Clinical trial results:
The ELTION study – A multicenter open-label interventional study of Eltrombopag in patients with poor graft function after allogeneic hematopoietic stem cell transplantation

Summary

EudraCT number	2018-001129-15
Trial protocol	ES
Global end of trial date	03 November 2020

Results information

Result version number	v1 (current)
This version publication date	19 November 2021
First version publication date	19 November 2021

Trial information

Trial identification

Sponsor protocol code	CETB115EES03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03718533
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	03 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) as determined by platelets, hemoglobin and neutrophil counts, by 16 weeks after the initiation of eltrombopag.

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	17 December 2018
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	Spain: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 7 centers in 1 country (Spain).

Pre-assignment

Screening details:

A total of 25 participants were screened in this study of which 15 failed screening and 10 participants were enrolled in the study.

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:

Patients received eltrombopag orally once daily up to 36 weeks.

Arm type	Experimental
Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	ETB115
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Eltrombopag was provided as 50 mg or 25 mg film-coated tablets for oral use administration

Number of subjects in period 1	Eltrombopag
Started	10
Completed	3
Not completed	7
Relapse	1
Physician decision	2
Disease progression	1
Physician Decision and Adverse Event	1
Protocol deviation	1
Myelodysplastic syndrome and study indication	1

Baseline characteristics

Reporting groups	
Reporting group title	Eltrombopag
Reporting group description:	
Patients received eltrombopag orally once daily up to 36 weeks.	

Reporting group values	Eltrombopag	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: Years			
median	52.5		
full range (min-max)	23.0 to 72.0	-	
Sex: Female, Male Units: Participants			
Female	4	4	
Male	6	6	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	9	9	
Native American	1	1	

End points

End points reporting groups

Reporting group title	Eltrombopag
Reporting group description:	
Patients received eltrombopag orally once daily up to 36 weeks.	

Primary: Hematologic response rate by 16 weeks after the initiation of eltrombopag

End point title	Hematologic response rate by 16 weeks after the initiation of eltrombopag[1]

End point description:

Hematologic response rate was defined as the percentage of participants who met the criteria of either complete response (CR) or partial response (PR) by Week 16. PR was defined when any of the following: Platelet count ≥ 20000/microliter(μL) (with platelet transfusion independence), absolute neutrophil count (ANC) ≥1000/μL (when pretreatment ANC was <1000/μL) and/or hemoglobin (Hb) ≥100 gram(g)/ liter(L) (when pretreatment Hb was <100g/L) (with red blood cells transfusion independence), confirmed in two blood tests separated a minimum of 7 days. CR was defined when all of the following: platelet count ≥100000/μL, ANC ≥1500/μL (when pretreatment ANC was <1000/μL) and Hb ≥110 g/L (when pretreatment Hb was <100g/L), confirmed in two blood tests separated a minimum of 7 days. Participants who discontinued before Week 16 were considered as responders if, in the last evaluation, they had PR or CR. The 95% Confidence Interval (CI) was the binomial exact CI based on Clopper-Pearson method.

End point type	Primary

End point timeframe:

Baseline up to Week 16

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this outcome measure

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who had a response in the neutrophil lineage

End point title	Percentage of participants who had a response in the neutrophil lineage

End point description:

Percentage of participants who had a response (partial or complete) in the neutrophil lineage. A partial response in the neutrophil lineage was defined as absolute neutrophil count (ANC) ≥1000/ μL (when pretreatment ANC was <1000/μL) confirmed in two consecutive blood tests separated a minimum of 7 days. A complete response in the neutrophil lineage was defined as ANC ≥ 1500/ μL (when pretreatment ANC was <1000/μL) confirmed in two consecutive blood tests separated a minimum of 7 days.

Analysis population: All participants to whom study treatment was assigned and pretreatment ANC was <1000 µL. Only those participants who reached the study week were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Week 16, 20, 24, 30 and 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Percentage of Participants				
number (not applicable)				
Week 16 (n=1)	100			
Week 20 (n=1)	100			
Week 24 (n=1)	100			
Week 30 (n=1)	100			
Week 36 (n=1)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who had a response in the platelet lineage

End point title	Percentage of participants who had a response in the platelet lineage

End point description:

Percentage of participants who had a response (partial or complete) in the platelet lineage. A partial response in the platelet lineage was defined as platelet count ≥20000/µL (with platelet transfusion independence) confirmed in two consecutive blood tests separated a minimum of 7 days. A complete response in the platelet lineage was defined as platelet count ≥ 100000/µL confirmed in two consecutive blood tests separated a minimum of 7 days.

Analysis population: All participants to whom study treatment was assigned. Only those participants who reached the study week were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Week 16, 20, 24, 30 and 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (not applicable)				
Week 16 (n=6)	66.7			
Week 20 (n=6)	66.7			

Week 24 (n=6)	83.3			
Week 30 (n=5)	100			
Week 36 (n=3)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who had a response in the hemoglobin lineage

End point title	Percentage of participants who had a response in the hemoglobin lineage

End point description:

Percentage of participants who had a response (partial or complete) in the hemoglobin (Hb) lineage. A partial response in the Hb lineage was defined as Hb ≥100 g/L (when pretreatment Hb was <100g/L) (with red blood cells transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days. A complete response in the Hb lineage was defined as Hb≥ 110 g/L (when pretreatment Hb was <100g/L) confirmed in two consecutive blood tests separated a minimum of 7 days.

Analysis population: All participants to whom study treatment was assigned and pretreatment Hb <100g/L. Only those participants who reached the study week were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Week 16, 20, 24, 30 and 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage of participants				
number (not applicable)				
Week 16 (n=5)	60.0			
Week 20 (n=5)	60.0			
Week 24 (n=5)	80.0			
Week 30 (n=4)	100			
Week 36 (n=2)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with hematologic response (partial and complete) at Week 24 and 36

End point title	Percentage of participants with hematologic response (partial and complete) at Week 24 and 36

End point description:

Percentage of participants who met the criteria of either CR or PR at 24 weeks and 36 weeks after the initiation of eltrombopag. PR was defined when any of the following: Platelet count ≥20000/microliter (µL) (with platelet transfusion independence), absolute neutrophil count (ANC) ≥1000/µL (when pretreatment ANC was <1000/µL) and/or hemoglobin (Hb) ≥100 gram (g)/ liter (L) (when pretreatment Hb was <100g/L) (with RBC transfusion independence), confirmed in two blood tests separated a minimum of 7 days. CR was defined when all three of the following: platelet count ≥100000/µL, ANC ≥1500/µL (when pretreatment ANC was <1000/µL) and Hb ≥110 g/L (when pretreatment Hb was <100g/L), confirmed in two blood tests separated a minimum of 7 days.

Analysis population: All participants to whom study treatment was assigned. Only those participants who reached the study week were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Week 24 and 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (not applicable)				
Week 24 (n=6)	83.3			
Week 36 (n=3)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were previously platelet transfusion-dependent and did no longer require platelet transfusions after the initiation of eltrombopag

End point title	Percentage of participants who were previously platelet transfusion-dependent and did no longer require platelet transfusions after the initiation of eltrombopag

End point description:

Percentage of participants who received at least one platelet transfusion before starting treatment and who did no longer require platelet transfusion before and after the first 16 weeks of treatment.

Analysis population: All participants to whom study treatment was assigned and who received at least one platelet transfusion before starting treatment. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

From start of treatment to end of treatment, assessed up to 36 weeks

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of participants				
number (not applicable)				
From start of treatment to Week 16 (n=7)	0			
From Week 16 to end of treatment (n=3)	66.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were previously red blood cells transfusion-dependent and did no longer require red blood cells transfusions

End point title	Percentage of participants who were previously red blood cells transfusion-dependent and did no longer require red blood cells transfusions

End point description:

Percentage of participants who received at least one red blood cells transfusion before starting treatment and who did no longer require red blood cells transfusion before and after the first 16 weeks of treatment.

Analysis population: All participants to whom study treatment was assigned and who received at least one red blood cells transfusion before starting treatment. Only those participants with evaluable data at the specified time points for this outcome measure were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

From start of treatment to end of treatment, assessed up to 36 weeks

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage of participants				
number (not applicable)				
From start of treatment to Week 16 (n=6)	16.7			
From Week 16 to end of treatment (n=2)	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of transfusion independence

End point title	Duration of transfusion independence

End point description:

Duration of transfusion independence defined as the period of time where participants did not receive any platelet or red blood cells transfusions during the treatment period

Analysis population: All participants to whom study treatment was assigned.

End point type	Secondary

End point timeframe:

From start of treatment to end of treatment, assessed up to 36 weeks

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Days				
arithmetic mean (standard deviation)	137.7 (± 110.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinued or reduced the use of concomitant erythropoietin (EPO) therapy

End point title	Percentage of participants who discontinued or reduced the use of concomitant erythropoietin (EPO) therapy

End point description:

Percentage of participants who discontinued or reduced by ≥50% from baseline the use of concomitant EPO therapy while receiving eltrombopag.

Analysis population: All participants to whom study treatment was assigned with evaluable data for this outcome measure

End point type	Secondary

End point timeframe:

From start of treatment to end of treatment, assessed up to Week 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage of participants				
number (not applicable)				
Discontinued EPO therapy	37.5			
Reduced by 50% EPO therapy	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinued or reduced the use of concomitant granulocyte colony-stimulating factor (G-CSF) therapy

End point title	Percentage of participants who discontinued or reduced the use of concomitant granulocyte colony-stimulating factor (G-CSF) therapy

End point description:

Percentage of participants who discontinued or reduced by ≥50% from baseline the use of concomitant G-CSF therapy while receiving eltrombopag.

Analysis population: All participants to whom study treatment was assigned with evaluable data for this outcome measure

End point type	Secondary

End point timeframe:

From start of treatment to end of treatment, assessed up to Week 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of participants				
number (not applicable)				
Discontinued G-CSF therapy	85.7			
Reduced by 50% G-CSF therapy	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS defined as the time from the date of inclusion until the date of death due to any cause was calculated using Kaplan-Meier estimated. All patients who discontinued from the study, regardless the reason of discontinuation, were followed for survival, unless they withdrew their consent, died or were lost-to follow-up, in which case were censored at the last contact.
Note: 9999 indicates that median OS was not reached

End point type	Secondary

End point timeframe:

From start of treatment until the date of death, assessed up to 40 weeks

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Weeks				
median (standard error)	9999 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 24 and 36 weeks

End point title	Overall survival rate at 24 and 36 weeks

End point description:

Overall survival rate defined as the rate estimate of the percentage of participants who were alive at 24 and 36 weeks. All patients who discontinued from the study, regardless the reason of discontinuation, were followed for survival at Week 24 and 36, unless they withdrew their consent, died or were lost-to follow-up, in which case were censored at the last contact.

End point type	Secondary

End point timeframe:

Week 24 and 36

End point values	Eltrombopag			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24	90.0 (71.4 to 100.0)			
Week 36	80.0 (52.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day of first dose of study medication to the last dose of study medication plus 30 days, up to 40 weeks

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	23.1

Reporting groups

Reporting group title	Eltrombopag

Reporting group description:

Patients received eltrombopag orally once daily up to 36 weeks.

Serious adverse events	Eltrombopag		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Chimerism			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection reactivation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Eltrombopag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Breast operation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Papiloma excision			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Ovarian cyst			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Metrorrhagia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Clostridium test positive			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Urine analysis abnormal			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Hypoglobulinaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Upper gastrointestinal haemorrhage			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all)	 3 / 10 (30.00%) 5 1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Cytomegalovirus infection subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Escherichia urinary tract infection subjects affected / exposed occurrences (all)	 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 2 / 10 (20.00%) 2		

Hypercholesterolemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Iron overload subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2019	The purpose of this protocol amendment was to update the eligibility criteria for better clarifying the profile of patients to be included, and align with the current eltrombopag program risk language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported