Clinical trial results:
A randomized, blinded, placebo-controlled, dose finding study to assess the safety and efficacy of the oral thrombopoietin receptor agonist, eltrombopag, administered to subjects with acute myelogenous leukemia (AML) receiving induction chemotherapy.

Summary

EudraCT number	2013-000642-20
Trial protocol	BE HU PL GR
Global end of trial date	25 January 2017

Results information

Result version number	v1 (current)
This version publication date	10 February 2018
First version publication date	10 February 2018

Trial information

Trial identification

Sponsor protocol code	117146

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01890746
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.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	25 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of eltrombopag versus placebo in subjects receiving standard induction therapy for acute myeloid leukemia (AML).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2013
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	Australia: 19
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 43
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	148
EEA total number of subjects	22

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)	106
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants (Par.) diagnosed with Acute Myelogenous Leukemia (AML) of any subtype (except acute promyelocytic [M3] or acute megakaryocytic leukaemia [M7]) were eligible for the study.

Pre-assignment

Screening details:

Sufficient number of participants were screened and 148 participants were randomized and entered in to the study. Participants were stratified by antecedent malignant hematologic disorder (yes versus no) and age (18-60 years versus >60 years), before they were randomized to receive study treatments.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Eltrombopag (ELQ) QD

Arm description:

Par. received (rec) first line induction (IDN) chemotherapy (CTY) consisting of daunorubicin (DAU) bolus intravenous (IV) infusion (INF) on Days (D) 1-3 at a dose of 90 milligrams (mg)/square meter (m^2) for Par. 18-60 year (yr) or 60 mg/m^2 for >60 yr plus cytarabine (CB) 100 mg/m^2 continuous IV INF on D1-7. Par. rec ELT as 200 mg (100 mg for East-Asian Heritage [EAH]) once daily (QD) oral dose starting on D4 of initial IDN CTY at least 20 hours after end of D3 DAU INF. If platelet (PT) count was not >100 Giga (Gi)/Liter (L) after 7D the dose was increased to 300 mg (150 mg for EAH) QD until a PT count of at least 200 Gi/L was achieved, until remission was assessed by bone marrow biopsy, or for a maximum of 42D from the start of the CTY IDN cycle. Par. not aplastic after first cycle of IDN CTY rec re-IDN with a modified DAU dose of 45mg/m^2/day on D1-3 plus CB 100 mg/m^2/day on D1-7. For re-IDN Par., ELT was held from D1-3 of re-IDN, and resumed on D4 at the same dose and duration.

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:

Eltrombopag 200 mg orally, once daily, beginning on Day 4 of the first cycle of induction. After 7 days, the dose of IP was increased to 300 mg if platelet counts were <100 Gi/L. IP continued until achievement of platelet count of at least 200 Gi/L or assessment of remission of bone marrow status or a maximum of 42 days after initiation of most recent induction. In subjects of East Asian heritage (e.g., Japanese, Chinese, Taiwanese, Korean, Thai): 100 mg orally once daily (a 50% dose reduction) was used; After 7 days, the dose of IP was increased to 150 mg if platelet counts were <100 Gi/L.

Arm title	Placebo QD

Arm description:

Participants received first line IDN CTY consisting of DAU bolus IV INF on Days 1-3 at a dose of 90 mg/m^2 for participants 18-60 years old or 60 mg/m^2 for participants >60 years of age plus cytarabine continuous IV INF on Days 1-7 at a dose of 100 mg/m^2. Participants received placebo QD oral dose starting on Day 4 of initial IDN CTY at least 20 hours after end of Day 3 DAU INF up to a maximum duration of 42 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:

Placebo 200 mg orally, once daily, beginning on Day 4 of the first cycle of induction. After 7 days, the dose of IP was increased to 300 mg if platelet counts were <100 Gi/L. IP continued until achievement of platelet count of at least 200 Gi/L or assessment of remission of bone marrow status or a maximum of 42 days after initiation of most recent induction. In subjects of East Asian heritage (e.g., Japanese, Chinese, Taiwanese, Korean, Thai): 100 mg orally once daily (a 50% dose reduction) was used; After 7 days, the dose of IP was increased to 150 mg if platelet counts were <100 Gi/L.

Number of subjects in period 1	Eltrombopag (ELQ) QD	Placebo QD
Started	74	74
Completed	22	33
Not completed	52	41
Adverse event, serious fatal	39	30
Physician decision	3	2
Consent withdrawn by subject	5	8
Adverse event, non-fatal	1	-
Lost to follow-up	4	1

Baseline characteristics

Reporting groups

Reporting group title	Eltrombopag (ELQ) QD

Reporting group description:

Par. received (rec) first line induction (IDN) chemotherapy (CTY) consisting of daunorubicin (DAU) bolus intravenous (IV) infusion (INF) on Days (D) 1-3 at a dose of 90 milligrams (mg)/square meter (m^2) for Par. 18-60 year (yr) or 60 mg/m^2 for >60 yr plus cytarabine (CB) 100 mg/m^2 continuous IV INF on D1-7. Par. rec ELT as 200 mg (100 mg for East-Asian Heritage [EAH]) once daily (QD) oral dose starting on D4 of initial IDN CTY at least 20 hours after end of D3 DAU INF. If platelet (PT) count was not >100 Giga (Gi)/Liter (L) after 7D the dose was increased to 300 mg (150 mg for EAH) QD until a PT count of at least 200 Gi/L was achieved, until remission was assessed by bone marrow biopsy, or for a maximum of 42D from the start of the CTY IDN cycle. Par. not aplastic after first cycle of IDN CTY rec re-IDN with a modified DAU dose of 45mg/m^2/day on D1-3 plus CB 100 mg/m^2/day on D1-7. For re-IDN Par., ELT was held from D1-3 of re-IDN, and resumed on D4 at the same dose and duration.

Reporting group title	Placebo QD

Reporting group description:

Participants received first line IDN CTY consisting of DAU bolus IV INF on Days 1-3 at a dose of 90 mg/m^2 for participants 18-60 years old or 60 mg/m^2 for participants >60 years of age plus cytarabine continuous IV INF on Days 1-7 at a dose of 100 mg/m^2. Participants received placebo QD oral dose starting on Day 4 of initial IDN CTY at least 20 hours after end of Day 3 DAU INF up to a maximum duration of 42 days.

Reporting group values	Eltrombopag (ELQ) QD	Placebo QD	Total
Number of subjects	74	74	148
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	56.7	56.6	
standard deviation	± 12.25	± 11.58	-
Sex: Female, Male Units: Subjects			
Female	38	31	69
Male	36	43	79
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage|	1	2	3
Asian - Central/South Asian Heritage|	0	1	1
Asian - East Asian Heritage|	26	17	43
Asian - South East Asian Heritage|	0	1	1

White - Arabic/North African Heritage|	5	3	8
White - White/Caucasian/European Heritage|	42	50	92

End points

End points reporting groups

Reporting group title	Eltrombopag (ELQ) QD

Reporting group description:

Par. received (rec) first line induction (IDN) chemotherapy (CTY) consisting of daunorubicin (DAU) bolus intravenous (IV) infusion (INF) on Days (D) 1-3 at a dose of 90 milligrams (mg)/square meter (m^2) for Par. 18-60 year (yr) or 60 mg/m^2 for >60 yr plus cytarabine (CB) 100 mg/m^2 continuous IV INF on D1-7. Par. rec ELT as 200 mg (100 mg for East-Asian Heritage [EAH]) once daily (QD) oral dose starting on D4 of initial IDN CTY at least 20 hours after end of D3 DAU INF. If platelet (PT) count was not >100 Giga (Gi)/Liter (L) after 7D the dose was increased to 300 mg (150 mg for EAH) QD until a PT count of at least 200 Gi/L was achieved, until remission was assessed by bone marrow biopsy, or for a maximum of 42D from the start of the CTY IDN cycle. Par. not aplastic after first cycle of IDN CTY rec re-IDN with a modified DAU dose of 45mg/m^2/day on D1-3 plus CB 100 mg/m^2/day on D1-7. For re-IDN Par., ELT was held from D1-3 of re-IDN, and resumed on D4 at the same dose and duration.

Reporting group title	Placebo QD

Reporting group description:

Participants received first line IDN CTY consisting of DAU bolus IV INF on Days 1-3 at a dose of 90 mg/m^2 for participants 18-60 years old or 60 mg/m^2 for participants >60 years of age plus cytarabine continuous IV INF on Days 1-7 at a dose of 100 mg/m^2. Participants received placebo QD oral dose starting on Day 4 of initial IDN CTY at least 20 hours after end of Day 3 DAU INF up to a maximum duration of 42 days.

Primary: Number of participants with any adverse events (AE) and any serious adverse events (SAE) as a measure of safety and tolerability.

End point title	Number of participants with any adverse events (AE) and any serious adverse events (SAE) as a measure of safety and tolerability.[1]

End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An 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/incapacity, is a congenital anomaly/birth defect, is an important medical event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition, or is associated with liver injury and impaired liver function.

End point type	Primary

End point timeframe:

From the time the first dose of study treatment was administered until 30 days following discontinuation of investigational product regardless of initiation of a new cancer therapy or transfer to hospice

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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Participants				
Any AE|	72	66		
Any SAE|	24	14		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the left ventricular ejection fraction (LVEF).

End point title	Change from baseline in the left ventricular ejection fraction (LVEF).[2]

End point description:

LVEF is a measurement of the percentage of blood leaving heart each time it contracts. LVEF was assessed by an echocardiogram (ECHO) or Multiple Gated Acquisition scan (MUGA). Baseline was defined as the most recent, non-missing value prior to or on the first study treatment dose date. Change from Baseline was calculated as the Day 42 value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: LVEF percent				
arithmetic mean (standard deviation)				
change from baseline to end of study (n = 57, 62)|	-2.5 (± 7.81)	-4.3 (± 8.54)		
baseline to worse post-baseline case (n =58,63)|	-4.1 (± 8.61)	-5.7 (± 9.05)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with worst-case grade changes from Baseline in the hematology parameters

End point title	Number of participants with worst-case grade changes from Baseline in the hematology parameters[3]

End point description:

The number of participants with a maximum post-baseline grade increase of Grade 3 (G3) or Grade 4 (G4) from their baseline grade are presented. Hematology parameters included only lab tests that are gradable by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

End point type	Primary

End point timeframe:

Baseline and up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Participants				
Hemoglobin Low, G3|	53	46		
Leukocytes, G3|	10	10		
Leukocytes, G4|	9	5		
Lymphocytes Low, G3|	31	26		
Lymphocytes Low, G4|	35	38		
Neutrophils, G4|	44	39		
Platelets, G3|	1	0		
Platelets, G4|	63	56		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with worst-case grade changes from Baseline in the clinical chemistry parameters

End point title	Number of participants with worst-case grade changes from Baseline in the clinical chemistry parameters[4]

End point description:

The number of participants with a maximum post-baseline grade increase of Grade 3 or Grade 4 from their baseline grade are presented. Clinical Clinical Chemistry parameters included only lab tests that are gradable by CTCAE v4.0.

End point type	Primary

End point timeframe:

Baseline and up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

Notes:

[4] - 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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Participants				
Alanine Aminotransferase, G3|	1	5		
Albumin, G3|	6	4		
Aspartate Aminotransferase, G3|	0	1		
Bilirubin, G3|	1	4		
Bilirubin, G4|	0	1		
Calcium Low, G3|	0	1		
Creatinine, G3|	0	1		
Creatinine, G4|	1	0		

Glucose High, G3|	6	3		
Glucose High, G4|	0	1		
Magnesium Low, G3|	0	1		
Magnesium High, G3|	3	0		
Phosphate, G3|	10	19		
Phosphate, G4|	1	0		
Potassium Low, G3|	8	10		
Potassium Low, G4|	0	2		
Potassium High, G3|	4	0		
Potassium High, G4|	1	1		
Sodium Low, G3|	3	4		
Urate, G4|	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with liver events.

End point title	Number of participants with liver events.[5]

End point description:

The number of participants with liver enzyme (ALT, AST, ALP, Total bilirubin) abnormalities while receiving study treatment in each arm are presented.

End point type	Primary

End point timeframe:

8 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Participants	2	6		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with worst-case changes from Baseline in electrocardiogram (ECG) values

End point title	Number of participants with worst-case changes from Baseline in electrocardiogram (ECG) values[6]

End point description:

The number of participants with worst case post-baseline changes (normal, abnormal - not clinically significant [NCS], abnormal - clinically significant [NS]) in ECG QT prolonged values are presented. The protocol does not define the criteria for normal, abnormal-NCS and abnormal CS ECG. The outcome was based solely on the investigator interpretation of ECG tracings.

End point type	Primary

End point timeframe:

Baseline and Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[7]	71[8]		
Units: Participants				
Normal	34	33		
Abnormal - NCS	23	29		
Abnormal - CS	2	1		

Notes:

[7] - (n = 59, 63)

[8] - (n = 59, 63)

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with worst-case changes from Baseline in the Eastern Cooperative Oncology Group (ECOG) performance status

End point title	Number of participants with worst-case changes from Baseline in the Eastern Cooperative Oncology Group (ECOG) performance status[9]

End point description:

The number of participants with worst case post-baseline changes (improved, no change, deteriorated) are presented.

End point type	Primary

End point timeframe:

Baseline and Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

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: No Statistical analysis was performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	71		
Units: Participants				
Deteriorated|	36	36		
Improved|	0	1		
No Change|	37	34		

Statistical analyses

No statistical analyses for this end point

Primary: Worst-case change from Baseline in pulse rate values

End point title	Worst-case change from Baseline in pulse rate values[10]

End point description:

The worst-case post Baseline high and low changes in pulse rate values from Baseline are presented. Baseline was defined as the most recent, non-missing value prior to or on the first study treatment dose date. Post Baseline is defined as the highest and lowest non-missing post Baseline value respectively. Change from Baseline was calculated as the post Baseline value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

Notes:

[10] - 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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Beats/minute				
arithmetic mean (standard deviation)				
High, n=66, 67|	18.48 (± 20.616)	17.73 (± 15.112)		
Low, n=61, 55|	-10.36 (± 14.039)	-11.24 (± 12.123)		

Statistical analyses

No statistical analyses for this end point

Primary: Worst-case post Baseline change in blood pressure values from Baseline

End point title	Worst-case post Baseline change in blood pressure values from Baseline[11]

End point description:

The worst-case post Baseline high changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) values from Baseline are presented. Baseline was defined as the most recent, non-missing value prior to or on the first study treatment dose date. Change from Baseline was calculated as the visit value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

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: No Statistical analysis was performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP|	14.59 (± 17.936)	14.34 (± 14.626)		
DBP|	9.38 (± 12.000)	12.61 (± 10.947)		

Statistical analyses

No statistical analyses for this end point

Primary: Worst-case post Baseline change in temperature values from Baseline

End point title	Worst-case post Baseline change in temperature values from Baseline[12]

End point description:

The worst-case post Baseline high and low changes in temperature values from Baseline are presented. Baseline was defined as the most recent, non-missing value prior to or on the first study treatment dose date. Post Baseline was defined as the highest and lowest non-missing post Baseline value respectively. Change from Baseline was calculated as the post Baseline value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

Notes:

[12] - 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 performed for this endpoint.

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Degrees Celsius				
arithmetic mean (standard deviation)				
High, n=70, 69|	0.62 (± 0.941)	0.77 (± 0.879)		
Low, n=47, 43|	-0.44 (± 0.628)	-0.63 (± 0.592)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) parameter of daunorubicin: half-life (t1/2)

End point title	Plasma pharmacokinetics (PK) parameter of daunorubicin: half-life (t1/2)

End point description:

Daunorubicin half-life. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 1 Day 3

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: hour (h)				
geometric mean (confidence interval 95%)	15.754 (13.969 to 17.766)	13.709 (12.103 to 15.527)		

Statistical analyses

Statistical analysis title	Daunorubicin: t1/2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	114.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	99.5
upper limit	132.7

Secondary: Plasma pharmacokinetics (PK) parameter of daunorubicinol: half-life (t1/2)

End point title	Plasma pharmacokinetics (PK) parameter of daunorubicinol: half-life (t1/2)

End point description:

Daunorubicinol half-life. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 1 Day 3

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: hour (h)				
geometric mean (confidence interval 95%)	22.735 (21.187 to 24.396)	21.603 (20.232 to 23.067)		

Statistical analyses

Statistical analysis title	Daunorubicinol: t1/2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	105.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.1
upper limit	114

Secondary: Daunorubicin dose-normalized plasma: AUC(0-∞)

End point title	Daunorubicin dose-normalized plasma: AUC(0-∞)
End point description:	
Daunorubicin AUC(0-∞). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	8.0807 (7.0672 to 9.2396)	8.7880 (7.3893 to 10.451)		

Statistical analyses

Statistical analysis title	Daunorubicin: AUC(0-∞) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	92
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.8
upper limit	110.2

Secondary: Daunorubicinol dose-normalized plasma: AUC(0-∞)	
End point title	Daunorubicinol dose-normalized plasma: AUC(0-∞)
End point description:	
Daunorubicinol AUC(0-∞). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	63.997 (58.686 to 69.746)	62.835 (58.673 to 67.292)		

Statistical analyses

Statistical analysis title	Daunorubicinol: AUC(0-∞) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	101.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.9
upper limit	111.7

Secondary: Daunorubicin dose-normalized plasma: AUC(24-∞)	
End point title	Daunorubicin dose-normalized plasma: AUC(24-∞)
End point description:	
Daunorubicin AUC(24-∞). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	0.87496 (0.76202 to 1.0046)	0.72315 (0.62633 to 0.83493)		

Statistical analyses

Statistical analysis title	Daunorubicin AUC(24-∞) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	121
Confidence interval	
level	90 %
sides	2-sided
lower limit	102.5
upper limit	142.8

Secondary: Daunorubicinol dose-normalized plasma: AUC(24-∞)	
End point title	Daunorubicinol dose-normalized plasma: AUC(24-∞)
End point description:	
Daunorubicinol AUC(24-∞). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	24.537 (22.052 to 27.301)	23.039 (21.169 to 25.074)		

Statistical analyses

Statistical analysis title	Daunorubicinol AUC(24-∞) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	106.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	95
upper limit	119.4

Secondary: Daunorubicin dose-normalized plasma: AUC(0-t)

End point title	Daunorubicin dose-normalized plasma: AUC(0-t)

End point description:

Daunorubicin AUC(0-t). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 1 Day 3

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	7.9523 (6.9485 to 9.1012)	8.6723 (7.2855 to 10.323)		

Statistical analyses

Statistical analysis title	Daunorubicin AUC(0-t) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	91.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.5
upper limit	110

Secondary: Daunorubicinol dose-normalized plasma: AUC(0-t)

End point title	Daunorubicinol dose-normalized plasma: AUC(0-t)
End point description:	
daunorubicinol AUC(0-t). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	62.463 (57.268 to 68.129)	61.608 (57.500 to 66.009)		

Statistical analyses

Statistical analysis title	Daunorubicinol AUC(0-t) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	101.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.4
upper limit	111.2

Secondary: Daunorubicin dose-normalized plasma: AUC(24-t)

End point title	Daunorubicin dose-normalized plasma: AUC(24-t)

End point description:

Daunorubicin AUC(24-t). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 1 Day 3

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	0.76524 (0.65947 to 0.88797)	0.59660 (0.48882 to 0.72813)		

Statistical analyses

Statistical analysis title	Daunorubicin AUC(24-t) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	120
Confidence interval	
level	90 %
sides	2-sided
lower limit	100.7
upper limit	142.6

Secondary: Daunorubicinol dose-normalized plasma: AUC(24-t)	
End point title	Daunorubicinol dose-normalized plasma: AUC(24-t)
End point description:	
Daunorubicinol AUC(24-t). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 90%)	22.963 (20.557 to 25.651)	21.821 (20.020 to 23.783)		

Statistical analyses

Statistical analysis title	Daunorubicinol AUC(24-t) comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	105.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.6
upper limit	118.3

Secondary: Daunorubicin dose-normalized plasma: Cmax	
End point title	Daunorubicin dose-normalized plasma: Cmax
End point description:	
Daunorubicin Cmax. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 3	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	5.1527 (3.9561 to 6.7114)	6.4113 (4.6773 to 8.7882)		

Statistical analyses

Statistical analysis title	Daunorubicin: Cmax Cycle 1 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	80.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	57.2
upper limit	113

Secondary: Daunorubicinol dose-normalized plasma: Cmax

End point title	Daunorubicinol dose-normalized plasma: Cmax

End point description:

Daunorubicinol Cmax. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 1 Day 3

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: (ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	3.5770 (3.0433 to 4.2044)	3.3640 (2.8433 to 3.9799)		

Statistical analyses

Statistical analysis title	Daunorubicinol: Cmax Cycle 1 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	106.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.6
upper limit	129

Secondary: Cycle 2: Daunorubicin dose-normalized plasma: AUC(0-24)

End point title	Cycle 2: Daunorubicin dose-normalized plasma: AUC(0-24)
End point description:	
Cycle 2 Daunorubicin AUC(0-24). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 2 Day 1	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	10.315 (6.7932 to 15.662)	8.1146 (6.0221 to 10.934)		

Statistical analyses

Statistical analysis title	Daunorubicin: AUC(0-24) Cycle 2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	127.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	84.2
upper limit	191.9

Secondary: Cycle 2: Daunorubicinol dose-normalized plasma: AUC(0-24)

End point title	Cycle 2: Daunorubicinol dose-normalized plasma: AUC(0-24)

End point description:

Cycle 2 Daunorubicinol AUC(0-24). PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: (h*ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	34.067 (26.479 to 43.829)	30.820 (24.148 to 39.335)		

Statistical analyses

Statistical analysis title	Daunorubicinol: AUC(0-24) Cycle 2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	110.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.9
upper limit	145.7

Secondary: Cycle 2: Daunorubicin dose-normalized plasma: Cmax	
End point title	Cycle 2: Daunorubicin dose-normalized plasma: Cmax
End point description:	
Cycle 2 Daunorubicin Cmax. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 2 Day 1	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: (ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	11.141 (4.3653 to 28.432)	3.8905 (1.2805 to 11.820)		

Statistical analyses

Statistical analysis title	Daunorubicin: Cmax Cycle 2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	286.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.1
upper limit	910.7

Secondary: Cycle 2: Daunorubicinol dose-normalized plasma: Cmax	
End point title	Cycle 2: Daunorubicinol dose-normalized plasma: Cmax
End point description:	
Cycle 2 Daunorubicinol Cmax. PK analyses used actual relative time and actual dosing information in mg/m2. All parameter values were divided by daunorubicin dose in mg/m2 except t1/2.	
End point type	Secondary
End point timeframe:	
Cycle 2 Day 1	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: (ug/ml)/(mg/m2)				
geometric mean (confidence interval 95%)	4.0200 (2.5302 to 6.3870)	1.9868 (1.4247 to 2.7708)		

Statistical analyses

Statistical analysis title	Daunorubicinol: Cmax Cycle 2 comparison
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Ratio of geometric means
Point estimate	202.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	131.3
upper limit	311.8

Secondary: Number of platelet transfusions per week within cycles

End point title	Number of platelet transfusions per week within cycles

End point description:

This was the average number of platelet transfusions per week within cycles.

End point type	Secondary

End point timeframe:

Post-Base line up to Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Participants				
median (standard deviation)	1.5 (± 1.18)	1.4 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to platelet counts recovery >=20 Gi/L

End point title	Time to platelet counts recovery >=20 Gi/L

End point description:

Time to platelet counts 20 Gi/L for 3 consecutive days, unaided by transfusions, in patients with < 20 Gi/L after chemotherapy.

End point type	Secondary

End point timeframe:

From last dose of chemotherapy to up to end of study year 2 assessment

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	68		
Units: Participants	6	7		

Statistical analyses

Statistical analysis title	Time to platelet counts 20 Gi/L analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7461
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	2.48

Secondary: Time to platelet counts recovery >=100 Gi/L

End point title	Time to platelet counts recovery >=100 Gi/L

End point description:

Time to platelet counts 100 Gi/L, unaided by transfusions, in patients with < 100 Gi/L after chemotherapy.

End point type	Secondary

End point timeframe:

From last dose of chemotherapy to up to end of study year 2 assessment

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	73		
Units: Participants	48	51		

Statistical analyses

Statistical analysis title	Time to platelet counts 100 Gi/L analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6175
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.63

Secondary: Number of participants who achieved platelet count recovery by Day 21

End point title	Number of participants who achieved platelet count recovery by Day 21

End point description:

Number of participants with platelet counts 20 Gi/L for 3 consecutive days, unaided by transfusions, in patients with < 20 Gi/L after chemotherapy.

End point type	Secondary

End point timeframe:

By Day 21

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	68		
Units: Count of participants	4	7		

Statistical analyses

Statistical analysis title	Platelet count recovery by 21 days analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3224
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.5281
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1084
upper limit	2.2086

Secondary: Summary of platelet counts over time

End point title	Summary of platelet counts over time
End point description:	
Platelet counts over time	
End point type	Secondary
End point timeframe:	
Baseline, daily then weekly within cycle up to 42 days after last chemotherapy dose, end of therapy /remission assessment visit	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Gi/L				
median (full range (min-max))				
Baseline (n = 74, 74)|	51.5 (5 to 241)	50.0 (9 to 232)		
C1D1 (n = 59, 66)|	52.0 (5 to 241)	48.5 (9 to 232)		
C1D2 (n = 74, 74)|	43.5 (4 to 237)	42.0 (5 to 368)		
C1D3 (n = 72, 72)|	35.5 (4 to 226)	37.0 (7 to 220)		
C1D4 (n = 74, 69)|	36.5 (3 to 227)	29.0 (5 to 146)		
C1D5 (n = 73, 71)|	33.0 (3 to 201)	29.0 (5 to 146)		
C1D6 (n = 73, 69)|	32.0 (4 to 164)	30.0 (6 to 125)		
C1D7 (n = 73, 70)|	27.0 (3 to 123)	27.0 (4 to 102)		
C1D8 (n = 73, 69)|	24.0 (2 to 99)	22.0 (4 to 80)		
C1D9 (n= 72, 69)|	20.5 (1 to 109)	19.0 (5 to 59)		
C1D14 (n = 68, 68)|	16.5 (0 to 70)	18.0 (1 to 81)		
C1D21 (n = 51, 55)|	39.0 (5 to 325)	25.0 (2 to 232)		
C1D28 (n = 36, 29)|	484.5 (14 to 1590)	121.0 (7 to 539)		
C1D35 (n= 14, 14)|	547.0 (15 to 1493)	181.0 (10 to 424)		

C1D42 (n = 0, 1)|	0 (0.0 to 0.0)	304.0 (304 to 304)		
C2D1 (n =10, 12)|	31.0 (12 to 1059)	30.5 (10 to 432)		
C2D2 (n = 9, 12)|	26.0 (3 to 831)	28.5 (8 to 400)		
C2D3 (n = 10, 12)|	25.5 (0 to 730)	29.0 (8 to 437)		
C2D4 (n = 9, 12)|	32.0 (2 to 678)	35.5 (11 to 454)		
C2D5 (n= 10, 11)|	37.0 (9 to 516)	22.0 (12 to 476)		
C2D6 (n = 10, 12)|	27.0 (4 to 430)	33.0 (7 to 533)		
C2D7 (n = 7, 12)|	24.0 (6 to 295)	28.5 (12 to 390)		
C2D14 (n= 8, 11)|	10.5 (3 to 31)	16.0 (6 to 66)		
C2D21 (n = 8, 11)|	27.0 (9 to 86)	38.0 (8 to 141)		
C2D28 (n = 5, 6)|	68.0 (48 to 333)	173.0 (32 to 479)		
C2D35 (n = 2, 3)|	515.0 (412 to 618)	272.0 (26 to 329)		
C1D42 (n = 0, 2)|	0 (0.0 to 0.0)	147.5 (45 to 250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum duration (days) of platelet transfusion independence

End point title	Maximum duration (days) of platelet transfusion independence

End point description:

Maximum time period (in days) during which the patient did not receive any platelet transfusion

End point type	Secondary

End point timeframe:

At differnt time points from start of treatment and up to end of study year 2 assessment

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Days				
median (full range (min-max))	29.0 (2 to 57)	29.5 (2 to 77)		

Statistical analyses

Statistical analysis title	Platelet transfusion independence analyis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6942
Method	Wilcoxon rank-sum test

Secondary: Percentage of patients who achieved platelet transfusion independence ≥ 28 days

End point title	Percentage of patients who achieved platelet transfusion independence ≥ 28 days

End point description:

Percentage of patients who achieved platelet transfusion independence ≥ 28 days.

End point type	Secondary

End point timeframe:

From start of treatment and up to end of study year 2 assessment

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Percentage of participants	55	53		

Statistical analyses

Statistical analysis title	Platelet transfusion independence ≥ 28 days
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7397
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.1151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5585
upper limit	2.229

Secondary: Time to neutrophil engraftment based on number of events

End point title	Time to neutrophil engraftment based on number of events

End point description:	
Time to ANC Gi/L for 3 consecutive days in patients with ANC < 0.5 Gi/L after chemotherapy	
End point type	Secondary
End point timeframe:	
At different time points from last dose of chemotherapy up to end of study year 2 assessment	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	73		
Units: Participants	12	5		

Statistical analyses

Statistical analysis title	Neutrofil engraftment analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0781
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	6.38

Secondary: Summary of absolute neutrophil counts (ANC)	
End point title	Summary of absolute neutrophil counts (ANC)
End point description:	
Absolute neutrophil counts over time	
End point type	Secondary
End point timeframe:	
Baseline, daily then weekly within cycle up to 42 days after last chemotherapy dose, end of therapy /remission assessment visit	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Gi/L				
median (full range (min-max))				
Baseline (n = 71, 72)|	0.8 (0 to 37)	0.5 (0 to 50)		
C1D1 (n = 55, 63)|	0.8 (0 to 37)	0.6 (0 to 50)		
C1D2 (n= 70, 72)|	0.6 (0 to 41)	0.5 (0 to 41)		
C1D3 (n = 66, 70)|	0.6 (0 to 59)	0.4 (0 to 26)		
C1D4 (n = 70, 64)|	0.4 (0 to 35)	0.2 (0 to 17)		
C1D5 (n = 70, 63)|	0.3 (0 to 21)	0.2 (0 to 2)		
C1D6 (n = 68, 63)|	0.2 (0 to 35)	0.1 (0 to 1)		
C1D7 (n = 69, 62)|	0.1 (0 to 29)	0.1 (0 to 1)		
C1D8 (n = 66, 58)|	0.1 (0 to 21)	0.0 (0 to 1)		
C1D9 (n = 66, 59)|	0.0 (0 to 7)	0.0 (0 to 1)		
C1D14 (n = 61, 56)|	0.0 (0 to 1)	0.0 (0 to 0)		
C1D21 (n = 52, 51)|	0.6 (0 to 18)	0.3 (0 to 7)		
C1D28 (n= 37, 29)|	4.3 (0 to 47)	2.7 (0 to 25)		
C1D35 (n = 14, 14)|	2.2 (0 to 56)	1.7 (0 to 12)		
C1D42 (n= 0, 1)|	0.0 (0 to 0.0)	3.1 (3.1 to 3.1)		
C2D1 (n = 10, 9)|	0.1 (0 to 7)	0.0 (0 to 5)		
C2D2 (n = 10, 9)|	0.1 (0 to 3)	0.2 (0 to 4)		
C2D3 (n = 9, 8)|	0.2 (0 to 5)	0.5 (0 to 4)		
C2D4 (n = 9, 9)|	0.3 (0 to 3)	0.5 (0 to 2)		
C2D5 (n = 10, 10)|	0.2 (0 to 2)	0.1 (0 to 3)		
C2D6 (n = 10, 10)|	0.1 (0 to 1)	0.1 (0 to 3)		
C2D7 (n= 9, 8)|	0.0 (0 to 1)	0.1 (0 to 2)		
C2D14 (n = 7, 8)|	0.0 (0 to 0)	0.0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of hemoglobin

End point title	Summary of hemoglobin

End point description:

Hemoglobin level over time

End point type	Secondary

End point timeframe:

Baseline, daily then weekly within cycle up to 42 days after last chemotherapy dose, end of therapy /remission assessment visit

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: g/L				
median (full range (min-max))				
Baseline (n= 74, 74)|	87.6 (63 to 123)	87.0 (67 to 121)		
C1D1 (n= 60, 66)|	88.0 (67 to 123)	86.0 (67 to 121)		
C1D2 (n = 74, 74)|	88.0 (58 to 124)	83.0 (62 to 130)		
C1D3 (n = 74, 72)|	86.0 (52 to 108)	82.0 (59 to 130)		
C1D4 (n = 74, 70)|	83.0 (60 to 105)	81.5 (46 to 120)		
C1D5 (n = 74, 71)|	84.0 (60 to 114)	83.0 (50 to 126)		
C1D6 (n = 74, 70)|	86.0 (67 to 118)	82.0 (52 to 119)		
C1D7 (n = 74, 71)|	85.0 (58 to 116)	83.0 (57 to 110)		
C1D8 (n = 74, 70)|	85.3 (65 to 118)	84.0 (57 to 108)		
C1D9 (n = 74, 70)|	84.5 (64 to 114)	81.5 (62 to 109)		
C1D14 (n = 68, 68)|	85.0 (60 to 123)	84.0 (59 to 109)		
C1D21 (n = 52, 55)|	88.0 (77 to 117)	88.0 (72 to 116)		
C1D28 (n = 37, 29)|	99.0 (78 to 138)	98.0 (79 to 125)		
C1D35 (n = 14, 14)|	99.0 (81 to 131)	94.0 (74 to 130)		
C1D42 (n = 0, 1)|	0 (0.0 to 0.0)	98.0 (98 to 98)		
C2D1 (n = 10, 12)|	94.5 (76 to 124)	82.5 (72 to 111)		
C2D2 (n = 10, 12)|	88.5 (72 to 112)	86.5 (69 to 104)		
C2D3 (n = 10, 12)|	86.5 (65 to 110)	80.0 (68 to 97)		
C2D4 (n = 10, 12)|	89.0 (72 to 106)	86.5 (74 to 109)		
C2D5 (n = 10, 12)|	88.0 (67 to 101)	84.0 (72 to 93)		
C2D6 (n = 10, 12)|	84.0 (68 to 102)	85.0 (70 to 96)		
C2D7 (n = 10, 12)|	84.5 (66 to 99)	83.0 (57 to 97)		
C2D14 (n = 11, 8)|	77.5 (66 to 101)	87.0 (79 to 96)		
C2D21 (n = 11, 8)|	86.0 (43 to 99)	91.0 (74 to 110)		
C2D28 (n = 7, 5)|	89.0 (80 to 92)	80.0 (72 to 114)		
C2D35 (n = 3, 2)|	104.0 (101 to 107)	87.0 (85 to 119)		
C2D42 (n = 0, 2)|	0 (0.0 to 0.0)	90.5 (86 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and severity of hemorrhagic events

End point title	Incidence and severity of hemorrhagic events

End point description:

Incidence of bleeding events using WHO bleeding grade (G0=No bleeding, G1=Petechiae, G2=Mild blood loss, G3=Gross blood loss, G4=Debilitating blood loss) by week and cycle

End point type	Secondary

End point timeframe:

Baseline, weekly within induction and re-induction cycles, end of therapy

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Count of participants				
C1D7 - GRADE 0 (n = 73, 69)|	58	47		
C1D7 - GRADE 1 (n = 73, 69)|	9	16		
C1D7 - GRADE 2 (n = 73, 69)|	5	6		
C1D7 - GRADE 3 (n = 73, 69)|	1	0		
C1D14 - GRADE 0 (n = 68, 65)|	42	43		
C1D14 - GRADE 1 (n = 68, 65)|	16	13		
C1D14 - GRADE 2 (n = 68, 65)|	5	6		
C1D14 - GRADE 3 (n = 68, 65)|	1	0		
C1D21 - GRADE 0 (n = 52, 52)|	36	43		
C1D21 - GRADE 1 (n = 52, 53)|	13	7		
C1D21 - GRADE 2 (n = 52, 52)|	3	1		
C1D21 - GRADE 3 (n = 52, 52)|	0	1		
C1D28 - GRADE 0 (n = 37, 28)|	31	25		
C1D28 - GRADE 1 (n = 37, 28)|	4	3		
C1D28 - GRADE 2 (n = 37, 28)|	2	0		
C1D28 - GRADE 3 (n = 37, 28)|	0	0		
C1D35 - GRADE 0 (n =14, 13)|	12	11		
C1D35 - GRADE 1 (n =14, 13)|	2	2		
C1D35 - GRADE 2 (n =14, 13)|	0	0		
C1D35 - GRADE 3 (n =14, 13)|	0	0		
C1D42 - GRADE 0 (n =0, 1)|	0	0		
C1D42 - GRADE 1 (n =0, 1)|	0	1		
C1D42 - GRADE 2 (n =0, 1)|	0	0		
C1D42 - GRADE 3 (n =0, 1)|	0	0		
C2D1 - GRADE 0 (n = 10, 12)|	8	8		

C2D1 - GRADE 1 (n = 10, 12)|	1	4		
C2D1 - GRADE 2 (n = 10, 12)|	1	0		
C2D1 - GRADE 3 (n = 10, 12)|	0	0		
C2D7 - GRADE 0 (n = 10, 11)|	9	8		
C2D7 - GRADE 1 (n = 10, 11)|	0	3		
C2D7 - GRADE 2 (n = 10, 11)|	1	0		
C2D7 - GRADE 3 (n = 10, 11)|	0	0		
C2D14 - GRADE 0 (n = 8, 10)|	8	7		
C2D14 - GRADE 1 (n = 8, 10)|	0	3		
C2D14 - GRADE 2 (n = 8, 10)|	0	0		
C2D14 - GRADE 3 (n = 8, 10)|	0	0		
C2D21 - GRADE 0 (n = 8, 9)|	7	7		
C2D21 - GRADE 1 (n = 8, 9)|	1	2		
C2D21 - GRADE 2 (n = 8, 9)|	0	0		
C2D21 - GRADE 3 (n = 8, 9)|	0	0		
C2D28 - GRADE 0 (n = 5, 8)|	5	7		
C2D28 - GRADE 1 (n = 5, 8)|	0	1		
C2D28 - GRADE 2 (n = 5, 8)|	0	0		
C2D28 - GRADE 3 (n = 5, 8)|	0	0		
C2D35 - GRADE 0 (n = 3 , 3)|	3	2		
C2D35 - GRADE 1 (n = 3 , 3)|	0	1		
C2D35 - GRADE 2 (n = 3 , 3)|	0	0		
C2D35 - GRADE 3 (n = 3 , 3)|	0	0		
C2D42 - GRADE 0 (n = 0 , 1)|	0	0		
C2D42 - GRADE 1 (n = 0 , 1)|	0	1		
C2D42 - GRADE 2 (n = 0 , 1)|	0	0		
C2D42 - GRADE 3 (n = 0 , 1)|	0	0		
Remission visit GRADE 0 (n = 62, 62)|	56	58		
Remission visit GRADE 1 (n = 62, 62)|	2	4		
Remission visit GRADE 2 (n = 62, 62)|	3	0		
Remission visit GRADE 3 (n = 62, 62)|	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with disease response rate and type of response

End point title	Percentage of participants with disease response rate and type of response

End point description:

Disease response as assessed by the investigator using the AML International Working Group Response Assessment at the end of therapy/remission assessment visit; Complete remission (CR): Partial remission (PR):

End point type	Secondary

End point timeframe:

Day 42 of the latest chemotherapy cycle (Up to 8 weeks)

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Percentage of participants				
Overall response|	70	73		
Complete Remission (CR)|	65	70		
Partial Remission (PR)|	5	3		

Statistical analyses

Statistical analysis title	Disease response rate/type analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7122
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.8749
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4023
upper limit	1.8943

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
Overall survival defined as the time form randomization until the date of death due to any cause.	
End point type	Secondary
End point timeframe:	
From randomization to end of 2-year follow-up	

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Count of participants	39	30		

Statistical analyses

Statistical analysis title	Overall survival analysis
Comparison groups	Eltrombopag (ELQ) QD v Placebo QD
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0688
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	2.47

Secondary: Number of participants who required Medical resource utilization

End point title	Number of participants who required Medical resource utilization

End point description:

Medical Resource Utilization pertained to unscheduled hospitalizations, unscheduled office visits, unscheduled laboratory tests, and unscheduled procedures.

End point type	Secondary

End point timeframe:

At screening and from start of treatment to end of therapy/remission assessment visit (Day 42 of the latest chemotherapy cycle)

End point values	Eltrombopag (ELQ) QD	Placebo QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Count of participants				
In-patient hospitalizations/ admissions?|	3	4		
Diagnostic imaging procedures performed?|	3	4		
Health care resources use or emergency visits?|	8	6		
Out-patient lab tests performed?|	6	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit 2 up to the end of study ye

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Eltrombopag

Reporting group description:

Eltrombopag

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Eltrombopag	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 74 (32.43%)	14 / 71 (19.72%)	
number of deaths (all causes)	11	4	
number of deaths resulting from adverse events	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			

subjects affected / exposed	0 / 74 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 74 (2.70%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 74 (1.35%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 74 (2.70%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 74 (4.05%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Perirectal abscess			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	1 / 74 (1.35%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	2 / 74 (2.70%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudohyperkalaemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eltrombopag	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 74 (95.95%)	66 / 71 (92.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 74 (8.11%)	8 / 71 (11.27%)	
occurrences (all)	6	13	
Hypotension			
subjects affected / exposed	5 / 74 (6.76%)	6 / 71 (8.45%)	
occurrences (all)	6	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 74 (17.57%)	13 / 71 (18.31%)	
occurrences (all)	15	17	
Catheter site haemorrhage			
subjects affected / exposed	4 / 74 (5.41%)	1 / 71 (1.41%)	
occurrences (all)	5	1	
Chest pain			
subjects affected / exposed	0 / 74 (0.00%)	4 / 71 (5.63%)	
occurrences (all)	0	4	
Chills			
subjects affected / exposed	21 / 74 (28.38%)	14 / 71 (19.72%)	
occurrences (all)	24	23	
Fatigue			
subjects affected / exposed	10 / 74 (13.51%)	11 / 71 (15.49%)	
occurrences (all)	10	11	
Mucosal inflammation			
subjects affected / exposed	9 / 74 (12.16%)	9 / 71 (12.68%)	
occurrences (all)	10	11	
Oedema			
subjects affected / exposed	6 / 74 (8.11%)	6 / 71 (8.45%)	
occurrences (all)	6	6	
Oedema peripheral			
subjects affected / exposed	12 / 74 (16.22%)	13 / 71 (18.31%)	
occurrences (all)	14	15	
Pain			

subjects affected / exposed	3 / 74 (4.05%)	6 / 71 (8.45%)	
occurrences (all)	3	8	
Pyrexia			
subjects affected / exposed	25 / 74 (33.78%)	17 / 71 (23.94%)	
occurrences (all)	31	22	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 74 (1.35%)	5 / 71 (7.04%)	
occurrences (all)	1	6	
Cough			
subjects affected / exposed	18 / 74 (24.32%)	18 / 71 (25.35%)	
occurrences (all)	22	23	
Dyspnoea			
subjects affected / exposed	5 / 74 (6.76%)	11 / 71 (15.49%)	
occurrences (all)	5	12	
Epistaxis			
subjects affected / exposed	18 / 74 (24.32%)	14 / 71 (19.72%)	
occurrences (all)	23	20	
Haemoptysis			
subjects affected / exposed	7 / 74 (9.46%)	2 / 71 (2.82%)	
occurrences (all)	7	2	
Hiccups			
subjects affected / exposed	4 / 74 (5.41%)	4 / 71 (5.63%)	
occurrences (all)	5	6	
Hypoxia			
subjects affected / exposed	4 / 74 (5.41%)	2 / 71 (2.82%)	
occurrences (all)	4	3	
Nasal dryness			
subjects affected / exposed	3 / 74 (4.05%)	5 / 71 (7.04%)	
occurrences (all)	3	5	
Oropharyngeal pain			
subjects affected / exposed	13 / 74 (17.57%)	13 / 71 (18.31%)	
occurrences (all)	15	14	
Pleural effusion			

subjects affected / exposed	2 / 74 (2.70%)	5 / 71 (7.04%)	
occurrences (all)	2	6	
Productive cough			
subjects affected / exposed	8 / 74 (10.81%)	4 / 71 (5.63%)	
occurrences (all)	9	6	
Rhinorrhoea			
subjects affected / exposed	8 / 74 (10.81%)	8 / 71 (11.27%)	
occurrences (all)	10	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 74 (13.51%)	7 / 71 (9.86%)	
occurrences (all)	10	9	
Insomnia			
subjects affected / exposed	16 / 74 (21.62%)	23 / 71 (32.39%)	
occurrences (all)	19	26	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 74 (10.81%)	14 / 71 (19.72%)	
occurrences (all)	10	14	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 74 (6.76%)	8 / 71 (11.27%)	
occurrences (all)	5	10	
Blood bilirubin increased			
subjects affected / exposed	6 / 74 (8.11%)	8 / 71 (11.27%)	
occurrences (all)	6	8	
Neutrophil count decreased			
subjects affected / exposed	4 / 74 (5.41%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Platelet count decreased			
subjects affected / exposed	7 / 74 (9.46%)	4 / 71 (5.63%)	
occurrences (all)	8	4	
Serum ferritin increased			
subjects affected / exposed	6 / 74 (8.11%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Weight increased			

subjects affected / exposed	1 / 74 (1.35%)	5 / 71 (7.04%)	
occurrences (all)	1	5	
White blood cell count decreased			
subjects affected / exposed	9 / 74 (12.16%)	5 / 71 (7.04%)	
occurrences (all)	10	5	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	5 / 74 (6.76%)	5 / 71 (7.04%)	
occurrences (all)	5	6	
Transfusion reaction			
subjects affected / exposed	10 / 74 (13.51%)	8 / 71 (11.27%)	
occurrences (all)	13	16	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 71 (5.63%)	
occurrences (all)	1	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 74 (14.86%)	8 / 71 (11.27%)	
occurrences (all)	12	8	
Headache			
subjects affected / exposed	19 / 74 (25.68%)	20 / 71 (28.17%)	
occurrences (all)	23	30	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 74 (9.46%)	7 / 71 (9.86%)	
occurrences (all)	11	7	
Febrile neutropenia			
subjects affected / exposed	38 / 74 (51.35%)	42 / 71 (59.15%)	
occurrences (all)	45	53	
Neutropenia			
subjects affected / exposed	5 / 74 (6.76%)	5 / 71 (7.04%)	
occurrences (all)	6	6	
Thrombocytopenia			
subjects affected / exposed	4 / 74 (5.41%)	4 / 71 (5.63%)	
occurrences (all)	5	7	

Thrombocytosis			
subjects affected / exposed	5 / 74 (6.76%)	0 / 71 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 74 (2.70%)	4 / 71 (5.63%)	
occurrences (all)	3	4	
Abdominal distension			
subjects affected / exposed	2 / 74 (2.70%)	6 / 71 (8.45%)	
occurrences (all)	4	6	
Abdominal pain			
subjects affected / exposed	18 / 74 (24.32%)	17 / 71 (23.94%)	
occurrences (all)	22	18	
Abdominal pain lower			
subjects affected / exposed	0 / 74 (0.00%)	4 / 71 (5.63%)	
occurrences (all)	0	4	
Abdominal pain upper			
subjects affected / exposed	3 / 74 (4.05%)	12 / 71 (16.90%)	
occurrences (all)	3	14	
Constipation			
subjects affected / exposed	28 / 74 (37.84%)	21 / 71 (29.58%)	
occurrences (all)	36	27	
Diarrhoea			
subjects affected / exposed	42 / 74 (56.76%)	43 / 71 (60.56%)	
occurrences (all)	54	55	
Dry mouth			
subjects affected / exposed	7 / 74 (9.46%)	2 / 71 (2.82%)	
occurrences (all)	8	3	
Dyspepsia			
subjects affected / exposed	10 / 74 (13.51%)	9 / 71 (12.68%)	
occurrences (all)	11	13	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 74 (2.70%)	4 / 71 (5.63%)	
occurrences (all)	2	4	
Gingival bleeding			

subjects affected / exposed	6 / 74 (8.11%)	4 / 71 (5.63%)	
occurrences (all)	6	4	
Gingival pain			
subjects affected / exposed	4 / 74 (5.41%)	3 / 71 (4.23%)	
occurrences (all)	4	3	
Gingival swelling			
subjects affected / exposed	3 / 74 (4.05%)	5 / 71 (7.04%)	
occurrences (all)	5	5	
Haemorrhoids			
subjects affected / exposed	10 / 74 (13.51%)	9 / 71 (12.68%)	
occurrences (all)	10	10	
Lip dry			
subjects affected / exposed	4 / 74 (5.41%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Mouth haemorrhage			
subjects affected / exposed	5 / 74 (6.76%)	0 / 71 (0.00%)	
occurrences (all)	6	0	
Mouth ulceration			
subjects affected / exposed	2 / 74 (2.70%)	4 / 71 (5.63%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	37 / 74 (50.00%)	46 / 71 (64.79%)	
occurrences (all)	59	68	
Proctalgia			
subjects affected / exposed	4 / 74 (5.41%)	10 / 71 (14.08%)	
occurrences (all)	4	10	
Stomatitis			
subjects affected / exposed	19 / 74 (25.68%)	18 / 71 (25.35%)	
occurrences (all)	24	25	
Vomiting			
subjects affected / exposed	27 / 74 (36.49%)	27 / 71 (38.03%)	
occurrences (all)	39	45	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 71 (5.63%)	
occurrences (all)	1	4	

Erythema			
subjects affected / exposed	5 / 74 (6.76%)	5 / 71 (7.04%)	
occurrences (all)	5	5	
Hyperhidrosis			
subjects affected / exposed	5 / 74 (6.76%)	2 / 71 (2.82%)	
occurrences (all)	9	2	
Petechiae			
subjects affected / exposed	12 / 74 (16.22%)	10 / 71 (14.08%)	
occurrences (all)	14	12	
Pruritus			
subjects affected / exposed	8 / 74 (10.81%)	8 / 71 (11.27%)	
occurrences (all)	9	10	
Rash			
subjects affected / exposed	22 / 74 (29.73%)	13 / 71 (18.31%)	
occurrences (all)	28	16	
Rash maculo-papular			
subjects affected / exposed	8 / 74 (10.81%)	6 / 71 (8.45%)	
occurrences (all)	8	6	
Urticaria			
subjects affected / exposed	4 / 74 (5.41%)	4 / 71 (5.63%)	
occurrences (all)	6	5	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 74 (1.35%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Urinary hesitation			
subjects affected / exposed	5 / 74 (6.76%)	1 / 71 (1.41%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 74 (8.11%)	3 / 71 (4.23%)	
occurrences (all)	6	4	
Back pain			
subjects affected / exposed	4 / 74 (5.41%)	15 / 71 (21.13%)	
occurrences (all)	4	15	
Musculoskeletal pain			

subjects affected / exposed	4 / 74 (5.41%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Pain in extremity			
subjects affected / exposed	8 / 74 (10.81%)	8 / 71 (11.27%)	
occurrences (all)	8	8	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	4 / 74 (5.41%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Cellulitis			
subjects affected / exposed	0 / 74 (0.00%)	6 / 71 (8.45%)	
occurrences (all)	0	6	
Device related infection			
subjects affected / exposed	6 / 74 (8.11%)	9 / 71 (12.68%)	
occurrences (all)	6	10	
Oral candidiasis			
subjects affected / exposed	1 / 74 (1.35%)	6 / 71 (8.45%)	
occurrences (all)	1	7	
Pneumonia			
subjects affected / exposed	8 / 74 (10.81%)	3 / 71 (4.23%)	
occurrences (all)	9	3	
Sepsis			
subjects affected / exposed	5 / 74 (6.76%)	3 / 71 (4.23%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 74 (29.73%)	27 / 71 (38.03%)	
occurrences (all)	28	39	
Fluid imbalance			
subjects affected / exposed	12 / 74 (16.22%)	10 / 71 (14.08%)	
occurrences (all)	18	13	
Fluid overload			
subjects affected / exposed	6 / 74 (8.11%)	5 / 71 (7.04%)	
occurrences (all)	7	6	
Hyperkalaemia			

subjects affected / exposed	4 / 74 (5.41%)	2 / 71 (2.82%)	
occurrences (all)	5	2	
Hypoalbuminaemia			
subjects affected / exposed	6 / 74 (8.11%)	2 / 71 (2.82%)	
occurrences (all)	7	4	
Hypocalcaemia			
subjects affected / exposed	7 / 74 (9.46%)	10 / 71 (14.08%)	
occurrences (all)	9	10	
Hypokalaemia			
subjects affected / exposed	20 / 74 (27.03%)	27 / 71 (38.03%)	
occurrences (all)	22	36	
Hypomagnesaemia			
subjects affected / exposed	8 / 74 (10.81%)	13 / 71 (18.31%)	
occurrences (all)	12	20	
Hyponatraemia			
subjects affected / exposed	4 / 74 (5.41%)	4 / 71 (5.63%)	
occurrences (all)	5	6	
Hypophosphataemia			
subjects affected / exposed	10 / 74 (13.51%)	14 / 71 (19.72%)	
occurrences (all)	13	24	
Iron overload			
subjects affected / exposed	6 / 74 (8.11%)	3 / 71 (4.23%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2013	Amendment No. 1 changes from the original protocol were: The addition of an investigational product stopping criterion; Clarifications and corrections to existing language throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported