Clinical trial results:
A Phase 2, Randomized, Multicenter, Placebo-Controlled, Double-Blind, Parallel-Group Study, with an Open-Label Extension to Evaluate the Efficacy, Safety, and Pharmacokinetics of E5501 in Subjects with Chronic Hepatitis C Virus Related Thrombocytopenia who are Potential Candidates for Antiviral Treatment

Summary

EudraCT number	2010-024479-20
Trial protocol	DE BG
Global end of trial date	01 May 2014

Results information

Result version number	v1
This version publication date	10 March 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	E5501-G000-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01355289
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Medical Information, Eisai Limited, +44 08456761400, LmedInfo@eisai.net
Scientific contact	Medical Information, Eisai Limited, +44 08456761400, LmedInfo@eisai.net

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	01 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of E5501 by measuring platelet response in subjects with chronic hepatitis C virus (HCV)-related thrombocytopenia who require antiviral treatment

Protection of trial subjects:

This study was performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	65
EEA total number of subjects	11

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)	60
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening Period encompassed 14 days ±7 days. Prerandomization assessments took place in all subjects who had provided informed consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo, was administered orally, once daily for upto 21 days.

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

Dosage and administration details:

Once daily.

Arm title	Avatrombopag 10 mg

Arm description:

Avatrombopag 10 mg, was administered orally, once daily, preferably with food for upto 21 days.

Arm type	Active comparator
Investigational medicinal product name	Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg, tablet form, orally, once daily.

Arm title	Avatrombopag 20 mg

Arm description:

Avatrombopag 20 mg, was administered orally, once daily, preferably with food for upto 21 days.

Arm type	Active comparator
Investigational medicinal product name	Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
20 mg, tablet form, orally, once daily.

Arm title	Avatrombopag 30 mg

Arm description:
Avatrombopag 30 mg, was administered orally, once daily, preferably with food for upto 21 days.

Arm type	Active comparator
Investigational medicinal product name	Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
30 mg, tablet form, orally, once daily.

Number of subjects in period 1	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg
Started	17	16	18
Completed	16	16	18
Not completed	1	0	0
Adverse event, non-fatal	1	-	-
Not specified	-	-	-
Inadequate therapeutic effect	-	-	-

Number of subjects in period 1	Avatrombopag 30 mg
Started	14
Completed	12
Not completed	2
Adverse event, non-fatal	-
Not specified	1
Inadequate therapeutic effect	1

Period 2

Period 2 title	Open Label Extension (OLE)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Avatrombopag (Open label extension)

Arm description:

Avatrombopag was initiated at a dose of 20 mg, once daily in the OLE period. The avatrombopag dose was titrated up or down in accordance with their individual response within the range of a minimum of 5 mg and a maximum of 50 mg for up to 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Avatrombopag
Investigational medicinal product code	E5501
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5-50 mg, tablet form, orally, once daily.

Number of subjects in period 2	Avatrombopag (Open label extension)
Started	62
Completed	28
Not completed	34
Adverse event, non-fatal	1
Not specified	3
Lost to follow-up	1
Lack of efficacy	29

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo, was administered orally, once daily for upto 21 days.	
Reporting group title	Avatrombopag 10 mg
Reporting group description:	
Avatrombopag 10 mg, was administered orally, once daily, preferably with food for upto 21 days.	
Reporting group title	Avatrombopag 20 mg
Reporting group description:	
Avatrombopag 20 mg, was administered orally, once daily, preferably with food for upto 21 days.	
Reporting group title	Avatrombopag 30 mg
Reporting group description:	
Avatrombopag 30 mg, was administered orally, once daily, preferably with food for upto 21 days.	

Reporting group values	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg
Number of subjects	17	16	18
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	50.2	55.3	54.9
standard deviation	± 7.96	± 8.06	± 7.38
Gender categorical Units: Subjects			
Female	3	4	5
Male	14	12	13

Reporting group values	Avatrombopag 30 mg	Total	
Number of subjects	14	65	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	53.6		
standard deviation	± 7.26	-	
Gender categorical			
Units: Subjects			
Female	5	17	
Male	9	48	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo, was administered orally, once daily for upto 21 days.	
Reporting group title	Avatrombopag 10 mg
Reporting group description:	
Avatrombopag 10 mg, was administered orally, once daily, preferably with food for upto 21 days.	
Reporting group title	Avatrombopag 20 mg
Reporting group description:	
Avatrombopag 20 mg, was administered orally, once daily, preferably with food for upto 21 days.	
Reporting group title	Avatrombopag 30 mg
Reporting group description:	
Avatrombopag 30 mg, was administered orally, once daily, preferably with food for upto 21 days.	
Reporting group title	Avatrombopag (Open label extension)
Reporting group description:	
Avatrombopag was initiated at a dose of 20 mg, once daily in the OLE period. The avatrombopag dose was titrated up or down in accordance with their individual response within the range of a minimum of 5 mg and a maximum of 50 mg for up to 48 weeks.	

Primary: Number of participants who achieved Platelet Response (greater than or equal to 100 x 109/L) by Day 21 of Treatment Period A1 of Core Study

End point title	Number of participants who achieved Platelet Response (greater than or equal to 100 x 109/L) by Day 21 of Treatment Period A1 of Core Study
End point description:	
Responders are defined as a participant having a platelet count of greater than or equal to 100x109/L by Day 21 starting from an average baseline platelet count of greater than 20 x 109/L to less than or equal to 70 x 109/L.	
End point type	Primary
End point timeframe:	
Baseline to Day 21	

End point values	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg	Avatrombopag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	18	14
Units: Participants				
number (not applicable)				
Yes	1	6	12	9
No	16	10	6	5

Statistical analyses

Statistical analysis title	Difference of response rate (10 mg) vs placebo
Comparison groups	Avatrombopag 10 mg v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)
Point estimate	31.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.39
upper limit	57.84

Statistical analysis title	Difference of response rate (20 mg) vs placebo
Comparison groups	Placebo v Avatrombopag 20 mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)
Point estimate	60.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.3
upper limit	85.27

Statistical analysis title	Difference of response rate (30 mg) vs placebo
Comparison groups	Placebo v Avatrombopag 30 mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)
Point estimate	58.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.92
upper limit	85.88

Secondary: Change from Baseline of Local Platelet Count by Visit during Treatment Period A1 of Core Study

End point title	Change from Baseline of Local Platelet Count by Visit during Treatment Period A1 of Core Study

End point description:

Missing platelet counts were imputed using LOCF (last observation carried forward) approach for subjects who achieved platelet response at prior visits.

End point type	Secondary

End point timeframe:

Baseline, Day 7 and Day 14

End point values	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg	Avatrombopag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	18	14
Units: x109/L				
arithmetic mean (standard deviation)				
Day 7	-0.1 (± 7.15)	19.8 (± 17.59)	26.5 (± 22.06)	30.9 (± 37.65)
Day 14	-0.2 (± 13.79)	29.2 (± 18.32)	57.2 (± 31.39)	55.4 (± 37.47)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who achieved Platelet Count greater than 30 X 109/L from Baseline to Day 21 during Treatment Period A1 of Core Study

End point title	Number of Participants who achieved Platelet Count greater than 30 X 109/L from Baseline to Day 21 during Treatment Period A1 of Core Study

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 21

End point values	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg	Avatrombopag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	18	14
Units: Participants				
number (not applicable)				
Yes	1	9	16	11

No	16	7	2	3

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who initiated Antiviral Treatment by Day 21 of Period A1 of Core Study

End point title	Number of Participants who initiated Antiviral Treatment by Day 21 of Period A1 of Core Study

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 21

End point values	Placebo	Avatrombopag 10 mg	Avatrombopag 20 mg	Avatrombopag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	18	14
Units: Participants				
number (not applicable)				
Yes	1	6	13	9
No	16	10	5	5

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through the end of study

Adverse event reporting additional description:

Safety Analysis Set was used which combines data of the Core and Extension Phase and includes subjects who had at least 1 dose of avatrombopag. Placebo treatment arm was excluded since not part of study design for the Extension Phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Avatrombopag

Reporting group description:

During the core study, participants were administered a fixed dose of Avatrombopag 10mg, 20mg, or 30mg,orally, once daily, preferably with food for upto 21 days. The participants initiated Open label extension with Avontrombopag 20 mg, once daily. The avotrambopag dose was titrated up or down in accordance with their individual response, within the range of a minimum of 5mg and a maximum of 50 mg.

Serious adverse events	Avatrombopag		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 64 (20.31%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 64 (1.56%)		
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	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Neutropenia			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic mass			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Avatrombopag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 64 (85.94%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	12 / 64 (18.75%)		
occurrences (all)	17		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 64 (32.81%)		
occurrences (all)	31		
Leukopenia			

subjects affected / exposed	14 / 64 (21.88%)		
occurrences (all)	20		
Lymphopenia			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	20 / 64 (31.25%)		
occurrences (all)	25		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	13 / 64 (20.31%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	16 / 64 (25.00%)		
occurrences (all)	17		
Influenza like illness			
subjects affected / exposed	11 / 64 (17.19%)		
occurrences (all)	13		
Injection site erythema			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	7		
Irritability			
subjects affected / exposed	7 / 64 (10.94%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	9 / 64 (14.06%)		
occurrences (all)	13		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 6		
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6		
Ascites subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 7		
Diarrhoea subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 12		
Dyspepsia subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Haemorrhoids subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 6		
Nausea subjects affected / exposed occurrences (all)	20 / 64 (31.25%) 22		
Vomiting subjects affected / exposed occurrences (all)	8 / 64 (12.50%) 10		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 10		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Dyspnoea exertional subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 5		
Epistaxis			

subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 7		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 15 / 64 (23.44%) 15 12 / 64 (18.75%) 16		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 5 / 64 (7.81%) 6 13 / 64 (20.31%) 13		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 4 / 64 (6.25%) 4 4 / 64 (6.25%) 6		
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	 4 / 64 (6.25%) 5		

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