



Clinical trial results:

A randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral tosedostat to standard induction therapy in AML and RAEB 66 years and very poor risk AML 18 years.

A study in the frame of the masterprotocol of parallel randomized phase II studies in elderly AML

Summary

EudraCT number	2009-014455-68
Trial protocol	NL BE NO
Global end of trial date	19 September 2024

Results information

Result version number	v1 (current)
This version publication date	03 January 2026
First version publication date	03 January 2026

Trial information

Trial identification

Sponsor protocol code	HOVON103AMLTosedostat
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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, Erasmus MC, +31 107041560, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, Erasmus MC, +31 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	29 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2023
Global end of trial reached?	Yes
Global end of trial date	19 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For part A of the study (if applicable):

1. To assess the safety and tolerability of tosedostat added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) and select the feasible dose level for part B
2. To assess in a randomized comparison the effect of tosedostat on the CR rate.

For part B:

1. To assess the safety and tolerability of tosedostat added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) as regards the selected dose level of tosedostat
2. To assess in a randomized comparison the effect of tosedostat on the CR rate.

Protection of trial subjects:

Insurance and monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2010
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	Switzerland: 34
Country: Number of subjects enrolled	Netherlands: 192
Country: Number of subjects enrolled	Belgium: 54
Worldwide total number of subjects	280
EEA total number of subjects	246

Notes:

Subjects enrolled per age group

In utero	0
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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	280
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	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Control Group
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Daunomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunomycin Days 45mg/m² 3hr infusion on days 1,2,3

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cytarabine 200mg/m² continuous infusion(24hrs) on days 1 thru 7

Arm title	Experimental
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Daunomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunomycin Days 45mg/m² 3hr infusion on days 1,2,3

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cytarabine 200mg/m² continuous infusion(24hrs) on days 1 thru 7

Investigational medicinal product name	Tosedostat
Investigational medicinal product code	CHR2797
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

120, 180 or 240 mg/day for part A as dose finding phase.

Part B onwards: dose of 120mg/day

days 1 thru 56 Stop after day 35 if platelets < 30x10⁹/l and/or ANC< 0.5x10⁹/l

Number of subjects in period 1	Control Group	Experimental
Started	141	139
Completed	90	52
Not completed	51	87
Adverse reactions	18	28
Consent withdrawn by subject	-	8
Other	11	9
Lack of efficacy	22	42

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	280	280	
Age categorical			
Units: Subjects			
From 65-84 years	280	280	
Age continuous			
Units: years			
median	70		
full range (min-max)	66 to 81	-	
Gender categorical			
Units: Subjects			
Female	101	101	
Male	179	179	

End points

End points reporting groups

Reporting group title	Control Group
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	

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	Control Group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: Whole	141	139		

Attachments (see zip file)	List of reported non-SAE's/Tose-nonsaedata103-2Dec2025.pdf List of reported SAE's/Tose-saedata103-2Dec2025.pdf Statistical data section from publication/cancers-13-00672.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 protocol treatment 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 related to study drug. Grade 3 or 4 adverse events considered related to study drug must be followed until recovery or until 6 months after the last protocol treatment, whichever comes first.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Control Group
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Reporting group description: -

Reporting group title	Experimental
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Reporting group description: -

Serious adverse events	Control Group	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 141 (39.01%)	87 / 135 (64.44%)	
number of deaths (all causes)	108	126	
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		
subjects affected / exposed	2 / 141 (1.42%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
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		

subjects affected / exposed	2 / 141 (1.42%)	8 / 135 (5.93%)	
occurrences causally related to treatment / all	2 / 2	6 / 8	
deaths causally related to treatment / all	1 / 1	4 / 4	
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	0 / 135 (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		
subjects affected / exposed	12 / 141 (8.51%)	13 / 135 (9.63%)	
occurrences causally related to treatment / all	9 / 12	12 / 15	
deaths causally related to treatment / all	4 / 5	6 / 7	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders	Additional description: All combined		
subjects affected / exposed	7 / 141 (4.96%)	15 / 135 (11.11%)	
occurrences causally related to treatment / all	4 / 7	12 / 15	
deaths causally related to treatment / all	2 / 2	3 / 5	
Nervous system disorders			
Nervous system disorders	Additional description: All combined		
subjects affected / exposed	6 / 141 (4.26%)	9 / 135 (6.67%)	
occurrences causally related to treatment / all	3 / 6	4 / 9	
deaths causally related to treatment / all	1 / 2	0 / 3	
Blood and lymphatic system disorders			

Blood and lymphatic system disorders	Additional description: All combined		
subjects affected / exposed	4 / 141 (2.84%)	4 / 135 (2.96%)	
occurrences causally related to treatment / all	4 / 4	3 / 4	
deaths causally related to treatment / all	2 / 2	0 / 1	
Eye disorders	Additional description: All combined		
Eye disorders	Additional description: All combined		
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders	Additional description: All combined		
Gastrointestinal disorders	Additional description: All combined		
subjects affected / exposed	7 / 141 (4.96%)	6 / 135 (4.44%)	
occurrences causally related to treatment / all	5 / 7	5 / 7	
deaths causally related to treatment / all	3 / 3	0 / 0	
Hepatobiliary disorders	Additional description: All combined		
Hepatobiliary disorders	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin and subcutaneous tissue disorders	Additional description: All combined		
Skin and subcutaneous tissue disorders	Additional description: All combined		
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders	Additional description: All combined		
Renal and urinary disorders	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations	Additional description: All combined		
Infections and infestations	Additional description: All combined		
subjects affected / exposed	22 / 141 (15.60%)	49 / 135 (36.30%)	
occurrences causally related to treatment / all	21 / 23	45 / 53	
deaths causally related to treatment / all	8 / 8	22 / 24	
Metabolism and nutrition disorders			

Metabolism and nutrition disorders	Additional description: All combined		
subjects affected / exposed	2 / 141 (1.42%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control Group	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 141 (95.04%)	133 / 135 (98.52%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: All combined		
subjects affected / exposed	4 / 141 (2.84%)	0 / 135 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
Vascular disorders	Additional description: All combined		
subjects affected / exposed	35 / 141 (24.82%)	26 / 135 (19.26%)	
occurrences (all)	45	30	
Surgical and medical procedures			
Surgical and medical procedures	Additional description: All combined		
subjects affected / exposed	1 / 141 (0.71%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined		
subjects affected / exposed	38 / 141 (26.95%)	45 / 135 (33.33%)	
occurrences (all)	55	62	
Immune system disorders			
Immune system disorders	Additional description: All combined		
subjects affected / exposed	4 / 141 (2.84%)	10 / 135 (7.41%)	
occurrences (all)	4	12	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All combined		
subjects affected / exposed	2 / 141 (1.42%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal			

disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined		
subjects affected / exposed	32 / 141 (22.70%)	35 / 135 (25.93%)	
occurrences (all)	45	50	
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined		
subjects affected / exposed	16 / 141 (11.35%)	20 / 135 (14.81%)	
occurrences (all)	19	21	
Investigations			
Investigations	Additional description: All combined		
subjects affected / exposed	42 / 141 (29.79%)	57 / 135 (42.22%)	
occurrences (all)	105	127	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined		
subjects affected / exposed	5 / 141 (3.55%)	4 / 135 (2.96%)	
occurrences (all)	6	4	
Cardiac disorders			
Cardiac disorders	Additional description: All combined		
subjects affected / exposed	23 / 141 (16.31%)	44 / 135 (32.59%)	
occurrences (all)	31	55	
Nervous system disorders			
Nervous system disorders	Additional description: All combined		
subjects affected / exposed	21 / 141 (14.89%)	20 / 135 (14.81%)	
occurrences (all)	27	25	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All combined		
subjects affected / exposed	84 / 141 (59.57%)	67 / 135 (49.63%)	
occurrences (all)	152	107	
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: All combined		
subjects affected / exposed	5 / 141 (3.55%)	3 / 135 (2.22%)	
occurrences (all)	5	3	
Eye disorders			
Eye disorders	Additional description: All combined		
subjects affected / exposed	12 / 141 (8.51%)	11 / 135 (8.15%)	
occurrences (all)	13	13	
Gastrointestinal disorders			

Gastrointestinal disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	92 / 141 (65.25%)	88 / 135 (65.19%)	
	197	173	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	5 / 141 (3.55%)	3 / 135 (2.22%)	
	5	5	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	68 / 141 (48.23%)	62 / 135 (45.93%)	
	101	93	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	12 / 141 (8.51%)	15 / 135 (11.11%)	
	17	15	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	1 / 141 (0.71%)	1 / 135 (0.74%)	
	1	1	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	13 / 141 (9.22%)	8 / 135 (5.93%)	
	17	8	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	Additional description: All combined		
	96 / 141 (68.09%)	88 / 135 (65.19%)	
	201	197	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	Additional description: All combined		
	60 / 141 (42.55%)	60 / 135 (44.44%)	
	149	142	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2011	Amendment 1 The reason for this amendment is to add participating centers and an update in the pharmacokinetics paragraph.
04 March 2013	Amendment 2 The reason for this amendment/addendum is: New version of the IMPD in which the shelf life of the medication is extended from 48 months to 60 months Update ABR and EudraCT form with already added centers Non-substantial amendment of the protocol (see summary of changes)
27 June 2024	Amendment 3 The reason for this amendment is to follow the advice given by the Federal Drug Association (FDA) following a previously imposed partial hold on all clinical tosedostat studies due to reports of several serious cardiac adverse events. This hold was reported on June 21, 2013. A risk-benefit evaluation was conducted regarding potential cardiac toxicities. Based on this evaluation, the FDA advised to: Limit the tosedostat dose to 120 mg per day Recommend specific criteria for excluding patients with cardiac risks Recommend minimal cardiac monitoring during the study We have taken this advice to heart and incorporated the recommendations into the protocol. Additionally, we have modified the inclusion and exclusion criteria for the following reasons: Exclude patients aged 18–65 years with high-risk AML due to the existence of another HOVON study in which these patients could be included Standardize criteria for liver and kidney function Adjust AML diagnosis to current criteria

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/33562393>