined as below the limit of detection of 9.3 IU/mL.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Grazoprevir 100 mg + RBV: HCV GT1a	Grazoprevir 100 mg + RBV: HCV GT1b/c		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: day				
least squares mean (standard error)	27.1 (± 2.5)	19.7 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first day of treatment (Day 1) through Day 14 of follow-up (up to 26 weeks)	
Adverse event reporting additional description:	
All randomized participants who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	MK-5172 100 mg + RBV 24 Weeks
Reporting group description:	
This group consists of all participants receiving 24 weeks of study therapy.	
Reporting group title	MK-5172 100 mg + RBV 12 Weeks
Reporting group description:	
This group consists of all participants who received only 12 weeks of study therapy.	

Serious adverse events	MK-5172 100 mg + RBV 24 Weeks	MK-5172 100 mg + RBV 12 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	MK-5172 100 mg + RBV 24 Weeks	MK-5172 100 mg + RBV 12 Weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	8 / 11 (72.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 15 (53.33%)	0 / 11 (0.00%)	
occurrences (all)	8	0	

Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Irritability			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	4 / 15 (26.67%)	4 / 11 (36.36%)	
occurrences (all)	6	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Eye disorders			

Eye inflammation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Abdominal pain lower			
subjects affected / exposed	2 / 15 (13.33%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 11 (18.18%)	
occurrences (all)	4	3	
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Lip dry			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
Paraesthesia oral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	3 / 15 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 11 (9.09%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported