

**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
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**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



## 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
<b>Arm title</b>	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.

<b>Arm title</b>	Group B+C
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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.

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Consent withdrawn by subject	3	2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

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Romiplostim 500 µg
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Reporting group description: -

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

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Investigations</b>			
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		
<b>Cardiac disorders</b>			
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		
<b>Nervous system disorders</b>			
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 occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Cholelithiasis migration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Hepatic mass subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Skin and subcutaneous tissue disorders Purpura subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Renal and urinary disorders Hematuria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 0 / 0		
Renal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 77 (1.30%) 0 / 1 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		
<b>Bone pain</b>			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Viral rash</b>			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Anal abscess</b>			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infection</b>			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia</b>			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Tracheobronchitis</b>			
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 %

<b>Non-serious adverse events</b>	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 occurrences (all)	5 / 77 (6.49%) 6		
Vascular disorders Haematoma subjects affected / exposed occurrences (all)  Hypertension subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 58  2 / 77 (2.60%) 9		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 9		
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)  Anaemia subjects affected / exposed occurrences (all)	7 / 77 (9.09%) 10  3 / 77 (3.90%) 16		
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)  Injection site haematoma subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 8  2 / 77 (2.60%) 9		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 15		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 7		
Epistaxis subjects affected / exposed occurrences (all)	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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported