



## 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
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#### 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:

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**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:

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**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:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Netherlands: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

Notes:

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**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
<b>Arm title</b>	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.

<b>Arm title</b>	Arm B
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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 (NeoRecormon<sup>TM</sup>) 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) ( $\leq 75\text{kg}$ ) 300  $\mu\text{g/day}$  s.c. ; 3x/wk during cycle 9 - 12 / 13 --> maintenance (If no HI was reached on Lenalidomide + EPO)

G-CSF (Neupogen) ( $> 75\text{kg}$ ) 480  $\mu\text{g/day}$  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
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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 (NeoRecormon <sup>TM</sup> ) 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 <sup>[1]</sup>
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		

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

Dictionary name	CTCAE
Dictionary version	3.0

### Reporting groups

Reporting group title	Arm A
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Reporting group description: -

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

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported