Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination With Intensive Induction and Consolidation Chemotherapy in Adults With Newly Diagnosed Nucleophosmin 1-mutated Acute Myeloid Leukemia

Summary

EudraCT number	2021-000761-33
Trial protocol	DE ES HU CZ IT FR PL
Global end of trial date	30 March 2023

Results information

Result version number	v1 (current)
This version publication date	04 January 2024
First version publication date	04 January 2024

Trial information

Trial identification

Sponsor protocol code	KB-ENTO-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05020665
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 116416

Notes:

Sponsors

Sponsor organisation name	Kronos Bio, Inc.
Sponsor organisation address	1300 So. El Camino Real, Suite 400, San Mateo, United States, CA 94402
Public contact	VP, Corporate Affairs, Kronos Bio, Inc., media@kronosbio.com
Scientific contact	VP, Corporate Affairs, Kronos Bio, Inc., media@kronosbio.com

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	30 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of entospletinib (ENTO) compared to placebo when added to chemotherapy in previously untreated nucleophosmin 1-mutated (NPM1-m) acute myeloid leukemia (AML), as defined by the rate of molecularly defined measurable residual disease (MRD).

Protection of trial subjects:

Study site personnel must obtain signed informed consent before any study-specific procedures (including central laboratory screening for the presence of NPM1 and fms like tyrosine kinase 3 [FLT3] mutations) were conducted, unless these were part of the standard of care, and must document the informed consent process in the subject's medical record. Consent must be obtained using the most current version of informed consent form (ICF) approved by the study site's Institutional Review Board/Independent Ethics Committee. Once the subject had signed the ICF, that indicated the beginning of the 14-day Screening Period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 November 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	15
EEA total number of subjects	10

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)	11
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 5 countries including the Czechia, France, Republic of Korea, Spain, and the United States from 24 November 2021 to 30 March 2023.

Pre-assignment

Screening details:

In this study subjects were randomized 1:1 to receive intensive chemotherapy in combination with either the spleen tyrosine kinase inhibitor, ENTO, or placebo. Randomization was stratified by age (< 60 vs ≥ 60 years) and anthracycline administered during induction (daunorubicin vs idarubicin).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ENTO

Arm description:

Subjects received ENTO twice daily (BID), along with intensive chemotherapy (cytarabine and anthracycline) by continuous intravenous (IV) infusion (cytarabine) or slow IV push (anthracycline).

Arm type	Experimental
Investigational medicinal product name	Entospletinib
Investigational medicinal product code	ENTO
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received ENTO BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous IV infusion (cytarabine) or slow IV push (anthracycline).

Arm title	Placebo

Arm description:

Subjects received placebo BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous IV infusion (cytarabine) or slow IV push (anthracycline).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous IV infusion (cytarabine) or slow IV push (anthracycline).

Number of subjects in period 1	ENTO	Placebo
Started	8	7
Completed	0	0
Not completed	8	7
Adverse event, serious fatal	2	1
Physician decision	-	1
Consent withdrawn by subject	-	1
Study terminated by Sponsor	5	4
Reason not specified	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ENTO
Reporting group description:	
Subjects received ENTO twice daily (BID), along with intensive chemotherapy (cytarabine and anthracycline) by continuous intravenous (IV) infusion (cytarabine) or slow IV push (anthracycline).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous IV infusion (cytarabine) or slow IV push (anthracycline).	

Reporting group values	ENTO	Placebo	Total
Number of subjects	8	7	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	5	11
From 65-84 years	2	2	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.6	54.6	
standard deviation	± 9.41	± 16.11	-
Gender categorical Units: Subjects			
Female	6	2	8
Male	2	5	7

End points

End points reporting groups

Reporting group title	ENTO
Reporting group description:	
Subjects received ENTO twice daily (BID), along with intensive chemotherapy (cytarabine and anthracycline) by continuous intravenous (IV) infusion (cytarabine) or slow IV push (anthracycline).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous IV infusion (cytarabine) or slow IV push (anthracycline).	

Primary: Measurable Residual Disease (MRD) Negative Complete Response (CR) Rate

End point title	Measurable Residual Disease (MRD) Negative Complete Response (CR) Rate[1]
End point description:	
MRD negative CR requires CR as defined by the European Leukemia Network (ELN) 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by International Working Group [IWG]) as assessed by study site investigators, and MRD negativity (<0.01%) in bone marrow as measured by a molecular NPM1-m assay (eg, next generation sequencing) in a central laboratory upon recovery of peripheral blood counts following completion of 2 cycles of chemotherapy, no later than Day 42 of Cycle 2. Data not collected as the study was terminated early.	
End point type	Primary
End point timeframe:	
Cycle 1 Day 1, up to Day 42 of chemotherapy cycle 2 (Cycle length = 42 days).	

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: Data not collected as the study was terminated early.

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Number of Subjects				

Notes:

[2] - Data not collected as the study was terminated early.

[3] - Data not collected as the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)
End point description:	
EFS is defined as the time from randomization to the earliest occurrence of induction treatment failure, relapse from CR, or death from any cause. Note: Induction treatment failure is failure to achieve morphological CR after completion of the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction). Data not collected as the study was terminated early.	

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, up to Day 42 of chemotherapy cycle 2 (Cycle length = 42 days).

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Number of Subjects				

Notes:

[4] - Data not collected as the study was terminated early.

[5] - Data not collected as the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free Survival (RFS)

End point title	Relapse-free Survival (RFS)

End point description:

RFS is defined as the time from CR until relapse or death from any cause as assessed by study site investigators.
Data not collected as the study was terminated early.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, up to Day 42 of chemotherapy cycle 2 (Cycle length = 42 days).

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Number of Subjects				

Notes:

[6] - Data not collected as the study was terminated early.

[7] - Data not collected as the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS defined as the time from randomization until death from any cause.
Data not collected as the study was terminated early.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, up to Day 42 of chemotherapy cycle 2 (Cycle length = 42 days).

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Number of Subjects				

Notes:

[8] - Data not collected as the study was terminated early.

[9] - Data not collected as the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Complete Response (CR) After 2 Cycles of Chemotherapy

End point title	Number of Subjects with Complete Response (CR) After 2 Cycles of Chemotherapy

End point description:

CR as defined by ELN 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by IWG) as assessed by study site investigators.
Intent-to-Treat (ITT) Analysis Set: All subjects who were randomized.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, up to Day 42 of chemotherapy cycle 2 (Cycle length = 42 days).

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Number of Subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects Who Experienced Treatment-emergent Adverse Events (TEAEs)

End point description:

TEAEs were defined as all events beginning or worsening from Cycle 1, Day 1 through 30 days following study treatment completion, was recorded according to the most current version of the Medical Dictionary for Regulatory Activities (MedDRA).
Clinically significant changes in safety laboratory assessments, electrocardiograms, echocardiogram/multi-gated acquisition (MUGA) scans and Eastern Cooperative Oncology Group performance status (ECOG PS) findings, as assessed by the Investigator, were recorded as TEAEs.
Safety Analysis Set: All subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, to 30 days following study treatment completion (Cycle length = 42 days), maximum up to 198 days.

End point values	ENTO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Number of Subjects	8	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events and deaths were collected from signing informed consent through 30 days after treatment completion, up to 212 days. Other adverse events were collected from Cycle 1 Day 1 through 30 days after treatment completion, up to 198 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	ENTO

Reporting group description:

Subjects received ENTO twice daily (BID), along with intensive chemotherapy (cytarabine and anthracycline) by continuous intravenous (IV) infusion (cytarabine) or slow IV push (anthracycline).

Reporting group title	Placebo

Reporting group description:

Subjects received placebo BID, along with intensive chemotherapy (cytarabine and anthracycline) by continuous intravenous (IV) infusion (cytarabine) or slow IV push (anthracycline)

Serious adverse events	ENTO	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	2 / 7 (28.57%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	3	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			

subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Klebsiella bacteraemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fungal sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ENTO	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	7 / 7 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	4	
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	3	2	
Chills			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Deformity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Medical device site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Non-cardiac chest pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	4	
Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	4	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	1	4	
Amylase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Blood bilirubin increased			

subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
C-reactive protein increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Lipase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Transaminases increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Lethargy			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Taste disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	5 / 7 (71.43%)	
occurrences (all)	4	7	
Thrombocytopenia			
subjects affected / exposed	4 / 8 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	29	34	
Anaemia			
subjects affected / exposed	3 / 8 (37.50%)	3 / 7 (42.86%)	
occurrences (all)	36	25	
Neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 7 (42.86%)	
occurrences (all)	19	20	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	16	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 8 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	7	3	
Diarrhoea			
subjects affected / exposed	3 / 8 (37.50%)	2 / 7 (28.57%)	
occurrences (all)	5	3	
Constipation			

subjects affected / exposed	3 / 8 (37.50%)	1 / 7 (14.29%)	
occurrences (all)	5	1	
Colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Large intestinal stenosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vomiting			

subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 8 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Dermatitis contact			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Intertrigo			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	

Back pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Cytarabine syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
COVID-19			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal infection			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Clostridium colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Folliculitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Herpes simplex reactivation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 7 (42.86%)	
occurrences (all)	12	8	

Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	3 / 7 (42.86%)	
occurrences (all)	2	3	
Hypervolaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	15	1	
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	3	2	
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypoproteinaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2021	Protocol Amendment 1: The description of induction treatment failure for purposes of event-free survival estimation was modified to "failure to achieve morphologic CR after completion of the last cycle of induction chemotherapy (no later than day 42 of the last cycle of induction)." -Revisions were made to clarify the requirements for bone marrow examination. -Amendment 1.0 changed the requirement for all subjects to receive 2 cycles of induction to administration of a second induction cycle contingent upon response to the initial induction cycle. A schematic depiction of study treatment from Cycle 1 Day 1 through completion of Chemotherapy Cycle 2 was added. -"Failure to achieve (or maintain) CR, CRh, or complete remission with incomplete blood count recovery (CRi) post-Chemotherapy Cycle 2" was added as a reason for study treatment discontinuation. -It was clarified that response assessments would be in accordance with the European LeukemiaNet (ELN) criteria but with minor modification for neutrophil and platelet count thresholds for a response of CR, as defined by International Working Group (IWG) criteria. -A statement of estimand for the primary endpoint was added. -Updates and clarifications were included for analyses of the secondary endpoints, event-free survival, relapse-free survival, and overall survival. -Additional explanatory details regarding the function of the DMC with implications for its role to oversee both safety and efficacy (or futility) for this trial were provided.
24 November 2021	Protocol Amendment 1.1: -The benefit/risk section was revised to include Leukemia & Lymphoma Society Study BAML-16-001-S6 data collected through 01 October 2021. -A section on COVID-19 considerations was added. Reference to the FDA guidance regarding risk mitigation efforts in clinical trial conduct during the COVID-19 pandemic era was removed in response to request from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM – Federal Institute for Drugs and Medical Devices). This was replaced with reference to European Union (EU) specific-guidances. -Screening for HIV was added to the study procedures. -Clarification regarding the timeframe for serious adverse event (SAE) reporting was added. -Pregnancy was added as a discontinuation criterion.
27 January 2022	Protocol Amendment 2: -Changes introduced in country-specific Amendment 1.1 were incorporated into this global amendment. -Modifications to allow for bone marrow examination up to Day 42 of Induction Cycle 1 in order to allow for recovery of peripheral blood counts before assigning remission status were included. -Requirements were added for ANC and platelet count to recover to > 1 × 109/L and > 100 × 109/L, respectively, prior to initiation of Consolidation Cycle 1 to allow for identification of subjects who achieved morphologic CR post-Induction Cycle 1 (based both on bone marrow and peripheral blood criteria) and for consistency with post-Chemotherapy Cycle 2. -A blanket exclusion was added for subjects with concurrent fms-like tyrosine kinase 3 (FLT3) mutation (including those without prior access to midostaurin). -Language was added allowing subjects who were HIV positive to enroll provided they met specific entry criteria. -Contraceptive guidance was revised to emphasize the lack of a known potential drug-drug interaction between ENTO and hormonal contraceptives that could potentially reduce their efficacy. Language was added to require the use of a barrier method (eg, male condom) in addition to one of the highly effective methods of contraception listed. -Appendix 9: Guidance on the Management of Clinical Trials During COVID-19 Pandemic was updated to include both US and EU guidances.

10 February 2022	Protocol Amendment 3: Clarification regarding the timeframe and procedures for SAE reporting was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination was due to significant challenges associated with enrollment of subjects with genetically-defined, newly diagnosed, AML who are candidates for intensive induction therapy and other challenges associated with post-COVID impacts.

Notes: