Clinical trial results:
Ixazomib citrate-thalidomide-low dose dexamethasone induction followed by maintenance therapy with ixazomib citrate or placebo in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplantation; a randomized phase II trial

Summary

EudraCT number	2013-003266-14
Trial protocol	NL SE NO DK
Global end of trial date	01 December 2021

Results information

Result version number	v1 (current)
This version publication date	17 December 2023
First version publication date	17 December 2023

Trial information

Trial identification

Sponsor protocol code	HOVON 126 MM/ NMSG 21.13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	Dr. Molewaterplein 40, Rotterdam, Netherlands, 3015 GD
Public contact	HOVON Data Center, HOVON, +31 010 704 1560, hovon@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, +31 010 704 1560, 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	01 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2021
Global end of trial reached?	Yes
Global end of trial date	01 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Maintenance treatment
- To compare progression free survival between maintenance therapy with Ixazomib versus placebo, both following induction therapy with ixazomib citrate – thalidomide – low dose dexamethasone

Induction treatment
- To determine overall response* rate of induction therapy with ixazomib citrate – thalidomide – low dose dexamethasone
* overall response will be defined as (stringent) complete response, very good partial response and partial response

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
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: 69
Country: Number of subjects enrolled	Norway: 36
Country: Number of subjects enrolled	Sweden: 26
Country: Number of subjects enrolled	Denmark: 16
Worldwide total number of subjects	147
EEA total number of subjects	147

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	144
85 years and over	2

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	Arm maintenance randomization (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A_Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Induction treatment for a maximum of 9 cycles q4 weeks:
Ixazomib citrate max 4 mg/day days 1,8,15;
Thalidomide 100 mg days 1-28;
Dexamethasone 40 mg days 1,8,15,22;

Maintenance Randomization to treatment q4 weeks:
Placebo max 4 mg days 1,8,15 until progression

Arm title	Arm B_ Ixazomib Citrate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ixazomib citrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Induction treatment for a maximum of 9 cycles q4 weeks:
Ixazomib citrate max 4 mg/day days 1,8,15;
Thalidomide 100 mg days 1-28;
Dexamethasone 40 mg days 1,8,15,22;

Maintenance treatment q4 weeks:
Ixazomib citrate max 4 mg days 1,8,15 until progression

Arm title	Not randomized

Arm description: -

Arm type	Not eligible for randomization

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A_Placebo	Arm B_ Ixazomib Citrate	Not randomized
Started	39	39	69
Completed	0	0	69
Not completed	39	39	0
Adverse reactions	4	-	-
Consent withdrawn by subject	-	4	-
Adverse event, non-fatal	-	5	-
At patient's request	1	-	-
other	5	2	-
Lack of efficacy	29	28	-

Baseline characteristics

Reporting groups

Reporting group title	Arm maintenance randomization

Reporting group description: -

Reporting group values	Arm maintenance randomization	Total	
Number of subjects	147	147	
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)	1	1	
From 65-84 years	144	144	
85 years and over	2	2	
Age continuous Units: years			
median	73		
full range (min-max)	64 to 90	-	
Gender categorical Units: Subjects			
Female	66	66	
Male	81	81	

End points

End points reporting groups

Reporting group title	Arm A_Placebo
Reporting group description: -	
Reporting group title	Arm B_ Ixazomib Citrate
Reporting group description: -	
Reporting group title	Not randomized
Reporting group description: -	

Primary: Primary endpoint

End point title	Primary endpoint[1][2]
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: See attached chart/documents for results.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: See attached chart/documents for results. Arm not randomized is added. This represents the patient group that were not eligible for randomization (and are not part of the primary endpoint analysis)

End point values	Arm A_Placebo	Arm B_ Ixazomib Citrate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: whole	39	39		

Attachments (see zip file)	List of reported non-SAE's/nonsaedata126-7Jun2023.pdf List of reported SAE's/saedata126-7Jun2023.pdf HOVON126 long term results publication

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

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	20 / 39 (51.28%)	24 / 39 (61.54%)	
number of deaths (all causes)	24	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
All combined			
subjects affected / exposed	4 / 39 (10.26%)	6 / 39 (15.38%)	
occurrences causally related to treatment / all	0 / 5	5 / 9	
deaths causally related to treatment / all	0 / 2	0 / 0	
Vascular disorders			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	5 / 39 (12.82%)	
occurrences causally related to treatment / all	0 / 1	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

All combined			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (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			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
All combined			
subjects affected / exposed	4 / 39 (10.26%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
All combined			
subjects affected / exposed	3 / 39 (7.69%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
All combined			
subjects affected / exposed	3 / 39 (7.69%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

All combined			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
All combined			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
All combined			
subjects affected / exposed	6 / 39 (15.38%)	9 / 39 (23.08%)	
occurrences causally related to treatment / all	10 / 14	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
All combined			
subjects affected / exposed	2 / 39 (5.13%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
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	38 / 39 (97.44%)	37 / 39 (94.87%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
All combined			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Vascular disorders			
All combined			
subjects affected / exposed	2 / 39 (5.13%)	5 / 39 (12.82%)	
occurrences (all)	2	5	
Surgical and medical procedures			

All combined subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 39 (2.56%) 2	
General disorders and administration site conditions All combined subjects affected / exposed occurrences (all)	11 / 39 (28.21%) 17	14 / 39 (35.90%) 21	
Reproductive system and breast disorders All combined subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	1 / 39 (2.56%) 1	
Respiratory, thoracic and mediastinal disorders All combined subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6	6 / 39 (15.38%) 7	
Psychiatric disorders All combined subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 7	3 / 39 (7.69%) 5	
Investigations All combined subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4	4 / 39 (10.26%) 6	
Injury, poisoning and procedural complications All combined subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 7	0 / 39 (0.00%) 0	
Cardiac disorders All combined subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 8	4 / 39 (10.26%) 4	
Nervous system disorders All combined subjects affected / exposed occurrences (all)	29 / 39 (74.36%) 47	0 / 39 (0.00%) 0	
Blood and lymphatic system disorders			

All combined subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 8	5 / 39 (12.82%) 11	
Ear and labyrinth disorders All combined subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 39 (7.69%) 5	
Eye disorders All combined subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	7 / 39 (17.95%) 11	
Gastrointestinal disorders All combined subjects affected / exposed occurrences (all)	12 / 39 (30.77%) 19	20 / 39 (51.28%) 31	
Skin and subcutaneous tissue disorders All combined subjects affected / exposed occurrences (all)	13 / 39 (33.33%) 17	9 / 39 (23.08%) 10	
Renal and urinary disorders All combined subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	4 / 39 (10.26%) 4	
Infections and infestations All combined subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 10	13 / 39 (33.33%) 17	
Metabolism and nutrition disorders All combined subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 6	4 / 39 (10.26%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2015	Version number 4 Version date 04 26FEB2015 Summary of changes compared to previous version 3 - Patient exclusion criterion changed: Significant hepatic dysfunction (total bilirubin ≥ 1.5 x ULN or transaminases ≥ 3 times normal level) except patient's with Gilbert's syndrome as defined by > 80% unconjugated bilirubin - Changed timing patient's physical evaluation during maintenance: physical evaluation during maintenance is now every 2 months (previous protocol version every month) - Dose modification instructions for Grade 2 Bullous Rash and Grade 3 Stevens –Johnson Syndrome added - Additional information FDG-PET-CT sub study.
18 April 2016	Version number 5 Version date 17FEB2016 Summary of changes compared to previous version 4 - Ixazomib is shipped refrigerated to the sites - Patient exclusion criterion added: Patient gives consent for extra bone marrow and blood sampling - Induction therapy should start within 4 weeks after patient registration; - PB cryopreservation: Should be performed at entry and at progressive disease only; - Randomization for the maintenance therapy should be done after the response evaluation of the last given induction cycle. In randomized patients maintenance therapy should start within 12 weeks after start last induction therapy (The process of randomization should only be started after the response evaluation of the last ixazomib citrate -thalidomide-low dose dexamethasone cycle is known. For this reason it is not possible, to start maintenance within 4 weeks after start of the last ixazomib induction cycle) - Herpes Zoster prophylaxis: All patients will receive valacyclovir during the induction and maintenance therapy until one month after administration of the last administration of Ixazomib citrate - Updated criteria for symptomatic MM

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33256392