



Clinical trial results:

A Phase 2/3 Study to Evaluate the Efficacy and Safety of Unesbulin in Unresectable or Metastatic, Relapsed or Refractory Leiomyosarcoma Summary

EudraCT number	2022-000073-12
Trial protocol	HU ES DE IT PL NL FR
Global end of trial date	17 July 2024

Results information

Result version number	v1 (current)
This version publication date	20 June 2025
First version publication date	20 June 2025

Trial information

Trial identification

Sponsor protocol code	PTC596-ONC-008-LMS
-----------------------	--------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05269355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	500 Warren Corp Centre Dr, Warren, United States, NJ 07059
Public contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.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	17 July 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 July 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess progression-free survival (PFS) of unesbulin plus dacarbazine versus placebo plus dacarbazine.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2022
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	United States: 202
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	358
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	256
From 65 to 84 years	101
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized 2:1 to 1 of the following treatment groups: 1. Unesbulin and Dacarbazine (N=239) or 2. Placebo and Dacarbazine (N=120). A total of 359 participants were randomized, of which 358 participants were treated.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Unesbulin and Dacarbazine

Arm description:

Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m²) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Arm type	Experimental
Investigational medicinal product name	Unesbulin
Investigational medicinal product code	PTC596
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Unesbulin was administered per schedule specified in the arm description.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	DTIC
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine was administered per schedule specified in the arm description.

Arm title	Placebo and Dacarbazine
------------------	-------------------------

Arm description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m² IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PTC596
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to unesbulin was administered per schedule specified in the arm description.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	DTIC
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine was administered per schedule specified in the arm description.

Number of subjects in period 1	Unesbulin and Dacarbazine	Placebo and Dacarbazine
Started	238	120
Received at Least 1 Dose of Study Drug	238	120
Completed	0	0
Not completed	238	120
Adverse event, serious fatal	3	5
Consent withdrawn by subject	18	5
Physician decision	6	4
Other Than Specified	5	1
Adverse event, non-fatal	15	8
Progressive Disease	104	68
Study Terminated by Sponsor	87	29

Baseline characteristics

Reporting groups

Reporting group title	Unesbulin and Dacarbazine
-----------------------	---------------------------

Reporting group description:

Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m²) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Reporting group title	Placebo and Dacarbazine
-----------------------	-------------------------

Reporting group description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m² IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Reporting group values	Unesbulin and Dacarbazine	Placebo and Dacarbazine	Total
Number of subjects	238	120	358
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	57.4 ± 10.98	58.6 ± 11.04	-
Sex: Female, Male Units: participants			
Female	187	93	280
Male	51	27	78
Ethnicity Units: Subjects			
Hispanic or Latino	36	26	62
Not Hispanic or Latino	170	87	257
Unknown or Not Reported	32	7	39
Race Units: Subjects			
Asian	17	8	25
American Indian/Alaska Native	0	1	1
Black/African American	20	6	26
Native Hawaiian/Other Pacific Islander	1	0	1
White/Caucasian	157	92	249
Other	38	12	50
Missing	2	1	3
Multiple	3	0	3

End points

End points reporting groups

Reporting group title	Unesbulin and Dacarbazine
-----------------------	---------------------------

Reporting group description:

Participants received unesbulin 300 milligrams (mg) tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/square meter (m²) intravenously (IV) once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Reporting group title	Placebo and Dacarbazine
-----------------------	-------------------------

Reporting group description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m² IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Primary: Progression Free Survival (PFS) Per Independent Central Review Using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1

End point title	Progression Free Survival (PFS) Per Independent Central Review Using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1
-----------------	---

End point description:

PFS was defined as the time from randomization to the documented disease progression or death due to any cause, whichever occurred first. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). The appearance of one or more new lesions was also considered progression. The modified intent-to-treat (mITT) set included randomized participants with 1 to 3 prior lines of therapy.

End point type	Primary
----------------	---------

End point timeframe:

Up to approximately 2 years

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	105		
Units: months				
median (confidence interval 95%)	3.6 (2.8 to 5.5)	2.6 (1.5 to 3.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Unesbulin and Dacarbazine v Placebo and Dacarbazine

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0017
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.83

Secondary: Objective Response Rate (ORR) Per Independent Central Review Using RECIST V1.1

End point title	Objective Response Rate (ORR) Per Independent Central Review Using RECIST V1.1
-----------------	--

End point description:

ORR was defined as percentage of participants who achieved a confirmed best overall response (BOR) of complete response (CR) or partial response (PR). CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The mITT set included randomized participants with 1 to 3 prior lines of therapy.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to approximately 2 years

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	105		
Units: percentage of participants				
number (confidence interval 95%)	8.1 (4.7 to 12.8)	2.1 (0.3 to 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Per Independent Central Review Using RECIST V1.1

End point title	Disease Control Rate (DCR) Per Independent Central Review Using RECIST V1.1
-----------------	---

End point description:

DCR was defined as percentage of participants who achieved a confirmed BOR of CR, PR, or at least 3 months of stable disease (SD). CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30%

decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. The mITT set included randomized participants with 1 to 3 prior lines of therapy.

End point type	Secondary
End point timeframe:	
Up to approximately 2 years	

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	105		
Units: percentage of participants				
number (confidence interval 95%)	36.4 (29.7 to 43.5)	27.1 (18.5 to 37.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival was defined as the time in months from the randomization date to the date of death from any cause or date last known alive for those who did not die. The mITT set included randomized participants with 1 to 3 prior lines of therapy. '9999' represents 'due to limited number of participants with an event, median and upper limit of 95% confidence interval (CI) could not be calculated.'	
End point type	Secondary
End point timeframe:	
Up to approximately 2 years	

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	105		
Units: months				
median (confidence interval 95%)	9999 (10.4 to 9999)	9999 (11.0 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response Per Independent Central Review Using RECIST V1.

1

End point title	Duration of Response Per Independent Central Review Using RECIST V1.1
-----------------	---

End point description:

Duration of response was defined as the time from the date of first confirmed response of CR or PR to the date of the first documented disease progression or death due to any cause, whichever occurred first. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Disease progression: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. The mITT set included randomized participants with 1 to 3 prior lines of therapy. '0.999 and 9999' represents 'due to limited number of participants with an event, data could not be calculated.'

End point type	Secondary
----------------	-----------

End point timeframe:

Up to approximately 2 years

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	105		
Units: months				
median (confidence interval 95%)	6.87 (0.999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs)
-----------------	---

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. A TEAE was defined as an AE that had an onset date on or after the first dose of study drug until 30 days after last dose or occurred prior to first dose of study drug and worsened in severity after first dose of study drug. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. The safety analysis set included all participants who received at least 1 dose of study drug (unesbulin/placebo or dacarbazine).

End point type	Secondary
----------------	-----------

End point timeframe:

From first dose of study drug up to approximately 2 years

End point values	Unesbulin and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	120		
Units: participants	236	112		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to approximately 2 years

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of study drug (unesbulin/placebo or dacarbazine).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	25.0
--------------------	------

Reporting groups

Reporting group title	Placebo and Dacarbazine
-----------------------	-------------------------

Reporting group description:

Participants received placebo matching to unesbulin tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m² IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Reporting group title	Unesbulin and Dacarbazine
-----------------------	---------------------------

Reporting group description:

Participants received unesbulin 300 mg tablets administered orally twice weekly in each 3-week treatment cycle in combination with dacarbazine 1000 mg/m² IV once every 21 days. Treatment was continued for each participant until evidence of unacceptable toxicity, disease progression, or treatment discontinuation for another reason.

Serious adverse events	Placebo and Dacarbazine	Unesbulin and Dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 120 (35.83%)	81 / 238 (34.03%)	
number of deaths (all causes)	27	49	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 120 (0.00%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			

subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 120 (1.67%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	5 / 120 (4.17%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 3	
Fatigue			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 120 (4.17%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage	Additional description: This is a sex-specific AE. Only female participants were at risk.		
subjects affected / exposed ^[1]	0 / 93 (0.00%)	1 / 187 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	6 / 120 (5.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 120 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 120 (0.83%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (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			
Accidental overdose			
subjects affected / exposed	0 / 120 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial thrombosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			

subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 120 (2.50%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	2 / 3	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	2 / 120 (1.67%)	6 / 238 (2.52%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 120 (1.67%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	1 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 120 (0.00%)	8 / 238 (3.36%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 120 (0.83%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 120 (1.67%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	0 / 120 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemoperitoneum			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 120 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Subcapsular hepatic haematoma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

COVID-19			
subjects affected / exposed	1 / 120 (0.83%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 120 (0.83%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	3 / 120 (2.50%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	2 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 120 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	1 / 120 (0.83%)	2 / 238 (0.84%)
occurrences causally related to treatment / all	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Malnutrition		
subjects affected / exposed	1 / 120 (0.83%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This is a sex-specific AE. Only female participants were at risk.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo and Dacarbazine	Unesbulin and Dacarbazine
Total subjects affected by non-serious adverse events		
subjects affected / exposed	112 / 120 (93.33%)	234 / 238 (98.32%)
Investigations		
White blood cell count decreased		
subjects affected / exposed	9 / 120 (7.50%)	36 / 238 (15.13%)
occurrences (all)	20	83
Platelet count decreased		
subjects affected / exposed	17 / 120 (14.17%)	51 / 238 (21.43%)
occurrences (all)	42	114
Neutrophil count decreased		
subjects affected / exposed	13 / 120 (10.83%)	60 / 238 (25.21%)
occurrences (all)	28	140
Blood creatinine increased		
subjects affected / exposed	5 / 120 (4.17%)	13 / 238 (5.46%)
occurrences (all)	6	28
Aspartate aminotransferase increased		
subjects affected / exposed	8 / 120 (6.67%)	20 / 238 (8.40%)
occurrences (all)	10	27

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 120 (8.33%) 13	18 / 238 (7.56%) 27	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	10 / 120 (8.33%) 13	32 / 238 (13.45%) 35	
Dysgeusia subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	17 / 238 (7.14%) 19	
Headache subjects affected / exposed occurrences (all)	14 / 120 (11.67%) 16	29 / 238 (12.18%) 42	
Neuropathy peripheral subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4	15 / 238 (6.30%) 21	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	35 / 120 (29.17%) 91	103 / 238 (43.28%) 260	
Thrombocytopenia subjects affected / exposed occurrences (all)	27 / 120 (22.50%) 76	75 / 238 (31.51%) 238	
Neutropenia subjects affected / exposed occurrences (all)	23 / 120 (19.17%) 53	88 / 238 (36.97%) 298	
Leukopenia subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 17	15 / 238 (6.30%) 81	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	12 / 120 (10.00%) 24	27 / 238 (11.34%) 69	
Fatigue subjects affected / exposed occurrences (all)	44 / 120 (36.67%) 51	93 / 238 (39.08%) 135	

Pyrexia			
subjects affected / exposed	9 / 120 (7.50%)	15 / 238 (6.30%)	
occurrences (all)	10	17	
Oedema peripheral			
subjects affected / exposed	12 / 120 (10.00%)	20 / 238 (8.40%)	
occurrences (all)	13	22	
Non-cardiac chest pain			
subjects affected / exposed	5 / 120 (4.17%)	15 / 238 (6.30%)	
occurrences (all)	6	19	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	44 / 120 (36.67%)	115 / 238 (48.32%)	
occurrences (all)	62	153	
Diarrhoea			
subjects affected / exposed	27 / 120 (22.50%)	131 / 238 (55.04%)	
occurrences (all)	36	216	
Constipation			
subjects affected / exposed	19 / 120 (15.83%)	50 / 238 (21.01%)	
occurrences (all)	23	57	
Abdominal pain upper			
subjects affected / exposed	6 / 120 (5.00%)	13 / 238 (5.46%)	
occurrences (all)	6	13	
Vomiting			
subjects affected / exposed	17 / 120 (14.17%)	43 / 238 (18.07%)	
occurrences (all)	20	61	
Abdominal pain			
subjects affected / exposed	11 / 120 (9.17%)	42 / 238 (17.65%)	
occurrences (all)	13	50	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 120 (8.33%)	29 / 238 (12.18%)	
occurrences (all)	12	33	
Dyspnoea			
subjects affected / exposed	23 / 120 (19.17%)	26 / 238 (10.92%)	
occurrences (all)	25	32	
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4	14 / 238 (5.88%) 14	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	12 / 120 (10.00%) 15	20 / 238 (8.40%) 23	
Back pain subjects affected / exposed occurrences (all)	13 / 120 (10.83%) 15	22 / 238 (9.24%) 24	
Myalgia subjects affected / exposed occurrences (all)	5 / 120 (4.17%) 5	19 / 238 (7.98%) 26	
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 8	14 / 238 (5.88%) 22	
COVID-19 subjects affected / exposed occurrences (all)	9 / 120 (7.50%) 9	13 / 238 (5.46%) 15	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 10	11 / 238 (4.62%) 12	
Decreased appetite subjects affected / exposed occurrences (all)	14 / 120 (11.67%) 16	37 / 238 (15.55%) 46	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2022	The overall reason for this version of the protocol was to modify the timing and description of the interim analysis for futility and efficacy evaluation. - The lower limit of Grade 1 thrombocytopenia platelet count was changed from 750000 to 75000. - The timing and description of the interim analysis for futility and efficacy evaluation were modified.
28 April 2023	The overall reason for this version of the protocol was to incorporate comprehensively all modifications requested by country-specific health authorities and Ethics Committees in response to the Clinical Trial Application. Additional updates were made for improved clarity and study conduct. - It was specified that Overall Survival was the key secondary endpoint. Additional details describing the analysis of this key secondary endpoint were added to the Synopsis. - It was clarified that no dose reduction of unesbulin/placebo was permitted. - An exception to Inclusion Criterion was added for participants with Gilbert's syndrome who had elevated bilirubin values. - Inclusion Criterion was modified to increase the eligibility limit for aspartate aminotransferase and alanine aminotransferase from 1.5 to 3 times the upper limit of normal. - It was clarified in Inclusion Criterion that prior lines of treatment may include but were not limited to single-agent doxorubicin or other anthracycline, doxorubicin plus ifosfamide, trabectedin, pazopanib, or gemcitabine with or without docetaxel. - Administration of live vaccines was added as an Exclusion Criterion and as a concomitant medication. - It was clarified that survival follow-up would continue every 3 months as per the Schedule of Assessments. - Treatment-emergent adverse events were defined.
28 November 2023	The main reasons for this version were to clarify study procedures in cases of DTIC interruption and revise the analysis of the key secondary endpoint (Overall Survival). Additional updates were made to reflect changes in study staff, improved clarity, and to address clerical errors. - It was clarified that a hierarchical testing procedure would be utilized. - For participants who have DTIC interrupted or held, it was added that clinical laboratory assessments would be required weekly for the first 3 weeks after DTIC reintroduction. For subsequent cycles, the clinical laboratory assessments could be performed at a minimum of once per cycle or more frequently per the investigator's discretion to ensure that the participant met the protocol-defined safety criteria. - The following statement was added: "DTIC should be reintroduced at least 48 hours after unesbulin dosing".

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.

The study was terminated early due to business decision.

Notes: