Clinical trial results:
A randomized phase II multicenter study to assess the tolerability and efficacy of the addition of ibrutinib to 10-day decitabine in UNFIT (i.e. HCT-CI 3) AML and high risk myelodysplasia (MDS) (IPSS-R > 4.5) patients aged >=66 years.

A study in the frame of the masterprotocol of parallel randomized phase II studies in UNFIT-older AML/high-risk MDS patients.

Summary

EudraCT number	2015-002855-85
Trial protocol	NL BE LT
Global end of trial date	10 July 2024

Results information

Result version number	v1 (current)
This version publication date	08 June 2025
First version publication date	08 June 2025

Trial information

Trial identification

Sponsor protocol code	HO135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	METC UMCG: 2015.550, Nederlands Trialregister: NTR6017, CCMO dossiernr: NL55164.042.15

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	Dr. Molewaterplein 40, Rotterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, 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	18 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2020
Global end of trial reached?	Yes
Global end of trial date	10 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess in a randomized comparison the effect of ibrutinib added to 10-day decitabine treatment on the cumulative CR/CRi rate after 3 cycles.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 85
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Switzerland: 40
Worldwide total number of subjects	148
EEA total number of subjects	108

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)	0

From 65 to 84 years	144
85 years and over	4

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	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	decitabine
Investigational medicinal product code	
Other name	DACOGEN
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The 5-Day dosing regimen is defined as 20 mg/m2 DACOGEN administered as a 1 hour IV infusion for 5 consecutive days every 4weeks. The 3-Day dosing regimen is defined as 15 mg/m2 DACOGEN administered as a 3 hour IV infusion every 8 hours for 3 consecutive days every 6 weeks

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	IMBRUVICA
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Oral use

Dosage and administration details:

The recommended dose of ibrutinib for MCL or MZL is 560 mg orally once daily until disease progression or no longer tolerated by the subject.

Arm title	Control

Arm description:

Standard of care; Decatibine

Arm type	Active comparator
Investigational medicinal product name	decitabine
Investigational medicinal product code	
Other name	DACOGEN
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The 5-Day dosing regimen is defined as 20 mg/m2 DACOGEN administered as a 1 hour IV infusion for 5 consecutive days every 4weeks. The 3-Day dosing regimen is defined as 15 mg/m2 DACOGEN administered as a 3 hour IV infusion every 8 hours for 3 consecutive days every 6 weeks

Number of subjects in period 1	Experimental	Control
Started	74	74
Completed	0	0
Not completed	74	74
Adverse reactions	14	7
Other	7	11
At patient's request	13	6
Lack of efficacy	40	50

Baseline characteristics

Reporting groups

Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	148	148	
Age categorical			
Previously untreated adults who were >=66 years old and not considered eligible for intensive chemotherapy, with a cytopathologically confirmed diagnosis of AML or with higher risk MDS (Revised International Prognostic Scoring System score .4.5), a World Health Organization (WHO) performance status #2, and written informed consent, were eligible.			
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)	0	0	
From 65-84 years	144	144	
85 years and over	4	4	
Age continuous			
Units: years			
median	76		
full range (min-max)	66 to 89	-	
Gender categorical			
Units: Subjects			
Female	56	56	
Male	92	92	

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description:	
Standard of care; Decatibine	

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	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Whole	74	74		

Attachments (see zip file)	HO135_Statistical data section from publication_22MAY2025. nonsaedata135-22May2025.pdf saedata135-22May2025.pdf

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 local investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Control group

Reporting group description: -

Reporting group title	Experimental group

Reporting group description:

Actual number of deaths all causes is 72. Patient died after randomization but before starting treatment.

Serious adverse events	Control group	Experimental group	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 73 (80.82%)	65 / 71 (91.55%)	
number of deaths (all causes)	70	71	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	6 / 73 (8.22%)	6 / 71 (8.45%)	
occurrences causally related to treatment / all	0 / 8	1 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Vascular disorders			
Vascular disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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 non-SAE chart for details		

subjects affected / exposed	5 / 73 (6.85%)	8 / 71 (11.27%)	
occurrences causally related to treatment / all	4 / 7	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
Immune system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 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 non-SAE chart for details		
subjects affected / exposed	6 / 73 (8.22%)	6 / 71 (8.45%)	
occurrences causally related to treatment / all	4 / 8	2 / 6	
deaths causally related to treatment / all	2 / 4	0 / 0	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 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 non-SAE chart for details		
subjects affected / exposed	2 / 73 (2.74%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	6 / 73 (8.22%)	6 / 71 (8.45%)	
occurrences causally related to treatment / all	2 / 6	4 / 6	
deaths causally related to treatment / all	1 / 2	0 / 0	
Nervous system disorders			
Nervous system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	7 / 73 (9.59%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	4 / 8	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	21 / 73 (28.77%)	23 / 71 (32.39%)	
occurrences causally related to treatment / all	29 / 32	24 / 30	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Eye disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	7 / 73 (9.59%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	1 / 7	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
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 non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 73 (2.74%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Endocrine disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 73 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	35 / 73 (47.95%)	35 / 71 (49.30%)	
occurrences causally related to treatment / all	32 / 48	22 / 48	
deaths causally related to treatment / all	7 / 10	6 / 9	

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

Non-serious adverse events	Control group	Experimental group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 73 (87.67%)	66 / 71 (92.96%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Vascular disorders			
Vascular disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	15 / 73 (20.55%)	12 / 71 (16.90%)	
occurrences (all)	15	14	
Surgical and medical procedures			

Surgical and medical procedures	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 73 (2.74%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	18 / 73 (24.66%)	18 / 71 (25.35%)	
occurrences (all)	21	24	
Immune system disorders			
Immune system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	2 / 73 (2.74%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	10 / 73 (13.70%)	12 / 71 (16.90%)	
occurrences (all)	12	14	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	3 / 73 (4.11%)	4 / 71 (5.63%)	
occurrences (all)	4	6	
Investigations			
Investigations	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	20 / 73 (27.40%)	16 / 71 (22.54%)	
occurrences (all)	41	27	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	5 / 71 (7.04%)	
occurrences (all)	1	5	
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see non-SAE chart for details		

subjects affected / exposed	10 / 73 (13.70%)	14 / 71 (19.72%)	
occurrences (all)	12	17	
Nervous system disorders			
Nervous system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	7 / 73 (9.59%)	9 / 71 (12.68%)	
occurrences (all)	10	11	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	13 / 73 (17.81%)	18 / 71 (25.35%)	
occurrences (all)	14	22	
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	1 / 73 (1.37%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Eye disorders			
Eye disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	4 / 73 (5.48%)	0 / 71 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	24 / 73 (32.88%)	25 / 71 (35.21%)	
occurrences (all)	33	39	
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	0 / 73 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	8 / 73 (10.96%)	14 / 71 (19.72%)	
occurrences (all)	8	16	
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	5 / 73 (6.85%)	6 / 71 (8.45%)	
occurrences (all)	5	6	
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	10 / 73 (13.70%)	4 / 71 (5.63%)	
occurrences (all)	12	4	
Infections and infestations			
Infections and infestations	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	37 / 73 (50.68%)	34 / 71 (47.89%)	
occurrences (all)	58	51	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All combined, see non-SAE chart for details		
subjects affected / exposed	13 / 73 (17.81%)	16 / 71 (22.54%)	
occurrences (all)	21	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2017	It involves adding a new centers: Isala Clinic, Zwolle OLVG, Amsterdam Reinier de graaf groep, Delft
22 April 2022	It involves a change of investigators in the following hospitals: Meander MC, Amersfoort MUMC, Maastricht Rijnstate, Arnhem

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/32915972