



Clinical trial results:

A Phase 1/2, Open-Label, Multicenter Study of INCB000928 Administered as a Monotherapy in Participants With Anemia Due to Myelodysplastic Syndromes or Multiple Myeloma

Summary

EudraCT number	2020-002771-35
Trial protocol	FR IT
Global end of trial date	15 August 2024

Results information

Result version number	v1
This version publication date	31 August 2025
First version publication date	31 August 2025

Trial information

Trial identification

Sponsor protocol code	INCB 00928-105
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cutoff, Wilmington, United States, 19803
Public contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.com
Scientific contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.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	15 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This Phase 1/2, open-label, dose-finding study was intended to evaluate the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of zilurgisertib administered as monotherapy in participants with myelodysplastic syndromes (MDSs) or multiple myeloma (MM) who were transfusion-dependent or presented with symptomatic anemia.

Protection of trial subjects:

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2021
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	France: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	21
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	20
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at 8 study centers in the United States, France, and Italy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zilurgisertib 50 mg QD

Arm description:

Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 50 milligrams (mg) once daily (QD) administered as a monotherapy for up to 6 months.

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

Dosage and administration details:

tablets administered once daily orally

Arm title	Zilurgisertib 100 mg QD
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Arm description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 100 mg QD administered as a monotherapy for up to 6 months.

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

Dosage and administration details:

tablets administered once daily orally

Arm title	Zilurgisertib 200 mg QD
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Arm description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 200 mg QD administered as a monotherapy for up to 6 months.

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

Dosage and administration details:
tablets administered once daily orally

Arm title	Zilurgisertib 400 mg QD
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Arm description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 400 mg QD administered as a monotherapy for up to 6 months.

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

Dosage and administration details:
tablets administered once daily orally

Arm title	Zilurgisertib 600 mg QD
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Arm description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 600 mg QD administered as a monotherapy for up to 6 months.

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

Dosage and administration details:
tablets administered once daily orally

Number of subjects in period 1	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD
Started	4	5	4
Completed	0	0	0
Not completed	4	5	4
Consent withdrawn by subject	1	-	2
Physician decision	-	1	-
Death	1	1	-
Study Terminated by Sponsor	1	3	2
Lost to follow-up	1	-	-
Started New Therapy; Did Not Return to Clinic	-	-	-

Number of subjects in period 1	Zilurgisertib 400 mg QD	Zilurgisertib 600 mg QD
Started	5	3
Completed	0	0
Not completed	5	3

Consent withdrawn by subject	1	-
Physician decision	-	-
Death	1	-
Study Terminated by Sponsor	2	3
Lost to follow-up	-	-
Started New Therapy; Did Not Return to Clinic	1	-

Baseline characteristics

Reporting groups

Reporting group title	Zilurgisertib 50 mg QD
Reporting group description: Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 50 milligrams (mg) once daily (QD) administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 100 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 100 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 200 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 200 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 400 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 400 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 600 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 600 mg QD administered as a monotherapy for up to 6 months.	

Reporting group values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD
Number of subjects	4	5	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	4	5	3
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	68.8	74.6	78.5
standard deviation	± 4.50	± 3.78	± 6.19
Sex: Female, Male Units: participants			
Female	2	1	2
Male	2	4	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	1	5	3
More than one race	0	0	0
Unknown or Not Reported	3	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1	5	4
Unknown or Not Reported	3	0	0

Reporting group values	Zilurgisertib 400 mg QD	Zilurgisertib 600 mg QD	Total
Number of subjects	5	3	21
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	5	3	20
85 years and over	0	0	1
Age Continuous			
Units: years			
arithmetic mean	74.8	75.7	-
standard deviation	± 4.87	± 6.66	-
Sex: Female, Male			
Units: participants			
Female	4	1	10
Male	1	2	11
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	3	3	15
More than one race	0	0	0
Unknown or Not Reported	0	0	3
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	3	16
Unknown or Not Reported	2	0	5

Subject analysis sets

Subject analysis set title	All participants
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib QD administered as a monotherapy for up to 6 months.

Subject analysis set title	Zilurgisertib 25 mg QD
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 25 milligrams (mg) once daily (QD) administered as a monotherapy from Day 1 to Day 16.

Reporting group values	All participants	Zilurgisertib 25 mg QD	
Number of subjects	21	1	
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	20		
85 years and over	1		
Age Continuous Units: years arithmetic mean standard deviation	±	±	
Sex: Female, Male Units: participants			
Female	10		
Male	11		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	15		
More than one race	0		
Unknown or Not Reported	3		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	16		
Unknown or Not Reported	5		

End points

End points reporting groups

Reporting group title	Zilurgisertib 50 mg QD
Reporting group description: Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 50 milligrams (mg) once daily (QD) administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 100 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 100 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 200 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 200 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 400 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 400 mg QD administered as a monotherapy for up to 6 months.	
Reporting group title	Zilurgisertib 600 mg QD
Reporting group description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 600 mg QD administered as a monotherapy for up to 6 months.	
Subject analysis set title	All participants
Subject analysis set type	Full analysis
Subject analysis set description: Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib QD administered as a monotherapy for up to 6 months.	
Subject analysis set title	Zilurgisertib 25 mg QD
Subject analysis set type	Full analysis
Subject analysis set description: Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 25 milligrams (mg) once daily (QD) administered as a monotherapy from Day 1 to Day 16.	

Primary: Number of participants with any treatment-emergent adverse event (TEAE)

End point title	Number of participants with any treatment-emergent adverse event (TEAE) ^[1]
End point description: An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug. A TEAE is an AE reported for the first time or the worsening of a pre-existing event after the first dose of study drug. The Full Analysis Set-MDS was comprised of all participants with myelodysplastic syndromes (MDS) or MDS/myeloproliferative neoplasm (MPN) overlap syndromes who received at least 1 dose of zilurgisertib.	
End point type	Primary
End point timeframe: up to 950 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: Statistical analysis was not conducted for this endpoint.

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[2]	5 ^[3]	4 ^[4]	5 ^[5]
Units: participants	4	5	4	5

Notes:

[2] - Full Analysis Set-MDS

[3] - Full Analysis Set-MDS

[4] - Full Analysis Set-MDS

[5] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[6]			
Units: participants	2			

Notes:

[6] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with any ≥Grade 3 TEAE

End point title	Number of participants with any ≥Grade 3 TEAE ^[7]
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End point description:

The severity of AEs was assessed using Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) Grades 1 through 5. The investigator made an assessment of intensity for each AE and SAE reported during the study and assigned it to one of the following categories. Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated. Grade 2: moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living. Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4: life-threatening consequences; urgent treatment indicated. Grade 5: fatal.

End point type	Primary
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End point timeframe:

up to 950 days

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: Statistical analysis was not conducted for this endpoint.

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[8]	5 ^[9]	4 ^[10]	5 ^[11]
Units: participants	2	3	2	2

Notes:

[8] - Full Analysis Set-MDS

[9] - Full Analysis Set-MDS

[10] - Full Analysis Set-MDS

[11] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
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Subject group type	Reporting group			
Number of subjects analysed	3 ^[12]			
Units: participants	2			

Notes:

[12] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with dose-limiting toxicities (DLTs)

End point title	Number of participants with dose-limiting toxicities (DLTs) ^[13]
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End point description:

A DLT was defined as the occurrence of any protocol-defined toxicities occurring during the first study drug treatment cycle, from C1D1 up to and including Cycle 1 Day 28 (per regimen cycle schedule), except those with a clear alternative explanation (e.g., disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. The DLT Evaluable Population was comprised of all participants in the FAS Population who met the following criteria: observed for at least the first treatment cycle (i.e., 28 days); received $\geq 75\%$ of doses of study treatment at the level assigned to that cohort (i.e., 21 days of treatment) or had a DLT during the first study treatment cycle; did not receive any strong or potent CYP3A4/5 inhibitor or inducer during the first study drug treatment cycle (DLT assessment period); was not part of a backfill cohort.

End point type	Primary
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End point timeframe:

up to Day 28

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: Statistical analysis was not conducted for this endpoint.

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[14]	3 ^[15]	4 ^[16]	3 ^[17]
Units: participants	0	0	0	0

Notes:

[14] - DLT Evaluable Population

[15] - DLT Evaluable Population

[16] - DLT Evaluable Population

[17] - DLT Evaluable Population

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[18]			
Units: participants	1			

Notes:

[18] - DLT Evaluable Population

Statistical analyses

No statistical analyses for this end point

Primary: Maximum tolerated dose (MTD)

End point title	Maximum tolerated dose (MTD) ^[19]
End point description: The MTD was defined as the dose at which the observed DLT rate was closest to the target DLT rate of 28% using an isotonic method that took the assumption of a monotonic dose-toxicity relationship into account. 9999=The MTD was not defined due to early termination of the study.	
End point type	Primary
End point timeframe: up to Day 28	

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: Statistical analysis was not conducted for this endpoint.

End point values	All participants			
Subject group type	Subject analysis set			
Number of subjects analysed	21 ^[20]			
Units: milligrams	9999			

Notes:

[20] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Primary: Recommended dose for expansion (RDE)

End point title	Recommended dose for expansion (RDE) ^[21]
End point description: RDE doses were defined as pharmacodynamically active. RDE doses were not to have exceeded the MTD defined in each treatment group. 9999=The RDE was not defined due to early termination of the study.	
End point type	Primary
End point timeframe: up to Day 28	

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: Statistical analysis was not conducted for this endpoint.

End point values	All participants			
Subject group type	Subject analysis set			
Number of subjects analysed	21 ^[22]			
Units: milligrams	9999			

Notes:

[22] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with anemia response

End point title	Percentage of participants with anemia response
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End point description:

Participants with anemia response were those with a hemoglobin (Hgb) increase of ≥ 1.5 grams per deciliter (g/dL) relative to baseline for any 8-week period (with each assessment meeting this requirement) during the first 24 weeks of treatment if transfusion independent at baseline. Transfusion-independent participants at baseline were those that did not receive ≥ 4 units of red blood cell (RBC) transfusions during the 28 days immediately preceding Cycle 1 Day 1 or did not receive ≥ 4 units of RBC transfusions in the 8 weeks immediately preceding Cycle 1 Day 1, for an Hgb level of < 8.5 g/dL, in the absence of bleeding or treatment-induced anemia. Participants must have been on treatment for ≥ 8 consecutive weeks or discontinued treatment before Week 8. Only participants who were transfusion independent at baseline were analyzed. The 95% confidence interval was calculated using exact binomial distribution.

End point type	Secondary
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End point timeframe:

up to Week 24

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2 ^[23]	4 ^[24]	2 ^[25]	4 ^[26]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	0.0 (0.0 to 60.2)	0.0 (0.0 to 84.2)	0.0 (0.0 to 60.2)

Notes:

[23] - Full Analysis Set-MDS

[24] - Full Analysis Set-MDS

[25] - Full Analysis Set-MDS

[26] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[27]			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)			

Notes:

[27] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of anemia response (DoAR)

End point title	Duration of anemia response (DoAR)
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End point description:

DoAR was the interval from the first onset of anemia response (AR) to the earliest date of loss of AR that persisted for ≥ 4 weeks or death from any cause. Participants with AR had a hemoglobin (Hgb) increase of ≥ 1.5 grams per deciliter (g/dL) relative to baseline for any 8-week period (with each assessment meeting this requirement) during the first 24 weeks of treatment if transfusion independent at baseline. Transfusion-independent participants at baseline were those that did not receive ≥ 4 units of red blood cell (RBC) transfusions during the 28 days immediately preceding Cycle 1 Day 1 or did not receive ≥ 4 units of RBC transfusions in the 8 weeks immediately preceding Cycle 1 Day 1, for an Hgb level of < 8.5 g/dL, in the absence of bleeding or treatment-induced anemia. Participants must have been on treatment for ≥ 8 consecutive weeks and have discontinued treatment before Week 8. Only participants who were transfusion independent at baseline and had a response were analyzed.

End point type	Secondary
End point timeframe:	
up to 920 days	

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[28]	0 ^[29]	0 ^[30]	0 ^[31]
Units: days				
median (standard error)	()	()	()	()

Notes:

[28] - Full Analysis Set-MDS

[29] - Full Analysis Set-MDS

[30] - Full Analysis Set-MDS

[31] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[32]			
Units: days				
median (standard error)	()			

Notes:

[32] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with RBC-transfusion independence (TI)

End point title	Percentage of participants with RBC-transfusion independence (TI)
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End point description:

Participants with RBC-transfusion independence were defined as those who did not require any RBC transfusion for at least 8 consecutive weeks during the first 24 weeks of treatment. Only participants who were transfusion dependent at Baseline were analyzed. The 95% confidence interval was calculated using exact binomial distribution.

End point type	Secondary
End point timeframe:	
up to Week 24	

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2 ^[33]	1 ^[34]	2 ^[35]	1 ^[36]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	100.0 (2.5 to 100.0)	0.0 (0.0 to 84.2)	0.0 (0.0 to 97.5)

Notes:

[33] - Full Analysis Set-MDS

[34] - Full Analysis Set-MDS

[35] - Full Analysis Set-MDS

[36] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[37]			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.5)			

Notes:

[37] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of RBC-transfusion independence (TI) period for participants achieving RBC-TI for at least 8 consecutive weeks during the first 24 weeks of treatment

End point title	Duration of RBC-transfusion independence (TI) period for participants achieving RBC-TI for at least 8 consecutive weeks during the first 24 weeks of treatment
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End point description:

Participants with RBC-TI were defined as those who did not require any RBC transfusion for at least 8 consecutive weeks during the first 24 weeks of treatment. Only participants who were transfusion dependent at Baseline and achieved transfusion independence were analyzed. 9999=Standard error cannot be calculated for a single participant.

End point type	Secondary
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End point timeframe:

up to 920 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[38]	1 ^[39]	0 ^[40]	0 ^[41]
Units: days				
median (standard error)	()	60 (± 9999)	()	()

Notes:

[38] - Full Analysis Set-MDS

[39] - Full Analysis Set-MDS

[40] - Full Analysis Set-MDS

[41] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[42]			
Units: days				

median (standard error)	()			
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Notes:

[42] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of red blood cell (RBC) transfusion through Weeks 12 and 24

End point title	Rate of red blood cell (RBC) transfusion through Weeks 12 and 24
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End point description:

The rate of RBC transfusion was defined as the average number of RBC units per participant-month during the treatment period. Only participants who were on treatment for at least 78 days were included in the analysis.

End point type	Secondary
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End point timeframe:

Weeks 12 and 24

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[43]	5 ^[44]	4 ^[45]	5 ^[46]
Units: RBC units per participant-month				
arithmetic mean (standard deviation)	2.53 (± 1.955)	1.34 (± 0.948)	3.01 (± 2.955)	2.71 (± 2.232)

Notes:

[43] - Full Analysis Set-MDS

[44] - Full Analysis Set-MDS

[45] - Full Analysis Set-MDS

[46] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[47]			
Units: RBC units per participant-month				
arithmetic mean (standard deviation)	1.19 (± 2.067)			

Notes:

[47] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: The largest increase from baseline in the mean Hgb values over any rolling 8-week treatment period during the first 24 weeks of treatment

End point title	The largest increase from baseline in the mean Hgb values over any rolling 8-week treatment period during the first 24 weeks
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End point description:

Baseline Hgb was measured up to 8 weeks prior to the first dose administration of zilurgisertib. The baseline Hgb was defined as the average of all eligible Hgb assessments. The Hgb assessment(s) within the window from the date received RBC transfusion+1 day to the date received RBC transfusion+14 days that didn't trigger another transfusion were excluded. Participants were included in the mean change from baseline in hemoglobin value analysis if the participant was in the FAS and met both of the following criteria: a. was on treatment for more than 8 weeks; b. had ≥ 1 valid post-baseline Hgb assessment(s).

End point type	Secondary
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End point timeframe:

up to Week 24

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3 ^[48]	4 ^[49]	3 ^[50]	5 ^[51]
Units: grams per liter				
arithmetic mean (standard deviation)	2.19 (\pm 2.782)	9.73 (\pm 2.842)	2.51 (\pm 3.681)	4.92 (\pm 10.240)

Notes:

[48] - Full Analysis Set-MDS

[49] - Full Analysis Set-MDS

[50] - Full Analysis Set-MDS

[51] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[52]			
Units: grams per liter				
arithmetic mean (standard deviation)	6.59 (\pm 4.229)			

Notes:

[52] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) in MDS participants

End point title	Overall response rate (ORR) in MDS participants
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End point description:

ORR was defined as the percentage of participants with complete response (CR) or partial response (PR). For MDS, CR: bone marrow with $\leq 5\%$ myeloblasts with normal maturation of all cell lines; HgB ≥ 11 g/dL, neutrophils $\geq 1.0 \times 10^9$ /L (L), platelets $\geq 100 \times 10^9$ /L, and no blasts in the peripheral blood. For MDS, PR: all CR criteria, but bone marrow blasts decreased by $\geq 50\%$ over pretreatment but still $> 5\%$; cellularity and morphology not relevant. For MDS/MPN overlap syndromes, CR: bone marrow with $\leq 5\%$ myeloblasts; no osteomyelofibrosis or \leq Grade 1 fibrosis; white blood cells $\leq 10 \times 10^9$ cells/L, HgB ≥ 11 g/dL, platelets $\geq 100 \times 10^9$ /L $\leq 450 \times 10^9$ /L, neutrophils $\geq 1.0 \times 10^9$ /L, no blasts, neutrophil precursors reduced to $\leq 2\%$, monocytes $\leq 1 \times 10^9$ /L in peripheral blood; complete resolution of medullary disease. For MDS/MPN overlap syndromes, PR: normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts reduced by 50%, but remaining $> 5\%$ of cellularity.

End point type	Secondary
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End point timeframe:
up to 920 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[53]	4 ^[54]	3 ^[55]	5 ^[56]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 60.2)	0.0 (0.0 to 60.2)	0.0 (0.0 to 70.8)	0.0 (0.0 to 52.2)

Notes:

[53] - Full Analysis Set-MDS only. MDS/MPN overlap syndromes were excluded.

[54] - Full Analysis Set-MDS only. MDS/MPN overlap syndromes were excluded.

[55] - Full Analysis Set-MDS only. MDS/MPN overlap syndromes were excluded.

[56] - Full Analysis Set-MDS only. MDS/MPN overlap syndromes were excluded.

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[57]			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 70.8)			

Notes:

[57] - Full Analysis Set-MDS only. MDS/MPN overlap syndromes were excluded.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of MDS participants with an event of progression or death

End point title	Percentage of MDS participants with an event of progression or death
-----------------	--

End point description:

Participants with MDS/MPN overlap syndromes were excluded from analysis. Data have been reported as the percentage of participants with an event of progression or death rather than median PFS (the interval from the first dose of study drug until the first documented progression or death) because 2 participants had an event of PFS or death. It was pre-specified in the SAP that the number of MDS participants with documented progression or death was to be summarized.

End point type	Secondary
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End point timeframe:

up to 920 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[58]	4 ^[59]	3 ^[60]	5 ^[61]
Units: percentage of participants				
number (not applicable)	25.0	0.0	0.0	20.0

Notes:

[58] - Full Analysis Set-MDS only

[59] - Full Analysis Set-MDS only

[60] - Full Analysis Set-MDS only

[61] - Full Analysis Set-MDS only

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[62]			
Units: percentage of participants				
number (not applicable)	0.0			

Notes:

[62] - Full Analysis Set-MDS only

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with an event of leukemia or death

End point title	Percentage of participants with an event of leukemia or death
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End point description:

Data have been reported as the percentage of participants with an event of leukemia or death rather than LFS (the interval from the first dose of study drug until the first documented leukemia transformation or death from any cause) because 3 participants had an event of leukemia or death. It was pre-specified in the SAP that the number of participants with leukemia transformation or death was to be summarized.

End point type	Secondary
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End point timeframe:

up to 920 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[63]	5 ^[64]	4 ^[65]	5 ^[66]
Units: percentage of participants				
number (not applicable)	25.0	20.0	0.0	20.0

Notes:

[63] - Full Analysis Set-MDS

[64] - Full Analysis Set-MDS

[65] - Full Analysis Set-MDS

[66] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
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Subject group type	Reporting group			
Number of subjects analysed	3 ^[67]			
Units: percentage of participants				
number (not applicable)	0.0			

Notes:

[67] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in multiple myeloma (MM) participants

End point title	ORR in multiple myeloma (MM) participants
End point description:	ORR was defined as the percentage of participants with stringent CR, CR, very good PR, and PR.
End point type	Secondary
End point timeframe:	up to 920 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[68]	0 ^[69]	0 ^[70]	0 ^[71]
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[68] - Full Analysis Set. No participants with MM were enrolled.

[69] - Full Analysis Set. No participants with MM were enrolled.

[70] - Full Analysis Set. No participants with MM were enrolled.

[71] - Full Analysis Set. No participants with MM were enrolled.

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[72]			
Units: percentage of participants				
number (confidence interval 95%)	(to)			

Notes:

[72] - Full Analysis Set. No participants with MM were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in MM participants

End point title	PFS in MM participants
End point description:	PFS was defined as the interval from the first dose of study drug until the first documented progression or death.

End point type	Secondary
End point timeframe: up to 920 days	

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[73]	0 ^[74]	0 ^[75]	0 ^[76]
Units: months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[73] - Full Analysis Set. No participants with MM were enrolled.

[74] - Full Analysis Set. No participants with MM were enrolled.

[75] - Full Analysis Set. No participants with MM were enrolled.

[76] - Full Analysis Set. No participants with MM were enrolled.

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[77]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[77] - Full Analysis Set. No participants with MM were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of zilurgisertib

End point title	Cmax of zilurgisertib
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End point description:

Cmax was defined as the maximum concentration of zilurgisertib. Analysis was conducted in the Pharmacokinetic (PK) Evaluable Population, comprised of all participants who received at least 1 dose of zilurgisertib and provided at least 1 postdose plasma sample (1 PK measurement). Only participants with available data were analyzed. One participant who was supposed to receive 100 mg actually received 25 mg. 7777=One participant did not have any PK data; 2 participants had values above the upper limit of quantification, meaning data for PK parameters could not be determined. 8888=Standard deviation was not calculated for a single participant. 9999=No participants were analyzed in this group at this time point.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycle 1: pre-dose; 2, 4, and 6 hours post-dose

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[78]	4 ^[79]	4 ^[80]	4 ^[81]
Units: nanomolar				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	181 (± 80.4)	249 (± 100)	569 (± 291)	1950 (± 642)
Cycle 1 Day 15, n=4, 4, 4, 2, 3, 0	350 (± 131)	636 (± 330)	1360 (± 613)	2620 (± 4620)

Notes:

[78] - PK Evaluable Population

[79] - PK Evaluable Population

[80] - PK Evaluable Population

[81] - PK Evaluable Population

End point values	Zilurgisertib 600 mg QD	Zilurgisertib 25 mg QD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[82]	1 ^[83]		
Units: nanomolar				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	7777 (± 7777)	79.9 (± 8888)		
Cycle 1 Day 15, n=4, 4, 4, 2, 3, 0	7777 (± 7777)	9999 (± 9999)		

Notes:

[82] - PK Evaluable Population

[83] - PK Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: tmax of zilurgisertib

End point title	tmax of zilurgisertib
End point description:	
tmax was defined as the time to the maximum observed concentration of zilurgisertib. Only participants with available data were analyzed. 7777=One participant did not have any PK data; 2 participants had values above the upper limit of quantification, meaning data for PK parameters could not be determined. -8888, 8888=Standard deviation was not calculated for a single participant. 9999=No participants were analyzed in this group at this time point.	
End point type	Secondary
End point timeframe:	
Days 1 and 15 of Cycle 1: pre-dose; 2, 4, and 6-8 hours post-dose	

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[84]	4 ^[85]	4 ^[86]	4 ^[87]
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	2.0 (2.0 to 4.0)	2.0 (2.0 to 2.0)	3.0 (2.0 to 4.0)	2.0 (2.0 to 2.0)
Cycle 1 Day 15, n=4, 4, 4, 2, 3, 0	2.0 (2.0 to 6.0)	2.0 (2.0 to 2.0)	3.0 (2.0 to 6.0)	2.0 (2.0 to 4.0)

Notes:

[84] - PK Evaluable Population

[85] - PK Evaluable Population

[86] - PK Evaluable Population

[87] - PK Evaluable Population

End point values	Zilurgisertib 600 mg QD	Zilurgisertib 25 mg QD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[88]	1 ^[89]		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	7777 (7777 to 7777)	2.0 (-8888 to 8888)		
Cycle 1 Day 15, n=4, 4, 4, 2, 3, 0	7777 (7777 to 7777)	9999 (9999 to 9999)		

Notes:

[88] - PK Evaluable Population

[89] - PK Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of zilurgisertib

End point title	AUClast of zilurgisertib
End point description:	
AUClast was defined as the area under the plasma concentration-time curve from time 0 to the last quantifiable measurable plasma concentration of zilurgisertib. Only participants with available data were analyzed. One participant who was supposed to receive 100 mg actually received 25 mg. 7777=One participant did not have any PK data; 2 participants had values above the upper limit of quantification, meaning data for PK parameters could not be determined. 8888=Standard deviation was not calculated for a single participant. 9999=No participants were analyzed in this group at this time point.	
End point type	Secondary
End point timeframe:	
Days 1 and 15 of Cycle 1: pre-dose; 2, 4, and 6-8 hours post-dose	

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[90]	4 ^[91]	4 ^[92]	4 ^[93]
Units: nanomolar x hour				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	749 (± 312)	1070 (± 471)	2540 (± 1150)	8050 (± 2680)
Cycle 1 Day 14, n=4, 4, 4, 2, 3, 0	1890 (± 749)	3090 (± 1620)	6850 (± 3050)	12300 (± 26100)

Notes:

[90] - PK Evaluable Population

[91] - PK Evaluable Population

[92] - PK Evaluable Population

[93] - PK Evaluable Population

End point values	Zilurgisertib 600 mg QD	Zilurgisertib 25 mg QD		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[94]	1 ^[95]		
Units: nanomolar x hour				
arithmetic mean (standard deviation)				
Cycle 1 Day 1, n=4, 4, 4, 4, 3, 1	7777 (± 7777)	343 (± 8888)		
Cycle 1 Day 14, n=4, 4, 4, 2, 3, 0	7777 (± 7777)	9999 (± 9999)		

Notes:

[94] - PK Evaluable Population

[95] - PK Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in hepcidin from Cycle 1 Day 15 to Cycle 7 Day 1

End point title	Percentage change in hepcidin from Cycle 1 Day 15 to Cycle 7 Day 1
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End point description:

Percentage change was calculated as the ([post-baseline value minus the baseline value] / [baseline value]) * 100. Analysis was conducted in the Pharmacodynamic (PD) Evaluable Population, comprised all participants who received at least 1 dose of zilurgisertib and provided at least 1 plasma/serum sample (1 PD measurement).

End point type	Secondary
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End point timeframe:

from Cycle 1 Day 15 to Cycle 7 Day 1

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[96]	4 ^[97]	4 ^[98]	5 ^[99]
Units: percentage				
arithmetic mean (standard deviation)	-24.53 (± 41.69)	-16.25 (± 47.06)	-11.25 (± 39.97)	-59.02 (± 32.35)

Notes:

[96] - PD Evaluable Population

[97] - PD Evaluable Population

[98] - PD Evaluable Population

[99] - PD Evaluable Population

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[100]			
Units: percentage				
arithmetic mean (standard deviation)	-63.79 (± 44.23)			

Notes:

[100] - PD Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ferritin

End point title	Change from Baseline in ferritin
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End point description:

Change from Baseline (CFB) was calculated as the post-Baseline value minus the Baseline value. Only participants with available data were analyzed. 9999=Standard deviation was not calculated for a single participant. 8888=Data were not collected in this treatment group at this time point.

End point type	Secondary
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End point timeframe:

Baseline; Cycle 1 Day 8; Cycle 1 Day 15; Cycles 2, 3, 4, 5, 6, and 7 Day 1

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[101]	5 ^[102]	4 ^[103]	5 ^[104]
Units: nanograms per milliliter				
arithmetic mean (standard deviation)				
Baseline, n=4, 5, 4, 5, 3	1022.35 (± 634.096)	930.18 (± 697.078)	2092.25 (± 1220.166)	2034.42 (± 1329.794)
CFB at Cycle 1 Day 8, n=3, 5, 4, 3, 2	47.67 (± 43.501)	-65.24 (± 57.388)	203.25 (± 523.789)	-98.83 (± 567.584)
CFB at Cycle 1 Day 15, n=2, 3, 4, 3, 2	292.00 (± 161.220)	17.30 (± 31.109)	67.50 (± 140.950)	-109.77 (± 98.223)
CFB at Cycle 2 Day 1, n=4, 3, 4, 3, 2	101.65 (± 245.814)	70.03 (± 76.619)	154.50 (± 53.658)	-92.87 (± 364.312)
CFB at Cycle 3 Day 1, n=4, 3, 4, 3, 3	307.58 (± 709.602)	-6.70 (± 46.054)	532.00 (± 833.804)	353.77 (± 314.682)
CFB at Cycle 4 Day 1, n=3, 2, 4, 5, 2	409.83 (± 689.052)	-21.15 (± 48.295)	875.00 (± 649.850)	619.00 (± 275.281)
CFB at Cycle 5 Day 1, n=3, 1, 4, 4, 2	349.00 (± 680.559)	172.00 (± 9999)	574.00 (± 394.335)	516.10 (± 502.323)
CFB at Cycle 6 Day 1, n=3, 2, 3, 2, 0	297.67 (± 614.180)	488.50 (± 152.028)	347.33 (± 362.417)	442.15 (± 264.246)
CFB at Cycle 7 Day 1, n=2, 1, 3, 2, 0	365.50 (± 658.316)	971.00 (± 9999)	315.33 (± 222.172)	507.35 (± 64.559)

Notes:

[101] - Full Analysis Set-MDS

[102] - Full Analysis Set-MDS

[103] - Full Analysis Set-MDS

[104] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[105]			
Units: nanograms per milliliter				
arithmetic mean (standard deviation)				
Baseline, n=4, 5, 4, 5, 3	1469.00 (± 1191.873)			
CFB at Cycle 1 Day 8, n=3, 5, 4, 3, 2	-110.00 (± 24.042)			

CFB at Cycle 1 Day 15, n=2, 3, 4, 3, 2	-96.00 (± 56.569)			
CFB at Cycle 2 Day 1, n=4, 3, 4, 3, 2	135.00 (± 200.818)			
CFB at Cycle 3 Day 1, n=4, 3, 4, 3, 3	-383.00 (± 536.324)			
CFB at Cycle 4 Day 1, n=3, 2, 4, 5, 2	-153.50 (± 82.731)			
CFB at Cycle 5 Day 1, n=3, 1, 4, 4, 2	-106.50 (± 211.425)			
CFB at Cycle 6 Day 1, n=3, 2, 3, 2, 0	8888 (± 8888)			
CFB at Cycle 7 Day 1, n=2, 1, 3, 2, 0	8888 (± 8888)			

Notes:

[105] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin at the end of treatment

End point title	Change from Baseline in hemoglobin at the end of treatment
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End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only participants with available data were analyzed.

End point type	Secondary
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End point timeframe:

up to 950 days

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[106]	5 ^[107]	4 ^[108]	5 ^[109]
Units: grams per liter				
arithmetic mean (standard deviation)				
Baseline, n=4, 5, 4, 5, 3	77.7750 (± 5.83688)	75.7200 (± 4.00899)	74.9354 (± 5.98330)	74.6767 (± 7.94708)
CFB at end of treatment, n=2, 3, 2, 3, 3	-1.7500 (± 4.59619)	10.1333 (± 12.87685)	4.0182 (± 7.61104)	16.9556 (± 12.34055)

Notes:

[106] - Full Analysis Set-MDS

[107] - Full Analysis Set-MDS

[108] - Full Analysis Set-MDS

[109] - Full Analysis Set-MDS

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[110]			
Units: grams per liter				
arithmetic mean (standard deviation)				
Baseline, n=4, 5, 4, 5, 3	79.4139 (± 4.14997)			

CFB at end of treatment, n=2, 3, 2, 3, 3	69.6667 (\pm 10.40833)			
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Notes:

[110] - Full Analysis Set-MDS

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of zilurgisertib

End point title	Ctrough of zilurgisertib
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End point description:

Ctrough was defined as the lowest concentration of zilurgisertib. Only participants with available data were analyzed. 7777=One participant did not have any PK data; 2 participants had values above the upper limit of quantification, meaning data for PK parameters could not be determined.

End point type	Secondary
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End point timeframe:

Day 15 of Cycle 1: pre-dose; 2, 4, and 6-8 hours post-dose

End point values	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Zilurgisertib 200 mg QD	Zilurgisertib 400 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[111]	4 ^[112]	4 ^[113]	2 ^[114]
Units: nanomolar				
arithmetic mean (standard deviation)	214 (\pm 91.8)	304 (\pm 175)	619 (\pm 241)	981 (\pm 3130)

Notes:

[111] - PK Evaluable Population

[112] - PK Evaluable Population

[113] - PK Evaluable Population

[114] - PK Evaluable Population

End point values	Zilurgisertib 600 mg QD			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[115]			
Units: nanomolar				
arithmetic mean (standard deviation)	7777 (\pm 7777)			

Notes:

[115] - PK Evaluable Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 950 days

Adverse event reporting additional description:

Analysis was conducted in the Full Analysis Set-MDS, comprised of all participants with myelodysplastic syndromes (MDS) or MDS/myeloproliferative neoplasm (MPN) overlap syndromes who received at least 1 dose of zilurgisertib.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Zilurgisertib 50 mg QD
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Reporting group description:

Participants with myelodysplastic syndromes (MDS) or multiple myeloma (MM) who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 50 milligrams (mg) once daily (QD) administered as a monotherapy for up to 6 months.

Reporting group title	Zilurgisertib 100 mg QD
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Reporting group description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 100 mg QD administered as a monotherapy for up to 6 months.

Reporting group title	Total
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Reporting group description:

Total

Reporting group title	Zilurgisertib 400 mg QD
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Reporting group description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 400 mg QD administered as a monotherapy for up to 6 months.

Reporting group title	Zilurgisertib 600 mg QD
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Reporting group description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 600 mg QD administered as a monotherapy for up to 6 months.

Reporting group title	Zilurgisertib 200 mg QD
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Reporting group description:

Participants with MDS or MM who were transfusion dependent or presented with symptomatic anemia received oral zilurgisertib 200 mg QD administered as a monotherapy for up to 6 months.

Serious adverse events	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	1 / 5 (20.00%)	7 / 21 (33.33%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events	1	0	1
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Zilurgisertib 400 mg QD	Zilurgisertib 600 mg QD	Zilurgisertib 200 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Zilurgisertib 50 mg QD	Zilurgisertib 100 mg QD	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	20 / 21 (95.24%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Vascular neoplasm			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	4 / 21 (19.05%)
occurrences (all)	1	1	4
Hyperthermia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Influenza like illness			

subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Malaise			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	3
Oedema peripheral			
subjects affected / exposed	2 / 4 (50.00%)	1 / 5 (20.00%)	6 / 21 (28.57%)
occurrences (all)	2	1	6
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	3 / 21 (14.29%)
occurrences (all)	1	1	3
Hiccups			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Insomnia			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Amylase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 5 (40.00%) 3	3 / 21 (14.29%) 5
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Blood phosphorus increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 21 (14.29%) 6
Lipase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 2
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 2
Serum ferritin increased			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Weight increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Injury, poisoning and procedural complications			
Bankart lesion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Contusion subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Fall subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Limb injury subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Joint injury subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Palpitations subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	1 / 21 (4.76%) 2
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Dizziness subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	3 / 21 (14.29%) 3
Blood and lymphatic system disorders			

Hypofibrinogenaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Neutropenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 21 (9.52%) 2
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 21 (9.52%) 2
Ear and labyrinth disorders External ear pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	1 / 21 (4.76%) 2
Abdominal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	3 / 21 (14.29%) 3
Colitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	1 / 5 (20.00%) 1	3 / 21 (14.29%) 5
Diarrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	0 / 5 (0.00%) 0	3 / 21 (14.29%) 5
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Gingival bleeding subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Odynophagia			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	4 / 21 (19.05%) 5
Stomatitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 21 (9.52%) 2
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Jaundice subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	3 / 21 (14.29%) 3
Dry skin subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 21 (9.52%) 2
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Skin lesion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Pruritus subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	3 / 21 (14.29%) 3
Renal and urinary disorders			

Haematuria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Renal colic subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	1 / 21 (4.76%) 2
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 21 (9.52%) 2
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	2 / 21 (9.52%) 2
Joint range of motion decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Tendonitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Infections and infestations COVID-19 pneumonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
COVID-19 subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1

Diverticulitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Mastitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Otitis externa subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	4 / 21 (19.05%) 6
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 21 (9.52%) 2
Hyperphosphataemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 21 (14.29%) 3
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	2 / 21 (9.52%) 3
Iron deficiency subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 21 (4.76%) 1

Non-serious adverse events	Zilurgisertib 400 mg QD	Zilurgisertib 600 mg QD	Zilurgisertib 200 mg QD
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 5 (100.00%)	2 / 3 (66.67%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Vascular neoplasm subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cyst			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hyperthermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood creatinine increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood phosphorus increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	0	2	4
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Serum ferritin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Bankart lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint injury			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Palpitations			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dizziness			
subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Blood and lymphatic system disorders			
Hypofibrinogenaemia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Neutropenia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Thrombocytopenia			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Ear and labyrinth disorders			
External ear pain			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain			
subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0

Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	1	2
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Ingrowing nail			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal colic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Myalgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Tendonitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Infections and infestations			
COVID-19 pneumonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Diverticulitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Mastitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Otitis externa subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0	2 / 4 (50.00%) 4
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Hyperphosphataemia			

subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Iron deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2020	The overall rationale for this amendment was to implement changes based on Health Authority comments and requests.
08 April 2021	The overall rationale for this amendment was to implement changes and clarifications to the protocol.
22 December 2021	The rationale for this amendment was to implement changes to clarify the dose-escalation scheme.
20 December 2022	The rationale for this amendment was to implement changes to clarify the dose-expansion scheme and to allow a more complete exploration of the safety and efficacy of 1 or more recommended doses for expansion (RDE[s]).
06 December 2023	The primary purpose of the amendment was to reduce the investigational sampling for participants on the study following the Sponsor's strategic decision to stop further recruitment. Participants were followed for efficacy and safety while on study but no further pharmacokinetic (PK) or pharmacodynamic (PD)/translational sampling occurred. Unnecessary assessments or samples were also removed.

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 sponsor terminated study enrollment as a strategic decision. Due to early study termination, no participants were enrolled in the expansion stage of the study.

Notes: