Clinical trial results:
A Feasibility Trial of MLN4924 (Pevonedistat, TAK 924, IND#142772) Given in Combination With Azacitidine, Fludarabine, and Cytarabine, in Children, Adolescents, and Young Adults With Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

Summary

EudraCT number	2019-002935-27
Trial protocol	Outside EU/EEA
Global end of trial date	22 September 2020

Results information

Result version number	v1 (current)
This version publication date	02 April 2022
First version publication date	02 April 2022

Trial information

Trial identification

Sponsor protocol code	ADVL1712

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03813147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Children's Oncology Group
Sponsor organisation address	800 Royal Oaks Dr Suite 210, Monrovia, United States, 91016
Public contact	Children’s Oncology Group, Thaila Beeles, tbeeles@childrensoncologygroup.org
Scientific contact	Children’s Oncology Group, Thalia Beeles, tbeeles@childrensoncologygroup.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002117-PIP01-17
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	22 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate tolerability, feasibility of pevonedistat, to define and describe toxicities, and to characterize the pharmacokinetics (PK) of pevonedistat.

Protection of trial subjects:

All the participants or parents or patient’s guardian were required to read and sign the inform consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	12
EEA total number of subjects	0

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)	1
Children (2-11 years)	5
Adolescents (12-17 years)	5
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at approximately 19 investigative sites in the United States of America from 16 May 2019 up to 22 September 2020.

Pre-assignment

Screening details:

Pediatric participants diagnosed with relapsed or refractory acute myeloid leukemia or myelodysplastic syndrome were enrolled in the single group to receive pevonedisat 20 mg/m^2 in combination with other chemotherapeutic agents.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pevonedistat 20 mg/m^2

Arm description:

Pevonedistat (20 mg/m^2 for participants ≥1 year of age; 15 mg/m^2 for participants less than 1 year of age), intravenous (IV) over 60 minutes on Days 1, 3, and 5. Azacitidine 75 mg/m^2 IV over 15 minutes once daily (QD) on Days 1-5. Fludarabine phosphate 30 mg/m^2 IV over 30 minutes QD and cytarabine 2000 mg/m^2 IV over 1-3 hours QD on Days 6-10 in 35 day cycle for 1 Cycle.

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

Dosage and administration details:

Pevonedistat IV injection.

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

Dosage and administration details:

Cytarabine IV injection.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Azacitidine IV injection.

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:
Fludarabine IV injection.

Number of subjects in period 1	Pevonedistat 20 mg/m^2
Started	12
Completed	0
Not completed	12
Withdrawal of Consent	1
Lost to follow-up	11

Baseline characteristics

Reporting groups	
Reporting group title	Pevonedistat 20 mg/m^2

Reporting group description:

Pevonedistat (20 mg/m^2 for participants ≥1 year of age; 15 mg/m^2 for participants less than 1 year of age), intravenous (IV) over 60 minutes on Days 1, 3, and 5. Azacitidine 75 mg/m^2 IV over 15 minutes once daily (QD) on Days 1-5. Fludarabine phosphate 30 mg/m^2 IV over 30 minutes QD and cytarabine 2000 mg/m^2 IV over 1-3 hours QD on Days 6-10 in 35 day cycle for 1 Cycle.

Reporting group values	Pevonedistat 20 mg/m^2	Total	
Number of subjects	12	12	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 11.8 ± 6.54	 -	
Gender categorical Units: Subjects			
Male	5	5	
Female	7	7	
Race Units: Subjects			
White	9	9	
Unknown	3	3	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Non-Hispanic and Latino	8	8	

End points

End points reporting groups

Reporting group title	Pevonedistat 20 mg/m^2

Reporting group description:

Pevonedistat (20 mg/m^2 for participants ≥1 year of age; 15 mg/m^2 for participants less than 1 year of age), intravenous (IV) over 60 minutes on Days 1, 3, and 5. Azacitidine 75 mg/m^2 IV over 15 minutes once daily (QD) on Days 1-5. Fludarabine phosphate 30 mg/m^2 IV over 30 minutes QD and cytarabine 2000 mg/m^2 IV over 1-3 hours QD on Days 6-10 in 35 day cycle for 1 Cycle.

Primary: Maximum Tolerated Dose (MTD) of Pevonedistat in Combination With with Azacitidine, Fludarabine, and Cytarabine

End point title	Maximum Tolerated Dose (MTD) of Pevonedistat in Combination With with Azacitidine, Fludarabine, and Cytarabine[1]

End point description:

The MTD is the maximum dose at which fewer than one-third of participants experience dose limiting toxicities (DLTs). DLT Analysis Set included all participants who must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. 9999 = MTD could not be established.

End point type	Primary

End point timeframe:

Cycle 1 (Cycle length = 35 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mg/m^2				
number (not applicable)	9999			

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D) of Pevonedistat in Combination With with Azacitidine, Fludarabine, and Cytarabine

End point title	Recommended Phase 2 Dose (RP2D) of Pevonedistat in Combination With with Azacitidine, Fludarabine, and Cytarabine[2]

End point description:

The RP2D is the maximum dose at which fewer than one-third of participants experience DLTs. DLT Analysis Set included all participants who must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. 9999 = RP2D could not be established.

End point type	Primary

End point timeframe:

Cycle 1 (Cycle length = 35 days)

Notes:

[2] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mg/m^2				
number (not applicable)	9999			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Dose Limiting Toxicities (DLTs) of Pevonedistat

End point title	Percentage of Participants with Dose Limiting Toxicities (DLTs) of Pevonedistat [3]

End point description:

Dose-limiting hematological and non-hematological toxicities were defined differently. All Grade 3 or greater non-hematological toxicity not clearly related to the underlying disease and attributable to protocol therapy will be considered a DLT. Hematological DLT attributable to protocol therapy was defined as failure to recover to a peripheral absolute neutrophil count (ANC) > 500 per meter cube (/m^3) and platelets > 20,000 per millimeter square (/mm^2) by 50 days from the start of fludarabine and cytarabine administration, not due to presence of leukemia or severe infection. DLT Analysis Set included all participants who must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity.

End point type	Primary

End point timeframe:

Cycle 1 (Cycle length = 35 days)

Notes:

[3] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	25.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced At Least one Treatment Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants Who Experienced At Least one Treatment Emergent Adverse Events (TEAEs)[4]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered drug; it does not necessarily have to have a causal relationship with the treatment. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days of the last administration of study drug. Safety Analysis Set included all participants who received at least one dose of the study drug.

End point type	Primary

End point timeframe:

Up to 30 days post last dose (Up to 2.5 months)

Notes:

[4] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	100.00			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced At Least one Serious Adverse Events (SAE)

End point title	Percentage of Participants Who Experienced At Least one Serious Adverse Events (SAE)[5]

End point description:

An SAE was defined as any untoward medical occurrence that: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) leads to a congenital anomaly/birth defect in the offspring of the participant or 6) is an medically important event that satisfies any of the following: a) May require intervention to prevent items 1 through 5 above. b) May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization. Safety Analysis Set included all participants who received at least one dose of the study drug.

End point type	Primary

End point timeframe:

Up to 30 days post last dose (Up to 2.5 months)

Notes:

[5] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	50.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Clinically Significant Abnormal Laboratory Values

End point title	Percentage of Participants with Clinically Significant Abnormal Laboratory Values[6]

End point description:

The laboratory assessments included hematology, serum chemistry and urinalysis. Any laboratory value outside of reference range and deemed abnormal as assessed by the investigator are reported. Safety Analysis Set included all participants who received at least one dose of the study drug.

End point type	Primary

End point timeframe:

Up to 30 days post last dose (Up to 2.5 months)

Notes:

[6] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced At Least one Treatment Emergent Adverse Events in Relationship to Study Drug

End point title	Percentage of Participants Who Experienced At Least one Treatment Emergent Adverse Events in Relationship to Study Drug[7]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered drug; it does not necessarily have to have a causal relationship with the treatment. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days of the last administration of study drug. Safety Analysis Set included all participants who received at least one dose of the study drug.

End point type	Primary

End point timeframe:

Up to 30 days post last dose (Up to 2.5 months)

Notes:

[7] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 1

End point title	Cmax: Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 1[8]

End point description:

Pharmacokinetic (PK) Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[8] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	206.6 (± 42.16)			

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 1

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 1[9]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[9] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	1.1 (1 to 3)			

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 5

End point title	Cmax: Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 5[10]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[10] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
geometric mean (standard deviation)	229.8 (± 35.29)			

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 5

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 5[11]

End point description:

Pharmacokinetic (PK) Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[11] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	1.1 (1 to 3)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 1

End point title	AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 1 [12]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[12] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/mL				
geometric mean (standard deviation)	783.3 (± 26.43)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 5

End point title	AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 5[13]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[13] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/ml				
geometric mean (standard deviation)	869.8 (± 23.68)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-infinity): Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 1

End point title	AUC (0-infinity): Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 1[14]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable. Number analysed are the number of participants with data available for analysis at the given timepoint.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[14] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: h*ng/ml				
geometric mean (standard deviation)	790.4 (± 26.98)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-infinity): Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 5

End point title	AUC (0-infinity): Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 5[15]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[15] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/mL				
geometric mean (standard deviation)	899.3 (± 23.64)			

Statistical analyses

No statistical analyses for this end point

Primary: CL: Clearance of Pevonedistat Cycle 1 Day 1

End point title	CL: Clearance of Pevonedistat Cycle 1 Day 1[16]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable. Number analysed are the number of participants with data available for analysis at the

given timepoint.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[16] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Liter per hour				
geometric mean (standard deviation)	30.1 (± 71.23)			

Statistical analyses

No statistical analyses for this end point

Primary: CL: Clearance of Pevonedistat Cycle 1 Day 5

End point title	CL: Clearance of Pevonedistat Cycle 1 Day 5[17]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[17] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Liter per hour				
geometric mean (standard deviation)	26.9 (± 63.73)			

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 5

End point title	T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 5[18]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[18] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
arithmetic mean (standard deviation)	4.9 (± 1.20)			

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 1

End point title	T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 1[19]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable. Number analysed are the number of participants with data available for analysis at the given timepoint.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[19] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
arithmetic mean (standard deviation)	4.5 (± 1.33)			

Statistical analyses

No statistical analyses for this end point

Primary: Vz: Volume of Distribution in Plasma of Pevonedistat Cycle 1 Day 1	
End point title	Vz: Volume of Distribution in Plasma of Pevonedistat Cycle 1 Day 1[20]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable. Number analysed are the number of participants with data available for analysis at the given timepoint.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[20] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Litre				
geometric mean (standard deviation)	184.1 (± 105.54)			

Statistical analyses

No statistical analyses for this end point

Primary: Vz: Volume of Distribution in Plasma of Pevonedistat Cycle 1 Day 5	
End point title	Vz: Volume of Distribution in Plasma of Pevonedistat Cycle 1 Day 5[21]

End point description:

PK Analysis Set included all participants in the Safety Analysis Set and for whom at least 1 PK parameter is evaluable.

End point type	Primary

End point timeframe:

Pre-dose (before start of pevonedistat infusion) and at multiple timepoints (Up to 2 hours) post end of infusion on Days 1 and 5 Cycle 1 Day 5 (Cycle length = 35 days)

Notes:

[21] - 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: The statistical analysis was not planned to be reported for this endpoint.

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Litre				
geometric mean (standard deviation)	183.8 (± 78.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission (CR)

End point title	Percentage of Participants With Complete Remission (CR)

End point description:

CR was defined by National Cancer Institue (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as attainment of an M1 bone marrow (< 5% blasts and adequate marrow cellularity) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral blood counts (ANC >= 1000 per microliter [/uL] and platelet count > 100,000/uL). Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length= 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission with Partial Recovery of Platelet Count (CRp)

End point title	Percentage of Participants With Complete Remission with Partial Recovery of Platelet Count (CRp)

End point description:

CRp was defined by NCI CTCAE Version 5.0 as attainment of an M1 bone marrow (< 5% blasts) and no evidence of circulating blasts or extramedullary disease and with recovery of ANC > 1000/uL and platelet transfusion independence (defined as no platelet transfusions x 1 week). Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length= 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission with Incomplete Blood Count Recovery (CRi)

End point title	Percentage of Participants With Complete Remission with Incomplete Blood Count Recovery (CRi)

End point description:

CRi was defined by NCI CTCAE Version 5.0 as attainment of an M1 bone marrow (<5% blasts) and no evidence of circulating
blasts or extramedullary disease and with ANC < 1000/uL or platelet count < 100,000/uL without platelet transfusion independence (defined as no platelet transfusions x 1 week). Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length = 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	25.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Partial Response (PR)

End point title	Percentage of Participants With Partial Response (PR)

End point description:

PR was defined by NCI CTCAE Version 5.0 as attainment of M2 marrow status (> 5% or < 25% blasts cells and adequate

cellularity) and at least 50% decrease in bone marrow blast percent from baseline. Bone marrow must have adequate cellularity (e.g. > 10% if a biopsy is performed) to determine response. A repeat bone marrow aspiration within 14 days may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration, and is left to the discretion of the investigator. Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length= 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment Failure (TF)

End point title	Percentage of Participants With Treatment Failure (TF)

End point description:

TF was defined by NCI CTCAE Version 5.0 as 1. An increase in the extent of bone marrow infiltration by leukemic cells (absolute increase of >= 20% blasts). 2. Development of extramedullary disease (EMD). 3. M2 marrow that does not qualify for PR status. 4. An M1 marrow with circulating blasts. 5. > 25% blasts in the bone marrow after Cycle 1 of therapy. 6. Participants who have persistent central nervous system (CNS) disease despite 6 doses of intrathecal (IT) cytarabine or IT triples. Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length = 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	75.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Overall Complete Remission Rate

End point title	Percentage of Participants With Overall Complete Remission Rate

End point description:

Overall complete remission rate was defined as percentage of participants with CR, CRp and CRi.CR was defined as attainment of an M1 bone marrow (<5% blasts and adequate marrow cellularity) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral blood counts (ANC>=1000/uL and platelet count >100,000/uL).CRp was defined as attainment of an M1 bone marrow (<5% blasts) and no evidence of circulating blasts or extramedullary disease and with recovery of ANC >1000/uL and platelet transfusion independence.CRi was defined as attainment of an M1 bone marrow (<5% blasts) and no evidence of circulating blasts or extramedullary disease and with ANC < 1000/uL or platelet count < 100,000/uL without platelet transfusion independence.Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length = 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	25.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Response

End point title	Duration of Complete Response

End point description:

Duration of disease response in months is defined as the time measured in months, from the date of first documented disease response to the date of first documentation of relapse or progression. For participant without
relapse or disease progression, duration of disease was censored at the last disease assessment date. Response-Evaluable Analysis Set included all participants who receive at least one dose of Pevonedistat, have a baseline disease assessment, and have at least one post-baseline disease assessment. 9999 = Median and full range of duration of complete response was not estimable due to fewer number of participants with events.

End point type	Secondary

End point timeframe:

Up to Cycle 1 (Cycle length = 35 days)

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: months				
median (full range (min-max))	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Parameter mRNA Transcript Levels of Pevonedistat

End point title	Pharmacodynamic Parameter mRNA Transcript Levels of Pevonedistat
End point description:	
Not Applicable	
End point type	Secondary
End point timeframe:	
Not Applicable	

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: Not Applicable				
number (not applicable)				

Notes:

[22] - The data is not available because the panned analysis was not conducted for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Parameter NEDDylated Protein Analysis

End point title	Pharmacodynamic Parameter NEDDylated Protein Analysis
End point description:	
End point type	Secondary
End point timeframe:	
Not Applicable	

End point values	Pevonedistat 20 mg/m^2			
Subject group type	Reporting group			
Number of subjects analysed	0[23]			
Units: Not Applicable				
number (not applicable)				

Notes:

[23] - The data is not available because the panned analysis was not conducted for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days post last dose (Up to 2.5 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Pevonedistat 20 mg/m^2

Reporting group description:

Pevonedistat (20 mg/m^2 for participants ≥1 year of age; 15 mg/m^2 for participants less than 1 year of age), intravenous (IV) over 60 minutes on Days 1, 3, and 5. Azacitidine 75 mg/m^2 IV over 15 minutes once daily (QD) on Days 1-5. Fludarabine phosphate 30 mg/m^2 IV over 30 minutes QD and cytarabine 2000 mg/m^2 IV over 1-3 hours QD on Days 6-10 in 35 day cycle for 1 Cycle.

Serious adverse events	Pevonedistat 20 mg/m^2		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			

subjects affected / exposed	3 / 12 (25.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pevonedistat 20 mg/m^2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Fatigue			

subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Face oedema			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Localised oedema			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Catheter site haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Tachypnoea subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4		
Hypoxia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Atelectasis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Epistaxis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Wheezing subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Productive cough subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Irritability subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Insomnia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
White blood cell count decreased			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	11		
Lymphocyte count decreased			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	10		
Neutrophil count decreased			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	8		
Blood bicarbonate decreased			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	8		
Platelet count decreased			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	6		
Blood bilirubin increased			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			

subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Weight decreased				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Blood calcium decreased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Electrocardiogram T wave abnormal				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Ejection fraction decreased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Cardiac murmur				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Lipase increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Weight increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
International normalised ratio increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Haemoglobin increased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Infusion related reaction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular access complication			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	6		
Sinus bradycardia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Angina pectoris			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Left ventricular dysfunction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		

Paraesthesia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Dyskinesia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Somnolence subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	10 / 12 (83.33%) 10		
Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Haemolysis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lymph node pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eye disorders			

Eye disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vitreous floaters			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Mouth haemorrhage			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Abdominal distension			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gingival pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lip pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth discolouration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pain of skin			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Petechiae			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Purpura			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Glycosuria			

subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Micturition urgency				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Pollakiuria				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Urinary incontinence				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Musculoskeletal and connective tissue disorders				
Muscular weakness				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Bone pain				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Arthralgia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Back pain				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Joint range of motion decreased				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Limb mass				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Muscle spasms				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Myalgia				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Phlebitis infective			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	9		
Hyponatraemia			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	9		
Hyperphosphataemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	7		
Hypokalaemia			

subjects affected / exposed	7 / 12 (58.33%)			
occurrences (all)	7			
Hypophosphataemia				
subjects affected / exposed	5 / 12 (41.67%)			
occurrences (all)	5			
Decreased appetite				
subjects affected / exposed	5 / 12 (41.67%)			
occurrences (all)	5			
Hypocalcaemia				
subjects affected / exposed	5 / 12 (41.67%)			
occurrences (all)	5			
Hypermagnesaemia				
subjects affected / exposed	4 / 12 (33.33%)			
occurrences (all)	4			
Hypercalcaemia				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Hypomagnesaemia				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	3			
Hyperkalaemia				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	3			
Hypertriglyceridaemia				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Hyperuricaemia				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Acidosis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Hypernatraemia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Hypoglycaemia				

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported