Clinical trial results:
A longitudinal 2-year bone marrow study of eltrombopag olamine (SB-497115-GR) in previously treated adults, with chronic immune (idiopathic) thrombocytopenic purpura (ITP).

Summary

EudraCT number	2009-010421-39
Trial protocol	DE CZ FR HU IT
Global end of trial date	06 May 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	09 April 2015

Trial information

Trial identification

Sponsor protocol code	TRA112940

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	23 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the levels of bone marrow fibers (reticulin and/or collagen) at baseline and any change from baseline after 1 and 2 years of treatment with eltrombopag in adult subjects with chronic ITP

Protection of trial subjects:

Additional testing in case of Abnormal Bone Marrow Biopsy Findings
Subjects with post-baseline increase in bone marrow fibers to grade MF-2 or -3 on European Consensus scale or grade 3 or 4 on the Bauermeister scale will have the following assessments performed: 1. Peripheral blood smear to evaluate the presence of teardrop erythrocytes, nucleated red blood cells or any other relevant abnormality. 2. Testing for JAK2 (V617F) mutation. 3. Ultrasound evaluation of the size of the liver and spleen. 4. Blood sample for TGF-β measurement.
Ultrasound of Liver and Spleen
During the study, ultrasound of liver and spleen will be performed when a post-baseline increase of clinically significant bone marrow abnormality such as reticulin grade of either MF-2 or MF-3 on European Consensus scale or Grade 3 or 4 on Bauermeister scale is recorded or at any other time at the investigator discretion.
Peripheral Blood Smear
A peripheral blood smear should be performed at the Screening Visit, pre-dose Day 1, once every 4 weeks (or every 8 weeks if the dose of eltrombopag and concomitant ITP, if any, is stable for 3 months) during the treatment period, at the end of treatment visit or at the early withdrawal, and at 4-week follow-up visit.
ECG
A 12-lead ECG will be obtained for each subject during screening. During the study, an ECG can also be performed at the discretion of investigator, when clinically indicated.
Renal Monitoring
Renal function will be assessed in all subjects pre-dose on Day 1. Throughout the study, serum creatinine will be measured once every two weeks and will serve as the main tool to check for global renal function.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2010
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	Czech Republic: 11
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Korea, Republic of: 20

Country: Number of subjects enrolled	Pakistan: 28
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Hong Kong: 12
Country: Number of subjects enrolled	India: 25
Worldwide total number of subjects	167
EEA total number of subjects	52

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)	151
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 167 participants (par.) were enrolled and received at least one dose of study medication. The 5 enrolled participants from center 082877 were excluded from the analysis due to the following: serious good clinical practice (GCP) findings related to informed consent, source documents and investigator study oversight.

Period 1

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

Arms

Arm title	Eltrombopag

Arm description:

Participants received an Open-label treatment of eltrombopag administered as a tablet for up to 2 years (104 weeks), followed by a follow-up period of up to 6 months (only 4 weeks for most participants). The starting dose of eltrombopag was 50 milligrams (mg), once daily (QD). East Asian participants started at a dose of 25 mg QD. The maximum dose allowed was 75 mg daily. Dose modifications were allowed based upon each participant's individual platelet count response.

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

Dosage and administration details:

Tablet in 12.5 mg, 25 mg, 50 mg, and 75 mg. Starting dose of 50mg once daily (25 mg once daily for subjects of East Asian ancestry). Dosing regimen then individualized based on platelet counts.

Number of subjects in period 1[1]	Eltrombopag
Started	162
Completed	118
Not completed	44
Adverse event, serious fatal	3
Consent withdrawn by subject	7
Physician decision	1
Adverse event, non-fatal	19
Lost to follow-up	3
Lack of efficacy	11

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 167 participants were enrolled and received at least one dose of study medication. The 5 enrolled participants from center 082877 were excluded from the analysis due to the following: serious good clinical practice (GCP) findings related to informed consent, source documents and investigator study oversight.

Baseline characteristics

Reporting groups	
Reporting group title	Eltrombopag

Reporting group description:

Participants received an Open-label treatment of eltrombopag administered as a tablet for up to 2 years (104 weeks), followed by a follow-up period of up to 6 months (only 4 weeks for most participants). The starting dose of eltrombopag was 50 milligrams (mg), once daily (QD). East Asian participants started at a dose of 25 mg QD. The maximum dose allowed was 75 mg daily. Dose modifications were allowed based upon each participant's individual platelet count response.

Reporting group values	Eltrombopag	Total	
Number of subjects	162	162	
Age categorical			
Units: Subjects			
Age continuous			
All Treated Subjects (ATS) Population: all participants who received at least one dose of study medication excluding the 5 participants from Center 082877.			
Units: years			
arithmetic mean	43.1		
standard deviation	± 16.31	-	
Gender categorical			
All Treated Subjects (ATS) Population: all participants who received at least one dose of study medication excluding the 5 participants from Center 082877.			
Units: Subjects			
Female	104	104	
Male	58	58	
Race			
All Treated Subjects (ATS) Population: all participants who received at least one dose of study medication excluding the 5 participants from Center 082877.			
Units: Subjects			
Asian - Central/South Asian Heritage	47	47	
Asian - East Asian Heritage	32	32	
Asian - South East Asian Heritage	1	1	
White - White/Caucasian/European Heritage	81	81	
Missing	1	1	

End points

End points reporting groups

Reporting group title	Eltrombopag

Reporting group description:

Participants received an Open-label treatment of eltrombopag administered as a tablet for up to 2 years (104 weeks), followed by a follow-up period of up to 6 months (only 4 weeks for most participants). The starting dose of eltrombopag was 50 milligrams (mg), once daily (QD). East Asian participants started at a dose of 25 mg QD. The maximum dose allowed was 75 mg daily. Dose modifications were allowed based upon each participant's individual platelet count response.

Primary: Number of participants with bone marrow (BM) fibers of MF Grade 0, 1, 2 and 3 on the European Consensus (EC) scale at Baseline

End point title	Number of participants with bone marrow (BM) fibers of MF Grade 0, 1, 2 and 3 on the European Consensus (EC) scale at Baseline[1]

End point description:

The evaluation of fibrosis was performed using BM biopsies in which the amount of fibrosis was assessed by the EC Grading Scale. This method distinguishes four degrees of fibrosis (myelofibrosis [MF]-0 to MF-3). MF Grade (G) 0 is scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM; MF Grade 1 is loose network of reticulin with many intersections, especially in perivascular areas; MF Grade 2 is diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; MF Grade 3 is diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. Baseline is defined as the most recent centrally-reviewed BM biopsy prior to first dose of eltrombopag in the study. All Treated Subjects (ATS) Population: all par. who received >=1 dose of study medication excluding the 5 par. from center 082877.

End point type	Primary

End point timeframe:

Baseline

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: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	159[2]			
Units: Participants				
MF-0	150			
MF-1	9			
MF-2	0			
MF-3	0			

Notes:

[2] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with a positive or negative collagen level at Baseline

End point title	Number of participants with a positive or negative collagen level at Baseline[3]

End point description:

The number of participants with a positive or negative collagen level was analyzed. Baseline is defined as the most recent centrally-reviewed BM biopsy prior to first dose of eltrombopag in the study.

End point type	Primary

End point timeframe:

Baseline

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: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	159[4]			
Units: Participants				
Negative	159			
Positive	0			

Notes:

[4] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with indicated grade change from Baseline in the EC grading scale at 1 year

End point title	Number of participants with indicated grade change from Baseline in the EC grading scale at 1 year[5]

End point description:

The change from baseline to on-treatment assessments of European Consensus (EC) scale was analyzed. On-treatment is defined as during the treatment period (including dose interruptions) and up to 14 days after the end of the treatment period. MF-0 is scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM; MF-1 is loose network of reticulin with many intersections, especially in perivascular areas; MF-2 is diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; MF-3 is diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. Baseline is defined as the most recent centrally-reviewed BM biopsy prior to first dose of eltrombopag in the study.

End point type	Primary

End point timeframe:

Baseline and 1 year

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: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	127[6]			
Units: Participants				
MF-0 to MF-0	82			
MF-0 to MF-1	33			
MF-0 to MF-2	2			
MF-0 to MF-3	2			
MF-1 to MF-0	3			
MF-1 to MF-1	2			
MF-1 to MF-2	1			
MF-1 to MF-3	0			
MF-2 to MF-0	0			
MF-2 to MF-1	0			
MF-2 to MF-2	0			
MF-2 to MF-3	0			
MF-3 to MF-0	0			
MF-3 to MF-1	0			
MF-3 to MF-2	0			
MF-3 to MF-3	0			
Missing to MF-0	2			
Missing to MF-1	0			
Missing to MF-2	0			
Missing to MF-3	0			

Notes:

[6] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with indicated change from Baseline in the EC grading scale at 2 years

End point title	Number of participants with indicated change from Baseline in the EC grading scale at 2 years[7]

End point description:

The change from baseline to on-treatment assessments of European Consensus (EC) scale was analyzed. On-treatment is defined as during the treatment period (including dose interruptions) and up to 14 days after the end of the treatment period. MF-0 is scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM; MF-1 is loose network of reticulin with many intersections, especially in perivascular areas; MF-2 is diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; MF-3 is diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. Baseline is defined as the most recent centrally-reviewed BM biopsy prior to first dose of eltrombopag in the study.

End point type	Primary

End point timeframe:

Baseline and 2 years

Notes:

[7] - 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: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	93[8]			
Units: Participants				
MF-0 to MF-0	79			
MF-0 to MF-1	9			
MF-0 to MF-2	0			
MF-0 to MF-3	0			
MF-1 to MF-0	2			
MF-1 to MF-1	1			
MF-1 to MF-2	0			
MF-1 to MF-3	0			
MF-2 to MF-0	0			
MF-2 to MF-1	0			
MF-2 to MF-2	0			
MF-2 to MF-3	0			
MF-3 to MF-0	0			
MF-3 to MF-1	0			
MF-3 to MF-2	0			
MF-3 to MF-3	0			
Missing to MF-0	2			
Missing to MF-1	0			
Missing to MF-2	0			
Missing to MF-3	0			

Notes:

[8] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with a positive or negative collagen level at 1 year

End point title	Number of participants with a positive or negative collagen level at 1 year[9]

End point description:

The change from Baseline to on-treatment assessments of collagen level was analyzed. On-treatment is defined as during the treatment period (including dose interruptions) and up to 14 days after the end of the treatment period.

End point type	Primary

End point timeframe:

1 year

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	127[10]			
Units: Participants				
Negative to Negative	120			
Negative to Positive	5			
Positive to Negative	0			
Positive to Positive	0			
Missing to Negative	2			
Missing to Positive	0			

Notes:

[10] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with a positive or negative collagen level at 2 year

End point title	Number of participants with a positive or negative collagen level at 2 year[11]

End point description:

The change from Baseline to on-treatment assessments of collagen level was analyzed. On-treatment is defined as during the treatment period (including dose interruptions) and up to 14 days after the end of the treatment period.

End point type	Primary

End point timeframe:

2 years

Notes:

[11] - 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: Data for this endpoint has been analysed descriptively using counts and percentages as planned in the study protocol and analysis plan.

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	93[12]			
Units: Participants				
Negative to Negative	90			
Negative to Positive	1			
Positive to Negative	0			
Positive to Positive	0			
Missing to Negative	2			
Missing to Positive	0			

Notes:

[12] - ATS Population.Par. with bone marrow biopsy data available in the relevant time period were included

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated maximum toxicity grade for the indicated clinical chemistry parameters at any time post-Baseline during the

study

End point title	Number of participants with the indicated maximum toxicity grade for the indicated clinical chemistry parameters at any time post-Baseline during the study

End point description:

Clinical chemistry parameters were summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0: G0, none; G1, mild; G2, moderate; G3, severe; G4, life-threatening or disabling. Clinical chemistry parameters included: albumin, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, calcium (hypercalcemia), calcium (hypocalcemia), potassium (hyperkalemia), potassium (hypokalemia), sodium (hypernatremia), sodium (hyponatremia), inorganic phosphorus, creatine kinase (CK) and creatinine. Baseline values were obtained at Day 1.Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). The maximum post-Baseline toxicity grade includes any scheduled or unscheduled post-Baseline assessment during.

End point type	Secondary

End point timeframe:

From Week 1 up to Week 104 and up to 6 months follow-up (4 weeks for most participants) (up to approximately 2.5 years)

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	162[13]			
Units: Participants				
Albumin, G0, n=162	151			
Albumin, G1, n=162	5			
Albumin, G2, n=162	6			
Albumin, G3, n=162	0			
Albumin, G4, n=162	0			
ALP, G0, n=162	125			
ALP, G1, n=162	35			
ALP, G2, n=162	2			
ALP, G3, n=162	0			
ALP, G4, n=162	0			
ALT, G0, n=162	109			
ALT, G1, n=162	37			
ALT, G2, n=162	8			
ALT, G3, n=162	7			
ALT, G4, n=162	1			
AST, G0, n=162	99			
AST, G1, n=162	48			
AST, G2, n=162	8			
AST, G3, n=162	5			
AST, G4, n=162	2			
Total bilirubin, G0, n=162	103			
Total bilirubin, G1, n=162	40			
Total bilirubin, G2, n=162	17			
Total bilirubin, G3, n=162	2			
Total bilirubin, G4, n=162	0			
Calcium (hypercalcemia), G0, n=162	159			
Calcium (hypercalcemia), G1, n=162	2			
Calcium (hypercalcemia), G2, n=162	1			

Calcium (hypercalcemia), G3, n=162	0			
Calcium (hypercalcemia), G4, n=162	0			
Calcium (hypocalcemia), G0, n=162	92			
Calcium (hypocalcemia), G1, n=162	57			
Calcium (hypocalcemia), G2, n=162	12			
Calcium (hypocalcemia), G3, n=162	0			
Calcium (hypocalcemia), G4, n=162	1			
Potassium (hyperkalemia), G0, n=162	138			
Potassium (hyperkalemia), G1, n=162	14			
Potassium (hyperkalemia), G2, n=162	5			
Potassium (hyperkalemia), G3, n=162	5			
Potassium (hyperkalemia), G4, n=162	0			
Potassium (hypokalemia), G0, n=162	123			
Potassium (hypokalemia), G1, n=162	35			
Potassium (hypokalemia), G2, n=162	0			
Potassium (hypokalemia), G3, n=162	4			
Potassium (hypokalemia), G4, n=162	0			
Sodium (hypernatremia), G0, n=162	138			
Sodium (hypernatremia), G1, n=162	20			
Sodium (hypernatremia), G2, n=162	2			
Sodium (hypernatremia), G3, n=162	2			
Sodium (hypernatremia), G4, n=162	0			
Sodium (hyponatremia), G0, n=162	137			
Sodium (hyponatremia), G1, n=162	21			
Sodium (hyponatremia), G2, n=162	0			
Sodium (hyponatremia), G3, n=162	3			
Sodium (hyponatremia), G4, n=162	1			
Inorganic phosphorus, G0, n=162	100			
Inorganic phosphorus, G1, n=162	0			
Inorganic phosphorus, G2, n=162	52			
Inorganic phosphorus, G3, n=162	10			
Inorganic phosphorus, G4, n=162	0			
CK, G0, n=16	15			
CK, G1, n=16	1			
CK, G2, n=16	0			
CK, G3, n=16	0			
CK, G4, n=16	0			
Creatinine, G0, n=162	149			
Creatinine, G1, n=162	8			
Creatinine, G2, n=162	3			
Creatinine, G3, n=162	0			
Creatinine, G4, n=162	2			

Notes:

[13] - ATS Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated maximum toxicity grade for the indicated hematology parameters at any time post-Baseline during the study

End point title	Number of participants with the indicated maximum toxicity grade for the indicated hematology parameters at any time post-Baseline during the study

End point description:

Hematology parameters were summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0: G0, none; G1, mild; G2, moderate; G3, severe; G4, life-threatening or disabling. Hematology parameters included: hemoglobin (increased), hemoglobin (anemia), lymphocyte count (increased), lymphocyte count (decreased), total absolute neutrophil count (ANC), platelet count and white blood cell (WBC) count. Baseline values were obtained at Day 1. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). The maximum post-Baseline toxicity grade includes any scheduled or unscheduled post-Baseline assessment during.

End point type	Secondary

End point timeframe:

From Week 1 up to Week 104 and up to 6 months follow-up (4 weeks for most participants) (up to approximately 2.5 years)

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	162[14]			
Units: Participants				
Hemoglobin (increased), G0, n=162	143			
Hemoglobin (increased), G1, n=162	17			
Hemoglobin (increased), G2, n=162	1			
Hemoglobin (increased), G3, n=162	1			
Hemoglobin (increased), G4, n=162	0			
Hemoglobin (anemia), G0, n=162	55			
Hemoglobin (anemia), G1, n=162	63			
Hemoglobin (anemia), G2, n=162	31			
Hemoglobin (anemia), G3, n=162	13			
Hemoglobin (anemia), G4, n=162	0			
Lymphocyte count (increased), G0, n=161	122			
Lymphocyte count (increased), G1, n=161	0			
Lymphocyte count (increased), G2, n=161	39			
Lymphocyte count (increased), G3, n=161	0			
Lymphocyte count (increased), G4, n=161	0			
Lymphocyte count (decreased), G0, n=161	86			
Lymphocyte count (decreased), G1, n=161	36			
Lymphocyte count (decreased), G2, n=161	26			
Lymphocyte count (decreased), G3, n=161	13			
Lymphocyte count (decreased), G4, n=161	0			
Total ANC, G0, n=161	140			
Total ANC, G1, n=161	12			
Total ANC, G2, n=161	3			
Total ANC, G3, n=161	3			

Total ANC, G4, n=161	3			
Platelet count, G0, n=162	2			
Platelet count, G1, n=162	8			
Platelet count, G2, n=162	3			
Platelet count, G3, n=162	26			
Platelet count, G4, n=162	123			
WBC, G0, n=162	135			
WBC, G1, n=162	21			
WBC, G2, n=162	3			
WBC, G3, n=162	3			
WBC, G4, n=162	0			

Notes:

[14] - ATS Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE) started on-therapy + 1 day, >1 to 30 days post therapy and >30 days post therapy

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE) started on-therapy + 1 day, >1 to 30 days post therapy and >30 days post therapy

End point description:

On-therapy + 1 day is defined as AEs started between the first dose of eltrombopag and up to the day after the last dose of eltrombopag; >1 to 30 days post therapy is defined as AEs that started more than 1 day and up to 30 days after the last dose of eltrombopag; >30 days post therapy is defined as AEs started that started more than 30 days after the last dose of eltrombopag. An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is defined as any untoward medical occurrence that, at any dose: results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability or incapacity, or is a congenital anomaly or birth defect. Medical or scientific judgment should be exercised in other situations.

End point type	Secondary

End point timeframe:

From Week 1 up to Week 104 and up to 6 months follow-up (4 weeks for most participants) (up to approximately 2.5 years)

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	162[15]			
Units: Participants				
Any AE, on-therapy + 1 day	141			
Any SAE, on-therapy + 1 day	41			
Any AE, >1 to 30 days post therapy	12			
Any SAE, >1 to 30 days post therapy	5			
Any AE, >30 days post therapy	9			
Any SAE, >30 days post therapy	1			

Notes:
[15] - ATS Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment SAEs and non-serious AEs are defined as events occuring from the start of the treatment (Day 1) up to Week 104 and including the follow-up period of up to 6 months (only 4 weeks for most participants) (up to approximately 2.5 years).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in participants of the ATS Population, comprised of all participants who had received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Eltrombopag

Reporting group description: -

Serious adverse events	Eltrombopag		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 162 (25.93%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Salivary gland cancer			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
T-cell lymphoma			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			

subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Local swelling				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				

Menorrhagia				
subjects affected / exposed	3 / 162 (1.85%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychosomatic disease				

subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Joint dislocation				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Road traffic accident			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cerebral venous thrombosis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transverse sinus thrombosis			
subjects affected / exposed	1 / 162 (0.62%)		
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 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 162 (1.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gingival bleeding			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Mallory-Weiss syndrome				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				

subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cholecystitis infective				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder empyema				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				

subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash pustular			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sialoadenitis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Eltrombopag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 162 (70.37%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	13 / 162 (8.02%)		
occurrences (all)	19		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	9 / 162 (5.56%) 13		
Fatigue subjects affected / exposed occurrences (all)	15 / 162 (9.26%) 16		
Influenza like illness subjects affected / exposed occurrences (all)	15 / 162 (9.26%) 23		
Pain subjects affected / exposed occurrences (all)	9 / 162 (5.56%) 23		
Pyrexia subjects affected / exposed occurrences (all)	18 / 162 (11.11%) 25		
Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all)	10 / 162 (6.17%) 15		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	24 / 162 (14.81%) 38		
Epistaxis subjects affected / exposed occurrences (all)	15 / 162 (9.26%) 21		
Oropharyngeal pain subjects affected / exposed occurrences (all)	16 / 162 (9.88%) 35		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 162 (8.02%) 20		
Aspartate aminotransferase increased			

subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	17		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	11 / 162 (6.79%)		
occurrences (all)	15		
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 162 (6.17%)		
occurrences (all)	12		
Headache			
subjects affected / exposed	30 / 162 (18.52%)		
occurrences (all)	129		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 162 (6.79%)		
occurrences (all)	14		
Iron deficiency anaemia			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	32		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	15		
Abdominal pain upper			
subjects affected / exposed	14 / 162 (8.64%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	21 / 162 (12.96%)		
occurrences (all)	34		
Dyspepsia			

subjects affected / exposed	16 / 162 (9.88%)		
occurrences (all)	25		
Gingival bleeding			
subjects affected / exposed	16 / 162 (9.88%)		
occurrences (all)	26		
Nausea			
subjects affected / exposed	21 / 162 (12.96%)		
occurrences (all)	37		
Vomiting			
subjects affected / exposed	15 / 162 (9.26%)		
occurrences (all)	29		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	17 / 162 (10.49%)		
occurrences (all)	36		
Pruritus			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	14		
Purpura			
subjects affected / exposed	10 / 162 (6.17%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 162 (13.58%)		
occurrences (all)	33		
Back pain			
subjects affected / exposed	17 / 162 (10.49%)		
occurrences (all)	33		
Pain in extremity			
subjects affected / exposed	14 / 162 (8.64%)		
occurrences (all)	30		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	17 / 162 (10.49%) 27 20 / 162 (12.35%) 49 13 / 162 (8.02%) 23		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 162 (5.56%) 13		

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