



Clinical trial results:

ReBeL study: a randomized phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients 18 years with relapsed follicular lymphoma

A HOVON/GLSG/NCRI study

Summary

EudraCT number	2011-000097-56
Trial protocol	DE GB
Global end of trial date	05 December 2024

Results information

Result version number	v1 (current)
This version publication date	23 November 2025
First version publication date	23 November 2025

Trial information

Trial identification

Sponsor protocol code	HOVON110
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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	Dr. Molewaterplein 40, Rotterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, 0031 (0)107041560, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, 0031 (0)107041560, hdc@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	17 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2024
Global end of trial reached?	Yes
Global end of trial date	05 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For the phase I part of the study: to determine the dose limiting toxicity (DLT) and recommended dose level (RDL) of lenalidomide and bendamustine given in combination with rituximab for the phase II part of the study

For the phase II of the study: to determine the efficacy and toxicity of the two arms of the study (arm A: lenalidomide and rituximab, and arm B: lenalidomide, rituximab and bendamustine) in patients with relapsed follicular lymphoma (FL)

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2012
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: 84
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Germany: 14
Worldwide total number of subjects	110
EEA total number of subjects	98

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)	63

From 65 to 84 years	47
85 years and over	0

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	Phase 1 Arm B

Arm description:

First arm is phase 1 testing and specifically dosefinding of experimental IMP combination of lenalidomide, rituximab, and bendamustine (LRB).

Arm type	Phase 1 dosefinding
Investigational medicinal product name	Bendamustine hydrochloride
Investigational medicinal product code	CEP-18083
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

• 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.2) • Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.2) • Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.2)

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	REVLIMID®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for PO administration

The recommended starting dose of lenalidomide is 25 mg/day PO on Days 1-21 of repeated 28-day cycles. Actual dose for this arm was 20 mg o.d.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	RO 45-2294
Other name	MABTHERA® / RITUXAN® / IDEC-C2B8
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Rituximab if given i.v. i.v. 1 Rituximab if given s.c.* 375 mg/m² (max. 800 mg) o.d. 1400 mg fixed dose o.d. i.v. s.c.

The next cycle will start at day 29 if the criteria given in 9.2.2 are met. o.d.: once daily Day 1 cycle 1

Arm title	Control group
Arm description:	
LR: lenalidomide and rituximab	
Arm type	Active comparator
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	REVLIMID®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for PO administration

The recommended starting dose of lenalidomide is 25 mg/day PO on Days 1-21 of repeated 28-day cycles. Actual dose for this arm was 20 mg o.d.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	RO 45-2294
Other name	MABTHERA® / RITUXAN® / IDEC-C2B8
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Rituximab if given i.v. i.v. 1 Rituximab if given s.c.* 375 mg/m² (max. 800 mg) o.d. 1400 mg fixed dose o.d. i.v. s.c.

The next cycle will start at day 29 if the criteria given in 9.2.2 are met. o.d.: once daily Day 1 cycle 1 Day 1 cycle 2-6

Arm title	Experimental
Arm description:	
Phase 2 arm B: LRB: lenalidomide, rituximab, and bendamustine	
Arm type	Experimental
Investigational medicinal product name	Bendamustine hydrochloride
Investigational medicinal product code	CEP-18083
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

• 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.2) • Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.2) • Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.2)

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	REVLIMID®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for PO administration

The recommended starting dose of lenalidomide is 25 mg/day PO on Days 1-21 of repeated 28-day cycles. Actual dose for this arm was 20 mg o.d.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	RO 45-2294
Other name	MABTHERA® / RITUXAN® / IDEC-C2B8
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Rituximab if given i.v. i.v. 1 Rituximab if given s.c.* 375 mg/m² (max. 800 mg) o.d. 1400 mg fixed dose o.d. i.v. s.c.

The next cycle will start at day 29 if the criteria given in 9.2.2 are met. o.d.: once daily Day 1 cycle 1 Day 1 cycle 2-6

Number of subjects in period 1	Phase 1 Arm B	Control group	Experimental
Started	18	45	47
Completed	9	16	20
Not completed	9	29	27
Consent withdrawn by subject	-	5	3
Other	1	4	3
Lack of efficacy	8	20	21

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	110	110	
Age categorical			
Units: Subjects			
Adults (18-64 years)	63	63	
From 65-84 years	47	47	
Age continuous			
Units: years			
median	62		
full range (min-max)	33 to 80	-	
Gender categorical			
Units: Subjects			
Female	43	43	
Male	67	67	

End points

End points reporting groups

Reporting group title	Phase 1 Arm B
Reporting group description: First arm is phase 1 testing and specifically dosefinding of experimental IMP combination of lenalidomide, rituximab, and bendamustine (LRB).	
Reporting group title	Control group
Reporting group description: LR: lenalidomide and rituximab	
Reporting group title	Experimental
Reporting group description: Phase 2 arm B: LRB: lenalidomide, rituximab, and bendamustine	

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: See attached chart/documents for results	

End point values	Phase 1 Arm B	Control group	Experimental	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	45	47	
Units: Whole	18	45	47	

Attachments (see zip file)	HO110_Statistical data section from saedata110-5Aug2025/saedata110-5Aug2025.pdf nonsaedata110-5Aug2025/nonsaedata110-5Aug2025.pdf
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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.

Adverse event reporting additional description:

Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Phase 1 Arm B
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Reporting group description:

First arm is phase 1 testing and specifically dosefinding of experimental IMP combination of lenalidomide, rituximab, and bendamustine (LRB).

Reporting group title	Control group
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Reporting group description:

LR: lenalidomide and rituximab

Reporting group title	Experimental
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Reporting group description:

Phase 2 arm B: LRB: lenalidomide, rituximab, and bendamustine

Serious adverse events	Phase 1 Arm B	Control group	Experimental
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 18 (50.00%)	23 / 45 (51.11%)	23 / 47 (48.94%)
number of deaths (all causes)	4	14	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified	Additional description: All combined		
subjects affected / exposed	4 / 18 (22.22%)	9 / 45 (20.00%)	9 / 47 (19.15%)
occurrences causally related to treatment / all	2 / 11	9 / 15	6 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined		
subjects affected / exposed	1 / 18 (5.56%)	4 / 45 (8.89%)	6 / 47 (12.77%)
occurrences causally related to treatment / all	0 / 1	1 / 4	6 / 8
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	3 / 18 (16.67%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined		
subjects affected / exposed	3 / 18 (16.67%)	4 / 45 (8.89%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	3 / 3	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorders	Additional description: All combined		

subjects affected / exposed	1 / 18 (5.56%)	1 / 45 (2.22%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Nervous system disorders			
Nervous system disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined		
subjects affected / exposed	1 / 18 (5.56%)	1 / 45 (2.22%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	1 / 1	0 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	3 / 45 (6.67%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 0	2 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal and urinary disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders	Additional description: All combined		
Endocrine disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders	Additional description: All combined		
Musculoskeletal and connective tissue disorders	Additional description: All combined		
subjects affected / exposed	1 / 18 (5.56%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations	Additional description: All combined		
Infections and infestations	Additional description: All combined		
subjects affected / exposed	2 / 18 (11.11%)	7 / 45 (15.56%)	9 / 47 (19.15%)
occurrences causally related to treatment / all	1 / 2	4 / 7	9 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders	Additional description: All combined		
Metabolism and nutrition disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	2 / 45 (4.44%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1 Arm B	Control group	Experimental
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	40 / 45 (88.89%)	46 / 47 (97.87%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: All combined		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	2 / 47 (4.26%)
occurrences (all)	0	1	2

Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	4 / 18 (22.22%)	5 / 45 (11.11%)	5 / 47 (10.64%)
occurrences (all)	4	5	6
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
General disorders and admin site conditions	Additional description: All combined		
subjects affected / exposed	7 / 18 (38.89%)	17 / 45 (37.78%)	21 / 47 (44.68%)
occurrences (all)	10	26	41
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	3 / 18 (16.67%)	1 / 45 (2.22%)	5 / 47 (10.64%)
occurrences (all)	3	2	6
Social circumstances			
Social circumstances	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined		
subjects affected / exposed	5 / 18 (27.78%)	8 / 45 (17.78%)	10 / 47 (21.28%)
occurrences (all)	8	10	15
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	1 / 18 (5.56%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Investigations			
Investigations	Additional description: All combined		
subjects affected / exposed	4 / 18 (22.22%)	6 / 45 (13.33%)	13 / 47 (27.66%)
occurrences (all)	6	14	17
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	1 / 45 (2.22%)	0 / 47 (0.00%)
occurrences (all)	0	1	0

Cardiac disorders			
Cardiac disorders	Additional description: All combined		
subjects affected / exposed	1 / 18 (5.56%)	2 / 45 (4.44%)	3 / 47 (6.38%)
occurrences (all)	1	2	6
Nervous system disorders			
Nervous system disorders	Additional description: All combined		
subjects affected / exposed	4 / 18 (22.22%)	7 / 45 (15.56%)	9 / 47 (19.15%)
occurrences (all)	5	7	10
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: All combined		
subjects affected / exposed	2 / 18 (11.11%)	2 / 45 (4.44%)	1 / 47 (2.13%)
occurrences (all)	2	2	2
Eye disorders			
Eye disorders	Additional description: All combined		
subjects affected / exposed	3 / 18 (16.67%)	1 / 45 (2.22%)	2 / 47 (4.26%)
occurrences (all)	3	1	3
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined		
subjects affected / exposed	6 / 18 (33.33%)	14 / 45 (31.11%)	20 / 47 (42.55%)
occurrences (all)	11	17	45
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined		
subjects affected / exposed	5 / 18 (27.78%)	15 / 45 (33.33%)	20 / 47 (42.55%)
occurrences (all)	8	21	28
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined		
subjects affected / exposed	0 / 18 (0.00%)	3 / 45 (6.67%)	2 / 47 (4.26%)
occurrences (all)	0	4	2
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	4 / 18 (22.22%) 8	5 / 45 (11.11%) 7	7 / 47 (14.89%) 7
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	Additional description: All combined		
	11 / 18 (61.11%) 32	20 / 45 (44.44%) 29	21 / 47 (44.68%) 49
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	0 / 18 (0.00%) 0	2 / 45 (4.44%) 3	6 / 47 (12.77%) 7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2011	<p>The amendment concerns an adjustment to the reporting of dose limit toxicity (DLT). The DLTs must be reported during cycles 3 through 6 using the rapid reporting procedure.</p> <p>Furthermore, the labels for Levact® have been modified.</p> <p>For the benefit of our central administration, we kindly request your response to be returned to the Clinical Hematology Secretariat, F4-224.</p>
16 December 2011	<p>Amendment 2</p> <p>On behalf of the Department of Clinical Hematology, you are hereby receiving amendment 2 with attachments of the aforementioned protocol for review at your next meeting.</p> <p>The amendment concerns adjusting the label of lenalidomide (study medication), as the supply will switch to lenalidomide in blister packs.</p> <p>Furthermore, there are some administrative adjustments in the protocol.</p>
01 June 2012	<p>Amendment 3</p> <p>The amendment concerns:</p> <p>A change in the protocol regarding the use of allopurinol before starting treatment (paragraph 9.2.3) and some minor corrections.</p> <p>Additional documents:</p> <p>IB rituximab version 16 IB lenalidomide version 15 Roche contract</p> <p>Addition of a site (Rijnstate Arnhem)</p> <p>Investigator in Enschede changed (Dr. De Groot Dr. Schaafsma)</p> <p>ABR form: D12 (clarification of reimbursement) explained.</p> <p>Adjustments to the EudraCT form regarding IMP Lenalidomide (PR1, PR4, and PR5):</p> <p>D.2.5. / D.2.5.1 / D.3.3 / D.9.2.1 / D9.2.3 / D.9.2.5.</p>

14 March 2013	<p>Amendment 4</p> <p>The main changes in this amendment are:</p> <p>For the Phase II part of the study, centers in England will also participate (National Cancer Research Institute UK).</p> <p>A change in the inclusion criteria: based on newly available data, patients previously treated with bendamustine may also participate in the study, provided they responded well earlier.</p> <p>The description of the risk management program regarding pregnancy tests due to the use of lenalidomide has been adjusted in the protocol.</p> <p>Update of the investigator's brochure for study medication Rituximab; new version 17 (July 2012).</p> <p>Update of the investigator's brochure for study medication Lenalidomide; new version 16.</p> <p>The complete Lenalidomide IB will be sent as soon as it is received. To prevent delays, the protocol and patient information have already been adjusted according to the new safety information received from the manufacturer of this study medication (Celgene).</p> <p>Furthermore, there are some administrative adjustments in the protocol, and based on a review by the National Cancer Research Institute UK, some clarifications have been added.</p> <p>Additionally, changes in the protocol, where applicable, have also been implemented in the patient information.</p>
07 October 2013	<p>Amendment 5</p> <p>Exclusion criteria added: Recent vaccination for yellow fever (within 4 weeks before registration).</p> <p>Update of the section: Guidelines concerning the risk of pregnancy during the use of bendamustine.</p> <p>Male subjects must not father children for six months after treatment.</p> <p>Adjustment in paragraph Special precautions and supportive care: "For patients who are treated with bendamustine, yellow fever vaccination or any vaccination with other live viruses is prohibited at least until one year after the last administration of bendamustine."</p> <p>Adjustment of inclusion criteria: Use adequate contraception not only during but also after therapy.</p>
18 September 2014	<p>Amendment 6</p> <p>The amendment concerns:</p> <p>Transition from the Phase I part of the study, where the recommended dose level was established, to the Phase II part of the study. The study documents have been adjusted accordingly.</p> <p>An update of the Investigator's Brochure for Lenalidomide and Rituximab.</p> <p>Expansion of sites participating in the Phase II part of the study:</p> <p>Maasstad Hospital MC Leeuwarden St. Elisabeth Tilburg Admiraal de Ruyter Hospital (locations Vlissingen and Goes)</p> <p>UMC St. Radboud will no longer participate in this research. New independent physicians: VUmc and Groene Hart Gouda.</p>

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/32072141>