Clinical trial results:
A Phase II randomized multicenter study to assess the efficacy of lenalidomide with or without erythropoietin and granulocyte-colony stimulating factor in patients with low and intermediate-1 risk myelodysplastic syndrome.

Summary

EudraCT number	2008-002195-10
Trial protocol	NL
Global end of trial date	21 December 2020

Results information

Result version number	v1 (current)
This version publication date	04 May 2023
First version publication date	04 May 2023

Trial information

Trial identification

Sponsor protocol code	HO89

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, hovon@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, hovon@erasmusmc.nl

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	06 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2018
Global end of trial reached?	Yes
Global end of trial date	21 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the efficacy of lenalidomide (Revlimid) in low/int-1 risk MDS with or without a treatment with Epo (NeoRecormon)/G-CSF (Neupogen) in terms of hematological improvement (HI) as defined by the modified response criteria of the IWG for MDS.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2009
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	Netherlands: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	56
From 65 to 84 years	141
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects gave written informed consent and were screened according to the inclusion- and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Treatment with lenalidomide monotherapy. The dosing regimen for lenalidomide (Revlimid) is 10 mg once daily, orally on days 1-21 every 28 days. If no HI according to the modified IWG response criteria for MDS is obtained after 6 cycles, the patient will go off protocol treatment. If HI is reached the patient will continue treatment till disease progression or baseline transfusion requirements.

Arm type	Active comparator
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide: 10 mg once daily, orally on days 1-21 every 28 days. Treatment -if HI is reached- till disease progression or baseline transfusion requirements.

Arm title	Arm B

Arm description:

Treatment with lenalidomide will be given for 4 cycles. If no HI is obtained Epo (NeoRecormon; 30000 IU weekly) will be added during 2 additional cycles. The dose of Epo (NeoRecormonTM) can be increased to 60000 IU weekly (during cycle 7 & 8). If no HI has been reached G-CSF (Neupogen) will be added at cycle 9-12. If no HI according to the modified IWG response criteria for MDS is obtained after these 12 cycles, the patient will go off protocol treatment. If HI is reached the patient will continue treatment till disease progression or baseline transfusion requirements.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide (Revlimid)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 10 mg/day p.o.; day 1-21 during cycle 1-12 / 13 --> maintenance until disease progression or baseline transfusion requirements.
Depending on achievement of HI the following will be given if necessary: Epo (NeoRecormon) and G-CSF (Neupogen)

Investigational medicinal product name	EPO (NeoRecormon)
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Epo (NeoRecormon) 30000 IU/day s.c.; 1x/wk during cycle 5 and 6 (if no HI was reached during cycle 1-4 with Lenalidomide)
Epo (NeoRecormon) 60000 IU/day s.c.; 1x/wk during cycle 7 -12 / 13 --> maintenance (if no-HI was reached with the 30000 IU dosage)

Investigational medicinal product name	G-CSF (Neupogen)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

G-CSF (Neupogen) (≤ 75kg) 300 µg/day s.c. ; 3x/wk during cycle 9 - 12 / 13 --> maintenance (If no HI was reached on Lenalidomide + EPO)
G-CSF (Neupogen) (> 75kg) 480 µg/day s.c. ; 3x/wk during cycle 9 - 12 / 13 --> maintenance (if no HI was reached on Lenalidomide + EPO)

Number of subjects in period 1	Arm A	Arm B
Started	100	100
Completed	0	0
Not completed	100	100
Other	24	26
Adverse Reactions	13	26
Lack of efficacy	63	48

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	200	200	
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)	56	56	
From 65-84 years	141	141	
85 years and over	3	3	
Age continuous Units: years			
median	71		
full range (min-max)	38 to 89	-	
Gender categorical Units: Subjects			
Female	86	86	
Male	114	114	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Treatment with lenalidomide monotherapy. The dosing regimen for lenalidomide (Revlimid) is 10 mg once daily, orally on days 1-21 every 28 days. If no HI according to the modified IWG response criteria for MDS is obtained after 6 cycles, the patient will go off protocol treatment. If HI is reached the patient will continue treatment till disease progression or baseline transfusion requirements.

Reporting group title	Arm B

Reporting group description:

Treatment with lenalidomide will be given for 4 cycles. If no HI is obtained Epo (NeoRecormon; 30000 IU weekly) will be added during 2 additional cycles. The dose of Epo (NeoRecormonTM) can be increased to 60000 IU weekly (during cycle 7 & 8). If no HI has been reached G-CSF (Neupogen) will be added at cycle 9-12. If no HI according to the modified IWG response criteria for MDS is obtained after these 12 cycles, the patient will go off protocol treatment. If HI is reached the patient will continue treatment till disease progression or baseline transfusion requirements.

Primary: Primary endpoint

End point title	Primary endpoint[1]

End point description:

End point type	Primary

End point timeframe:

See Publication

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: Statistical analysis has been uploaded in the chart section.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: Whole	96	95		

Attachments (see zip file)	List of reported SAE's/saedata89-14Dec2022.pdf List of reported non-SAE's/nonsaedata89-14Dec2022.pdf Publication HO89/HO89_statistical data.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs of CTCAE grade 2 or higher, with the exception of alopecia, nausea/vomiting and progression of the disease under study, have to be reported on the Adverse Events CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B

Reporting group description: -

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 96 (44.79%)	56 / 95 (58.95%)	
number of deaths (all causes)	63	69	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecif. (inc. cysts/polyp)	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	13 / 96 (13.54%)	11 / 95 (11.58%)	
occurrences causally related to treatment / all	12 / 15	9 / 13	
deaths causally related to treatment / all	3 / 3	2 / 3	
Vascular disorders			
Vascular disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	4 / 95 (4.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

General disorders and administration site conditions	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 96 (5.21%)	12 / 95 (12.63%)	
occurrences causally related to treatment / all	2 / 5	5 / 14	
deaths causally related to treatment / all	1 / 2	0 / 2	
Immune system disorders			
Immune system disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	5 / 95 (5.26%)	
occurrences causally related to treatment / all	2 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see SAE chart for details		

subjects affected / exposed	6 / 96 (6.25%)	11 / 95 (11.58%)	
occurrences causally related to treatment / all	1 / 7	3 / 15	
deaths causally related to treatment / all	0 / 1	0 / 3	
Nervous system disorders			
Nervous system disorder	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	5 / 95 (5.26%)	
occurrences causally related to treatment / all	0 / 0	4 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	6 / 96 (6.25%)	8 / 95 (8.42%)	
occurrences causally related to treatment / all	5 / 7	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 96 (5.21%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 96 (3.13%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal and urinary disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 96 (3.13%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	12 / 96 (12.50%)	20 / 95 (21.05%)	
occurrences causally related to treatment / all	10 / 16	16 / 20	
deaths causally related to treatment / all	1 / 1	2 / 4	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 96 (90.63%)	88 / 95 (92.63%)	
Vascular disorders			
Vascular	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 96 (4.17%)	2 / 95 (2.11%)	
occurrences (all)	5	2	
Surgical and medical procedures			
Surgery/intra-operative injury	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
General disorders and administration site conditions			

Constitutional symptoms	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	33 / 96 (34.38%)	32 / 95 (33.68%)	
occurrences (all)	44	43	
Pain	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	18 / 96 (18.75%)	11 / 95 (11.58%)	
occurrences (all)	25	16	
Syndromes	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy/immunology	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	2 / 95 (2.11%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Sexual/reproductive function	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary/upper respiratory	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	16 / 96 (16.67%)	21 / 95 (22.11%)	
occurrences (all)	21	25	
Cardiac disorders			
Cardiac arrythmia	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 96 (4.17%)	7 / 95 (7.37%)	
occurrences (all)	4	7	
Cardiac general	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	9 / 96 (9.38%)	5 / 95 (5.26%)	
occurrences (all)	13	6	
Nervous system disorders			
Neurology	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	16 / 96 (16.67%)	17 / 95 (17.89%)	
occurrences (all)	18	22	
Blood and lymphatic system disorders			
Blood/bone marrow	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	52 / 96 (54.17%)	42 / 95 (44.21%)	
occurrences (all)	108	92	
Coagulation	Additional description: All combined, see non-SAE chart for details		

subjects affected / exposed	0 / 96 (0.00%)	3 / 95 (3.16%)	
occurrences (all)	0	3	
Hemorrhage/bleeding	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	2 / 95 (2.11%)	
occurrences (all)	2	2	
Lymphatics	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 96 (0.00%)	7 / 95 (7.37%)	
occurrences (all)	0	7	
Ear and labyrinth disorders			
Auditory/ear	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	3 / 95 (3.16%)	
occurrences (all)	2	4	
Eye disorders			
Ocular/visual	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	4 / 95 (4.21%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Gastrointestinal	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	35 / 96 (36.46%)	28 / 95 (29.47%)	
occurrences (all)	59	41	
Hepatobiliary disorders			
Hepatobiliary/pancreas	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 96 (1.04%)	2 / 95 (2.11%)	
occurrences (all)	4	3	
Skin and subcutaneous tissue disorders			
Dermatology/skin	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	32 / 96 (33.33%)	24 / 95 (25.26%)	
occurrences (all)	43	34	
Renal and urinary disorders			
Renal/genitourinary	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	8 / 96 (8.33%)	5 / 95 (5.26%)	
occurrences (all)	10	7	
Endocrine disorders			
Endocrine	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 96 (2.08%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			

Musculoskeletal/soft tissue	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	12 / 96 (12.50%)	13 / 95 (13.68%)	
occurrences (all)	14	15	
Infections and infestations			
Infection	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	21 / 96 (21.88%)	33 / 95 (34.74%)	
occurrences (all)	45	55	
Metabolism and nutrition disorders			
Metabolic/laboratory	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	13 / 96 (13.54%)	19 / 95 (20.00%)	
occurrences (all)	33	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2011	Administrative update (new statistician); clarification of several sections; the protocol was not changed but the correct use was emphasized. Addition of Second Primary Malignancy reporting was added.
02 October 2014	§3 End of Recruitment date was adjusted & §9.3.1 Clarification of the dose reduction scheme
29 June 2020	With protocol amendment 29 JUNE2020 , the study will be stopped and all patients still on maintenance treatment will continue their current maintenance treatment outside the scope of this study. The continued supply of lenalidomide for the patients still on maintenance treatment after study stop is aligned between the sponsor, the principal investigator and Celgene/BMS. §3; §9.1; §9.2 and §9.5.1 are updated with this information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported