Clinical trial results:
Prospective validation of a predictive model of response to romiplostim in patients with IPSS low or intermediate-1 risk myelodysplastic syndrome (MDS) and thrombocytopenia - the EUROPE-trial

Summary

EudraCT number	2013-004328-12
Trial protocol	DE FR CZ
Global end of trial date	01 July 2021

Results information

Result version number	v1 (current)
This version publication date	23 July 2022
First version publication date	23 July 2022

Trial information

Trial identification

Sponsor protocol code	Europe

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02335268
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GMIHO Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH
Sponsor organisation address	Almstadtstrasse 7, Berlin, Germany, 10119
Public contact	European MDS Studies Coordination Office (EMSCO), GMIHO Gesellschaft für Medizinische Innovation - Hämatologie und Onkologie mbH, 0049 35125933100, info@gmiho.de
Scientific contact	European MDS Studies Coordination Office (EMSCO), GMIHO Gesellschaft für Medizinische Innovation - Hämatologie und Onkologie mbH, 0049 35125933100, info@gmiho.de

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	21 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2021
Global end of trial reached?	Yes
Global end of trial date	01 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate prospectively whether the current TPO level based response model can predict response to romiplostim in thrombocytopenic patients with IPPS low/int-1 MDS

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also be carried out in keeping with applicable local law(s) and regulation(s).
Patients with no hematological response at any time of treatment stopped treatment immediately.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2015
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	Czechia: 7
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	17
From 65 to 84 years	56

85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From May 2015 through July 2019, a total of 125 patients were screened at 19 study sites in France, 9 study sites in Germany and 1 study site in the Czech Republic. Of them, 77 were eligible for study participation.

Pre-assignment

Screening details:

77 patients were assigned into two different model groups at the time of screening based on previous PTE and centrally assessed TPO serum levels. 51 patients were assigned to Group A (TPO < 500 ng/L and PTE < 6 units/past year) and 26 patients to Group B+C (TPO > 500 ng/L, and/or PTE ≥ 6 units/past year).

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Thrombopoietin (TPO) < 500 ng/L and PTE < 6 units/past year

Arm type	Experimental
Investigational medicinal product name	Romiplostim
Investigational medicinal product code	
Other name	Nplate®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting dose 750 µg once a week (7d ± 2d), subcutaneous injection, 4 months maximum duration, for responders treatment period was extended for up to 1 year (8 months extension period). The dose was adjusted based on the subject’s platelet count.

Arm title	Group B+C

Arm description:

Thrombopoietin (TPO) > 500 ng/L, and/or PTE ≥ 6 units/past year

Arm type	Experimental
Investigational medicinal product name	Romiplostim
Investigational medicinal product code	
Other name	Nplate®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting dose 750 µg once a week (7d ± 2d), subcutaneous injection, 4 months maximum duration for non-responders. The dose was adjusted based on the subject’s platelet count.

Number of subjects in period 1	Group A	Group B+C
Started	51	26
Completed	34	20
Not completed	17	6
Adverse event, serious fatal	-	1
Physician decision	5	1
Consent withdrawn by subject	3	2
Adverse event, non-fatal	5	1
increase in blasts	2	-
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	77	77	
Age categorical			
The 77 patients who received treatment were of an average age of 74 years (range: 42 to 93 years) and the majority of them was male (49 of 77 subjects; 63.6%).			
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)	17	17	
From 65-84 years	56	56	
85 years and over	4	4	
Gender categorical Units: Subjects			
Female	28	28	
Male	49	49	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Thrombopoietin (TPO) < 500 ng/L and PTE < 6 units/past year	
Reporting group title	Group B+C
Reporting group description:	
Thrombopoietin (TPO) > 500 ng/L, and/or PTE ≥ 6 units/past year	

Primary: Hematologic improvement of platelets (HI-P)

End point title	Hematologic improvement of platelets (HI-P)
End point description:	
The primary efficacy endpoint was the rate of HI-P defined as an absolute increase of platelet count to ≥ 30/nL for patients starting at > 20/nL or an increase of platelets from < 20/nL to > 20/nL and by at least 100%, according to IWG 2006 criteria lasting for ≥ 8 weeks after at least 16 Weeks of romiplostim treatment.	
End point type	Primary
End point timeframe:	
after 4 months on therapy (week 16)	

End point values	Group A	Group B+C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	22		
Units: Platelets (/nL)				
median (full range (min-max))	71.75 (-15.5 to 342.5)	18.75 (-25.0 to 161.0)		

Statistical analyses

Statistical analysis title	Efficacy analysis
Statistical analysis description:	
The primary dataset for analysis was the FAS which includes all patients who fulfilled the inclusion criteria and gave their written informed consent.	
Comparison groups	Group A v Group B+C
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

16 weeks

Adverse event reporting additional description:

Patients were asked at each visit whether they have experienced AEs or SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Romiplostim 500 µg

Reporting group description: -

Serious adverse events	Romiplostim 500 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 77 (25.97%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
AML			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal cancer			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hemorrhage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Central venous catheterization			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Drug-specific antibody			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Monocyte count increased			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Physical examination			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Syncope			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal angiectasia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hematochezia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal mass			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pancreatitis acute			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis migration			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic mass			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral rash			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 77 (1.30%)		
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	Romiplostim 500 µg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 77 (19.48%)		
Investigations			
Blast cells present			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	6		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	58		
Hypertension			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	9		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	7 / 77 (9.09%)		
occurrences (all)	10		
Anaemia			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	16		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	8		
Injection site haematoma			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	9		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 7 2 / 77 (2.60%) 29		
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 37		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 11 2 / 77 (2.60%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2015	Version 4.0 dated 20 May 2015: included minor specifications of the AML progression, HI-N response definition and extension of the screening period
30 August 2017	Version 5.0 dated 10 Jun 2017: included specification of visit assessments, statistical distributions of patients in the strata and instructions for reconstitution of the study drug
14 November 2019	Version 6.0 dated 30 Aug 2019: re-calculation of sample size due to poor recruitment in two of the three study arms, update of addresses and contact information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported