Clinical trial results:
A multi-centre single-arm study to evaluate the efficacy and safety of BOCEPREVIR 44 weeks in addition to standard of care (SOC) in previously treatment failure (relapser, non-responders, both partial and null) patients with chronic hepatitis C genotype 1 (G1) and cirrhosis (F4 Metavir). (MK-3034-105)

Summary

EudraCT number	2012-002772-13
Trial protocol	IT
Global end of trial date	17 November 2015

Results information

Result version number	v1 (current)
This version publication date	16 October 2016
First version publication date	16 October 2016

Trial information

Trial identification

Sponsor protocol code	MK-3034-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01756079
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	17 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2015
Global end of trial reached?	Yes
Global end of trial date	17 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was done to find out if the addition of boceprevir to standard of care (SOC) treatment with peginterferon alfa-2b (PegIFN-2b) + ribavirin (RBV) is effective for participants with chronic hepatitis C (CHC) genotype 1 and cirrhosis who were not successfully treated by previous SOC. All participants were to receive treatment with SOC alone for 4 weeks and then boceprevir was to be added to the treatment regimen for 44 additional weeks of combined treatment.

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 participants: A participant was to be discontinued from all study therapy if they met the per-protocol criteria for virologic failure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 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	Italy: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	38

From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled adult participants with hepatitis C (CHC) genotype 1 and cirrhosis who failed a prior treatment with peginterferon alpha (PegIFN-2b) and ribavirin (RBV). Other inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

A total of 130 participants were screened. Sixty participants passed screening, but 2 of these participants were excluded before assignment because standard of care treatment was not received during the Lead-in Period.

Period 1

Period 1 title	Lead-in: Day 0 to Week 4
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Participants

Arm description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Ribivirin
Investigational medicinal product code	
Other name	Rebetol, RBV
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribivirin oral capsule weight-based dose from 800-1400 mg/day divided into two daily doses throughout the study

Investigational medicinal product name	Pegintron
Investigational medicinal product code	
Other name	Peginterferon alfa-2b (PegIFN-2b)
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIFN-2b 1.5 µg/kg subcutaneous injection once weekly throughout the study

Number of subjects in period 1	Overall Participants
Started	58
Completed	58

Period 2

Period 2 title	Treatment/Follow-up: Week 4 to Week 72
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Participants

Arm description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Pegintron
Investigational medicinal product code	
Other name	Peginterferon alfa-2b (PegIFN-2b)
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

PegIFN-2b 1.5 µg/kg subcutaneous injection once weekly throughout the study

Investigational medicinal product name	Ribivirin
Investigational medicinal product code	
Other name	Rebetol, RBV
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribivirin oral capsule weight-based dose from 800-1400 mg/day divided into two daily doses throughout the study

Investigational medicinal product name	Boceprevir
Investigational medicinal product code	
Other name	Victrelis, BOC
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Boceprevir 800 mg oral capsule three times daily during the Treatment Period (Week 4 to Week 48)

Number of subjects in period 2	Overall Participants
Started	58
Treated in Treatment Period	54
Completed	23
Not completed	35
Consent withdrawn by subject	4
Adverse event, non-fatal	5
No information available	2
No boceprevir during Treatment Period	4
Lack of efficacy	20

Baseline characteristics

Reporting groups	
Reporting group title	Lead-in: Day 0 to Week 4

Reporting group description: -

Reporting group values	Lead-in: Day 0 to Week 4	Total	
Number of subjects	58	58	
Age Categorical Units: Subjects			
Adults (18-64 years)	38	38	
From 65-84 years	20	20	
Age Continuous Units: years			
arithmetic mean	59.3		
standard deviation	± 9.2	-	
Gender Categorical Units: Subjects			
Female	19	19	
Male	39	39	

End points

End points reporting groups

Reporting group title	Overall Participants

Reporting group description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Reporting group title	Overall Participants

Reporting group description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Subject analysis set title	ITT Set: Participants Treated in the Treatment Period
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Subject analysis set title	Safety Set 2: Participants Treated in the Treatment Period
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Primary: Percentage of Participants who Achieve Sustained Virological Response at Follow-up Week 24 (SVR24)

End point title	Percentage of Participants who Achieve Sustained Virological Response at Follow-up Week 24 (SVR24)[1]

End point description:

Hepatitis C Virus (HCV) ribonucleic acid (RNA) was measured using a polymerase chain reaction assay. SVR24 was
defined as HCV RNA less than the Limit of Quantification (<25 International Units (IU)/mL) 24 weeks after the end of the
Treatment Period. The Intent to Treat population included all participants who received at least 1 administration of boceprevir during the Treatment Period.

End point type	Primary

End point timeframe:

Week 72 (24 weeks after end of 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: No statistical analysis was planned for Percentage of Participants who Achieve Sustained Virological Response at Follow-up Week 24 (SVR24)

End point values	ITT Set: Participants Treated in the Treatment Period			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage of participants				
number (confidence interval 95%)	35.2 (22.7 to 49.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with One or More Adverse Events

End point title	Percentage of Participants with One or More Adverse Events[2]

End point description:

Adverse events were monitored during the Lead-in and Treatment Periods. Safety Analysis Set 2 included all participants who received boceprevir during the Treatment Period.

End point type	Primary

End point timeframe:

Up to 48 weeks (Lead-in and Treatment Periods)

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: No statistical analysis was planned for Percentage of Participants with One or More Adverse Events

End point values	Safety Set 2: Participants Treated in the Treatment Period			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage of participants				
number (not applicable)	98.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with an Adverse Event Leading to Discontinuation of Study Medication

End point title	Percentage of Participants with an Adverse Event Leading to Discontinuation of Study Medication[3]

End point description:

Adverse events were monitored during the Lead-in and Treatment Periods. Safety Analysis Set 2 included all participants who received boceprevir during the Treatment Period.

End point type	Primary

End point timeframe:

Up to 48 weeks (Lead-in and Treatment Periods)

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: No statistical analysis was planned for Percentage of Participants with an Adverse Event Leading to Discontinuation of Study Medication

End point values	Safety Set 2: Participants Treated in the Treatment Period			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage of participants				
number (not applicable)	9.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 72 weeks (including Lead-in, Treatment, and Follow-up Periods)

Adverse event reporting additional description:

Safety Analysis Set 1 included all participants who received PegIFN-2b + RBV during the Lead-in Period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Safety Set 1: Participants Treated in the Lead-in Period

Reporting group description:

Participants received PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) for 4 weeks during the Lead-in Period and then 44 additional weeks of treatment in the Treatment Period receiving PegIFN-2b (once weekly, 1.5 µg/kg subcutaneously) + RBV (capsules, orally, weight-based dose from 800-1400 mg/day divided into two daily doses) + boceprevir (capsules, orally, 800 mg three times per day). After completion of treatment, follow-up continued for an additional 24 weeks.

Serious adverse events	Safety Set 1: Participants Treated in the Lead-in Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 58 (17.24%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperpyrexia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Parathyroid fever			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Set 1: Participants Treated in the Lead-in Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	11		
Asthenia			
subjects affected / exposed	35 / 58 (60.34%)		
occurrences (all)	42		
Fatigue			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	12		
Pyrexia			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	35		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	15		
Dyspnoea			

subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Irritability			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	14 / 58 (24.14%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	8		
Syncope			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	44 / 58 (75.86%)		
occurrences (all)	82		
Leukopenia			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	16 / 58 (27.59%)		
occurrences (all)	22		
Thrombocytopenia			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	8		

Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Pruritus generalized			

subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Renal and urinary disorders Nocturia subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all)	 4 / 58 (6.90%) 4 3 / 58 (5.17%) 3		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 3 / 58 (5.17%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 5 / 58 (8.62%) 6 5 / 58 (8.62%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 12 / 58 (20.69%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2013	Amendment 1: The visit window was changed from 2 to 3 days; the limit for diagnosis of cirrhosis by elastography was changed from 0.20 to 0.30; details on contraception with reference to boceprevir were added; details on exclusion based on oesophageal varices were added as replacement of a former exclusion criterion; details on exclusion for limits of total bilirubin were added and direct bilirubin was replaced by total bilirubin; exclusion criterion applicable to use of prohibited medications was added; criteria for assignment of screening number and treatment number were detailed; storage procedures for ribavirin were changed; procedures for co-administration of boceprevir with an oral contraceptive were detailed; duration of post-study contraception for males and females was added; rules for dose modification of ribavirin were added; other minor or typographic changes were made effective.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported