Clinical trial results:
A Phase II/III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 and MK-8742 in Subjects with Chronic Hepatitis C Virus Infection and Chronic Kidney Disease

Summary

EudraCT number	2013-003858-25
Trial protocol	LT ES SE EE NL
Global end of trial date	02 September 2015

Results information

Result version number	v1 (current)
This version publication date	04 September 2016
First version publication date	04 September 2016

Trial information

Trial identification

Sponsor protocol code	5172-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02092350
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., ClinicalTrialDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialDisclosure@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	02 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety and efficacy of combination treatment with grazoprevir (GZR; MK-5172) + elbasvir (EBR; MK-8742) for cirrhotic and non-cirrhotic participants with chronic Genotype 1 (GT1) hepatitis C virus (HCV) infection and chronic kidney disease (CKD).

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	17 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United States: 153
Worldwide total number of subjects	237
EEA total number of subjects	49

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)	197
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multi-site study enrolled adult, male and female participants with hepatitis C virus (HCV) genotype (GT) 1 with chronic kidney disease (CKD).

Pre-assignment

Screening details:

The screening period lasted for up to 60 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Treatment + Intensive PK

Arm description:

Participants received grazoprevir (GZR) 100 mg tablet + elbasvir (EBR) 50 mg tablet once daily (q.d.) by mouth for 12 weeks, followed by a 24-week follow-up period. A subset of participants also underwent intensive pharmacokinetics (PK) testing.

Arm type	Experimental
Investigational medicinal product name	Elbasvir
Investigational medicinal product code	
Other name	MK-8742
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

EBR 50 mg tablet taken q.d. by mouth.

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:

GZR 100 mg tablet taken q.d. by mouth.

Arm title	Deferred Treatment

Arm description:

Participants received placebo to GZR and EBR q.d. by mouth for 12 weeks. Then, after a 4-week drug-free period, participants received a fixed dose combination (FDC) tablet containing GZR 100 mg + EBR 50 mg tablet q.d. by mouth for 12 weeks, followed by a 24-week follow-up period.

Arm type	Placebo
Investigational medicinal product name	Placebo to Grazoprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matched to GZR.

Investigational medicinal product name	Grazoprevir + Elbasvir
Investigational medicinal product code	
Other name	MK-5172A; Zepatier™
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single FDC tablet containing GZR 100 mg + EBR 50 mg taken q.d. by mouth.

Investigational medicinal product name	Placebo to Elbasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet matched to EBR.

Number of subjects in period 1	Immediate Treatment + Intensive PK	Deferred Treatment
Started	123	114
Completed	113	102
Not completed	10	12
Adverse event, serious fatal	2	5
Physician decision	1	1
Consent withdrawn by subject	2	2
Screen Failure	1	-
Adverse event, non-fatal	-	3
Lost to follow-up	3	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Immediate Treatment + Intensive PK
Reporting group description:	
Participants received grazoprevir (GZR) 100 mg tablet + elbasvir (EBR) 50 mg tablet once daily (q.d.) by mouth for 12 weeks, followed by a 24-week follow-up period. A subset of participants also underwent intensive pharmacokinetics (PK) testing.	
Reporting group title	Deferred Treatment
Reporting group description:	
Participants received placebo to GZR and EBR q.d. by mouth for 12 weeks. Then, after a 4-week drug-free period, participants received a fixed dose combination (FDC) tablet containing GZR 100 mg + EBR 50 mg tablet q.d. by mouth for 12 weeks, followed by a 24-week follow-up period.	

Reporting group values	Immediate Treatment + Intensive PK	Deferred Treatment	Total
Number of subjects	123	114	237
Age categorical			
Units: Subjects			
Age Continuous |			
Units: years			
arithmetic mean	56.6	55.2	
standard deviation	± 9	± 10	-
Gender, Male/Female			
Units: Participants			
Female	30	33	63
Male	93	81	174

End points

End points reporting groups

Reporting group title	Immediate Treatment + Intensive PK

Reporting group description:

Participants received grazoprevir (GZR) 100 mg tablet + elbasvir (EBR) 50 mg tablet once daily (q.d.) by mouth for 12 weeks, followed by a 24-week follow-up period. A subset of participants also underwent intensive pharmacokinetics (PK) testing.

Reporting group title	Deferred Treatment

Reporting group description:

Participants received placebo to GZR and EBR q.d. by mouth for 12 weeks. Then, after a 4-week drug-free period, participants received a fixed dose combination (FDC) tablet containing GZR 100 mg + EBR 50 mg tablet q.d. by mouth for 12 weeks, followed by a 24-week follow-up period.

Primary: Percentage of participants with sustained virologic response 12 weeks after completing study therapy (SVR12)

End point title	Percentage of participants with sustained virologic response 12 weeks after completing study therapy (SVR12)[1]

End point description:

SVR12 was defined as HCV ribonucleic acid (RNA) lower than the limit of quantification (LLoQ) 12 weeks after completing study (GZR + EBR) therapy. HCV RNA was measured using the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0®, which has a LLoQ of 15 IU/mL. The modified Full Analysis set (mFAS) includes all participants receiving ≥1 dose of drug and without missing data due to death or early discontinuation from study therapy for reasons unrelated to response to HCV treatment.

End point type	Primary

End point timeframe:

Week 24 (Immediate Treatment + Intensive PK) or Week 40 (Deferred Treatment)

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: For details of the single-arm statistical analysis, which cannot be shown in the EudraCT system, see www.clinicaltrials.gov record NCT02092350.

End point values	Immediate Treatment + Intensive PK	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	99		
Units: Percentage of participants				
number (confidence interval 95%)	99.1 (95.3 to 100)	98 (92.9 to 99.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants experiencing an adverse event (AE) during the initial treatment and 14-day follow-up periods

End point title	Number of participants experiencing an adverse event (AE) during the initial treatment and 14-day follow-up periods[2]

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. This analysis includes the Immediate Treatment + Intensive PK group and the placebo treatment period for the Deferred Treatment group. The All Participants as Treated (APaT) population includes all enrolled participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to Week 14

Notes:

[2] - 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: Per protocol, only descriptive statistics are presented.

End point values	Immediate Treatment + Intensive PK	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	113		
Units: Participants	93	96		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants discontinuing study drug due to AEs during the initial treatment period

End point title	Number of participants discontinuing study drug due to AEs during the initial treatment period[3]

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. This analysis includes the Immediate Treatment + Intensive PK group and the placebo treatment period for the Deferred Treatment group. The APaT population includes all enrolled participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to Week 12

Notes:

[3] - 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: Per protocol, only descriptive statistics are presented.

End point values	Immediate Treatment + Intensive PK	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	113		
Units: Participants	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with sustained virologic response 24 weeks after completing study therapy (SVR24)

End point title	Percentage of participants with sustained virologic response 24 weeks after completing study therapy (SVR24)

End point description:

SVR24 was defined as HCV RNA lower than LLoQ 24 weeks after completing study therapy. HCV RNA was measured using the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0®, which has a LLoQ of 15 IU/mL. The mFAS includes all participants receiving ≥1 dose of drug and without missing data due to death or early discontinuation from study therapy for reasons unrelated to response to HCV treatment.

End point type	Secondary

End point timeframe:

Week 36 (Immediate Treatment + Intensive PK) or Week 52 (Deferred Treatment)

End point values	Immediate Treatment + Intensive PK	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	99		
Units: Percentage of participants				
number (confidence interval 95%)	97.4 (92.5 to 99.5)	98 (92.9 to 99.8)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

SVR4 was defined as HCV RNA lower than LLoQ 4 weeks after completing study therapy. HCV RNA was measured using the COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0®, which has a LLoQ of 15 IU/mL. The mFAS includes all participants receiving ≥1 dose of drug and without missing data due to death or early discontinuation from study therapy for reasons unrelated to response to HCV treatment.

End point type	Secondary

End point timeframe:

Week 16 (Immediate Treatment + Intensive PK) or Week 32 (Deferred Treatment)

End point values	Immediate Treatment + Intensive PK	Deferred Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	101		
Units: Percentage of participants				
number (confidence interval 95%)	100 (96.9 to 100)	99 (94.6 to 100)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Immediate Treatment + Intensive PK: up to Week 36; Deferred Treatment GZR Placebo + EBR Placebo: up to Week 16; Deferred Treatment GZR 100 mg + EBR 50 mg: Week 16 to up to Week 52.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The All Participants as Treated (APaT) population includes all enrolled participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Immediate + Intensive PK: GZR 100 mg + EBR 50 mg 12 Weeks

Reporting group description:

Participants received GZR 100 mg tablet + EBR 50 mg tablet q.d. by mouth for 12 weeks. A subset of participants also underwent intensive PK testing.

Reporting group title	Deferred treatment: GZR Placebo + EBR Placebo 12 Weeks

Reporting group description:

Participants received placebo to GZR and EBR q.d. by mouth for 12 weeks, followed by a 4-week drug-free period.

Reporting group title	Deferred treatment: GZR 100 mg + EBR 50 mg 12 Weeks

Reporting group description:

Participants received a FDC tablet containing GZR 100 mg + EBR 50 mg tablet q.d. by mouth for 12 weeks, followed by a 24-week follow-up period.

Serious adverse events	Immediate + Intensive PK: GZR 100 mg + EBR 50 mg 12 Weeks	Deferred treatment: GZR Placebo + EBR Placebo 12 Weeks	Deferred treatment: GZR 100 mg + EBR 50 mg 12 Weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 122 (24.59%)	22 / 113 (19.47%)	25 / 102 (24.51%)
number of deaths (all causes)	2	4	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 122 (0.00%)	2 / 113 (1.77%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cryoglobulinaemia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 122 (1.64%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			

subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 122 (1.64%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal effusion			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
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			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Electrocardiogram abnormal			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dialysis related complication			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital injury			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post procedural haematoma			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative fever			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	2 / 122 (1.64%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
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 failure congestive			
subjects affected / exposed	2 / 122 (1.64%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			

subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular haemorrhage			

subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
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 / 122 (0.00%)	0 / 113 (0.00%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 122 (0.00%)	2 / 113 (1.77%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Citrobacter sepsis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected fistula			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinitis			

subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nocardiosis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 122 (1.64%)	1 / 113 (0.88%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 122 (1.64%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 122 (0.82%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 122 (0.82%)	1 / 113 (0.88%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 113 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Immediate + Intensive PK: GZR 100 mg + EBR 50 mg 12 Weeks	Deferred treatment: GZR Placebo + EBR Placebo 12 Weeks	Deferred treatment: GZR 100 mg + EBR 50 mg 12 Weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 122 (54.92%)	68 / 113 (60.18%)	39 / 102 (38.24%)
Vascular disorders			
Hypertension			

subjects affected / exposed	7 / 122 (5.74%)	6 / 113 (5.31%)	2 / 102 (1.96%)
occurrences (all)	7	6	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 122 (6.56%)	18 / 113 (15.93%)	4 / 102 (3.92%)
occurrences (all)	9	22	4
Headache			
subjects affected / exposed	23 / 122 (18.85%)	18 / 113 (15.93%)	7 / 102 (6.86%)
occurrences (all)	26	23	8
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 122 (5.74%)	6 / 113 (5.31%)	4 / 102 (3.92%)
occurrences (all)	9	6	4
Fatigue			
subjects affected / exposed	13 / 122 (10.66%)	17 / 113 (15.04%)	10 / 102 (9.80%)
occurrences (all)	15	17	10
Pyrexia			
subjects affected / exposed	6 / 122 (4.92%)	6 / 113 (5.31%)	3 / 102 (2.94%)
occurrences (all)	7	6	4
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 122 (1.64%)	6 / 113 (5.31%)	1 / 102 (0.98%)
occurrences (all)	2	6	1
Abdominal pain			
subjects affected / exposed	10 / 122 (8.20%)	3 / 113 (2.65%)	3 / 102 (2.94%)
occurrences (all)	13	3	3
Constipation			
subjects affected / exposed	8 / 122 (6.56%)	6 / 113 (5.31%)	3 / 102 (2.94%)
occurrences (all)	8	7	3
Diarrhoea			
subjects affected / exposed	6 / 122 (4.92%)	15 / 113 (13.27%)	5 / 102 (4.90%)
occurrences (all)	6	22	6
Nausea			
subjects affected / exposed	18 / 122 (14.75%)	18 / 113 (15.93%)	11 / 102 (10.78%)
occurrences (all)	24	21	12
Vomiting			

subjects affected / exposed	9 / 122 (7.38%)	9 / 113 (7.96%)	7 / 102 (6.86%)
occurrences (all)	13	11	10
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 122 (7.38%)	2 / 113 (1.77%)	5 / 102 (4.90%)
occurrences (all)	10	2	6
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 122 (3.28%)	12 / 113 (10.62%)	1 / 102 (0.98%)
occurrences (all)	4	12	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 122 (8.20%)	12 / 113 (10.62%)	2 / 102 (1.96%)
occurrences (all)	10	12	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 122 (0.00%)	6 / 113 (5.31%)	1 / 102 (0.98%)
occurrences (all)	0	6	1
Myalgia			
subjects affected / exposed	0 / 122 (0.00%)	8 / 113 (7.08%)	2 / 102 (1.96%)
occurrences (all)	0	9	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 122 (5.74%)	3 / 113 (2.65%)	4 / 102 (3.92%)
occurrences (all)	8	3	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2014	AM2: The purpose of this amendment was to update the list of prohibited medications to include rosuvastatin and atorvastatin at specified dose limits, to update HCV RNA <LLoQ instead of <25 IU/mL, and to clarify that prohibited medications can be resumed 2 weeks after taking the final dose of study drug.
28 May 2014	AM3: The purpose of this amendment was to update the list of allowed and prohibited statin drugs and to add a list of prohibited hepatotoxic agents.
10 June 2014	AM4: The purpose of this amendment was to update laboratory exclusion values for platelets and to update inclusion criteria pertaining to liver disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported