Clinical trial results:
A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), and Acute Myeloid Leukemia (AML)

Summary

EudraCT number	2018-003395-12
Trial protocol	ES GB CZ HU AT IT
Global end of trial date	25 May 2023

Results information

Result version number	v1 (current)
This version publication date	26 April 2024
First version publication date	26 April 2024

Trial information

Trial identification

Sponsor protocol code	ASTX727-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03306264
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc.
Sponsor organisation address	4420 Rosewood Drive, Suite 200, Pleasanton, CA, United States, 94588
Public contact	Karen Mosher, Astex Pharmaceuticals, Inc., KMosher@taihooncology.com
Scientific contact	Karen Mosher, Astex Pharmaceuticals, Inc., KMosher@taihooncology.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	25 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of the ASTX727-02 study is to establish the safety and effectiveness of ASTX727 in adult subjects with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) using a pharmacokinetics (PK) bridging approach.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2018
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: 110
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	220
EEA total number of subjects	81

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)	39
From 65 to 84 years	168
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

A total of 227 subjects took part in the study from 15 February 2018 to 25 May 2023. 138 subjects with a diagnosis of MDS or CMML took part from the United States and Canada. 89 participants with a diagnosis of AML took part from Austria, Canada, Czech Republic, France, Germany, Hungary, Italy, Spain, and United Kingdom.

Pre-assignment

Screening details:

Total 138 subjects with MDS/CMML were enrolled & randomised in 1:1 ratio to receive ASTX727/decitabine in crossover manner. Total 89 subjects with AML were enrolled & randomised in 1:1 ratio to receive ASTX727/decitabine in crossover manner. Out of 227 subjects, 220 subjects received study treatment for which data has been reported in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MDS or CMML: ASTX727 or IV Decitabine

Arm description:

Subjects with MDS or CMML received ASTX727 tablet, containing the fixed-dose combination of 35 milligrams (mg) decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by intravenous (IV) infusion of decitabine 20 mg/meter per square (m^2), once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	Dacogen
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 milligrams per square meters (mg/m2) 1-hour IV infusion daily.

Investigational medicinal product name	ASTX727
Investigational medicinal product code	
Other name	Decitabine + Cedazuridine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ASTX727 tablet administered orally daily ×5

Arm title	AML: ASTX727 or IV Decitabine

Arm description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease

progression, unacceptable toxicity, participant discontinued treatment, or was withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	Dacogen
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 20 milligrams per square meters (mg/m2) 1-hour IV infusion daily.	
Investigational medicinal product name	ASTX727
Investigational medicinal product code	
Other name	Decitabine + Cedazuridine
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: ASTX727 tablet administered orally daily ×5	

Number of subjects in period 1	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine
Started	133	87
Completed	0	0
Not completed	133	87
Death	58	68
Complete Consent Withdrawal	4	7
Study Terminated by Sponsor	43	5
Rollover to ASTX727-06	28	6
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	MDS or CMML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with MDS or CMML received ASTX727 tablet, containing the fixed-dose combination of 35 milligrams (mg) decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by intravenous (IV) infusion of decitabine 20 mg/meter per square (m^2), once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Reporting group title	AML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, participant discontinued treatment, or was withdrawn from the study.

Reporting group values	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine	Total
Number of subjects	133	87	220
Age categorical Units: Subjects			
18 to 64 years	36	3	39
65 to 84 years	93	75	168
≥85 years	4	9	13
Gender categorical Units: Subjects			
Female	46	34	80
Male	87	53	140
Ethnicity Units: Subjects			
Hispanic or Latino	6	0	6
Not Hispanic or Latino	125	0	125
Unknown or Not Reported	2	87	89
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	0	4
White	121	0	121
More than one race	0	0	0
Unknown or Not Reported	5	87	92

End points

End points reporting groups

Reporting group title	MDS or CMML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with MDS or CMML received ASTX727 tablet, containing the fixed-dose combination of 35 milligrams (mg) decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by intravenous (IV) infusion of decitabine 20 mg/meter per square (m^2), once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Reporting group title	AML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, participant discontinued treatment, or was withdrawn from the study.

Subject analysis set title	MDS or CMML: IV Decitabine
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDS or CMML received decitabine 20 mg/m^2 IV injection, once daily, on Days 1 to 5 in cycle 1 or 2 (each cycle = 28 days).

Subject analysis set title	MDS or CMML: ASTX727
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with MDS or CMML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, given by mouth, once daily, on Days 1 to 5 in cycle 1 or 2 (each cycle = 28 days). From cycle 3, subjects received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Subject analysis set title	AML: IV Decitabine
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with AML received decitabine 20 mg/m^2 IV injection, once daily, on Days 1 to 5 in cycle 1 or 2 (each cycle = 28 days).

Subject analysis set title	AML: ASTX727
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, given by mouth, once daily, on Days 1 to 5 in cycle 1 or 2 (each cycle = 28 days). From cycle 3, subjects received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Subject analysis set title	Arm: AML: ASTX727 or IV Decitabine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (each cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Primary: Total 5-day Area Under the Curve From 0 to 24 Hours (AUC0-24) After Treatment With ASTX727 Versus IV Decitabine

End point title	Total 5-day Area Under the Curve From 0 to 24 Hours (AUC0-24) After Treatment With ASTX727 Versus IV Decitabine[1]

End point description:

Primary Endpoint Pharmacokinetics (PK) Analysis Set included subjects who received full dose of ASTX727 within 3 hours of the intended dosing time, and no vomiting within 6 hours of dosing and had at least 2 days of evaluable decitabine (AUC0-24) measurements in the ASTX727 cycle, i.e, Day 1 and either Day 2 or Day 5 and received the full IV decitabine dose as a 1-hour infusion.

End point type	Primary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1 to 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 to 5 of Cycle 1 and 2 (each cycle= 28 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: No statistical analysis was performed for this outcome measure.

End point values	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	69		
Units: Ratio of Geometric LSM				
least squares mean (confidence interval 90%)	98.93 (92.66 to 105.6)	99.64 (91.23 to 108.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	MDS/CMML: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[2]

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation subjects administered a drug; it does not necessarily have to have a causal relationship with this treatment. TEAEs were defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment, whichever occurred first. Safety Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 30 days after last dose of study treatment (up to approximately 2.7 years)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive data was planned to be reported for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: subjects	133			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	AML: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[3]

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation subjects administered a drug; it does not necessarily have to have a causal relationship with this treatment. TEAEs were defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment, whichever occurred first. Safety Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 30 days after last dose of study treatment (up to approximately 2.4 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: subjects	86			

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Number of Subjects With Grade 3 or Higher TEAEs

End point title	MDS/CMML: Number of Subjects With Grade 3 or Higher

End point description:

TEAEs were defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment, whichever occurred first. Severity of AEs were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal. Safety Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 30 days after last dose of study treatment (up to approximately 2.7 years)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the MDS/CMML arm was applicable for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: subjects	128			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Number of Subjects With Grade 3 or Higher TEAEs

End point title	AML: Number of Subjects With Grade 3 or Higher TEAEs[5]

End point description:

TEAEs were defined as events that first occurred or worsened on or after the date of the first dose of study treatment until 30 days after the last dose of study treatment or until the start of a post-treatment alternative anti-cancer treatment, whichever occurred first. Severity of AEs were graded using CTCAE version 4.03. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal. Safety Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 30 days after last dose of study treatment (up to approximately 2.4 years)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: subjects	79			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Percentage of Long Interspersed Nucleotide Elements (LINE)-1 Demethylation

End point title	Maximum Percentage of Long Interspersed Nucleotide Elements (LINE)-1 Demethylation

End point description:

Pharmacodynamic (PD) LINE-1 Analysis Set included subjects who received any amount of study treatment and have LINE-1 methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of the respective cycle. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 1 and 2 (as Baseline), and Days 8, 15 and 22 of Cycles 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: IV Decitabine	MDS or CMML: ASTX727	AML: IV Decitabine	AML: ASTX727
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	63	39	34
Units: percentage of demethylation				
least squares mean (confidence interval 95%)				
Cycle 1 (n=62,62,39,33)	14.019 (12.528 to 15.510)	13.289 (11.798 to 14.780)	8.243 (6.340 to 10.147)	9.357 (7.288 to 11.426)
Cycle 3 (n=63,63,29,34)	11.968 (10.503 to 13.434)	11.151 (9.685 to 12.616)	8.153 (6.226 to 10.079)	8.037 (6.258 to 9.816)

Statistical analyses

No statistical analyses for this end point

Secondary: Total 5-day Area Under the Curve From 0 to Infinity (AUC0-inf) After Treatment With ASTX727 Versus IV Decitabine

End point title	Total 5-day Area Under the Curve From 0 to Infinity (AUC0-inf) After Treatment With ASTX727 Versus IV Decitabine

End point description:

Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and who received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine. Number of Subjects analysed signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1 to 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 to 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	69		
Units: Ratio of Geometric LSM				
least squares mean (confidence interval 90%)	98.00 (91.80 to 104.6)	99.61 (91.20 to 108.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total 5-day Area Under the Curve From 0 to Last Quantifiable Concentration (AUC0-last) After Treatment With ASTX727 Versus IV Decitabine

End point title	Total 5-day Area Under the Curve From 0 to Last Quantifiable Concentration (AUC0-last) After Treatment With ASTX727 Versus IV Decitabine

End point description:

Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine. Number of Subjects analysed signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1 to 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 to 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	70		
Units: Ratio of Geometric LSM				
least squares mean (confidence interval 90%)	98.11 (91.88 to 104.8)	98.11 (89.75 to 107.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total 5-day Area Under the Curve From 0 to 8 Hours (AUC0-8) After Treatment With ASTX727 Versus IV Decitabine

End point title	Total 5-day Area Under the Curve From 0 to 8 Hours (AUC0-8) After Treatment With ASTX727 Versus IV Decitabine

End point description:

Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine. Number of Subjects analysed signifies those who were evaluable for this endpoint

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 to 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 to 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	70		
Units: Ratio of Geometric LSM				
least squares mean (confidence interval 90%)	97.93 (91.74 to 104.5)	97.55 (89.32 to 106.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From 0 to Infinity (AUC0-inf) After Treatment With ASTX727 Versus IV Decitabine

End point title	Area Under the Curve From 0 to Infinity (AUC0-inf) After Treatment With ASTX727 Versus IV Decitabine

End point description:

Overall PK Analysis Set included subjects not included in Primary Endpoint PK Analysis Set, received any amount of study treatment, complied with protocol sufficiently to ensure PK samples were collected, provided sufficient samples to measure available plasma concentrations for decitabine. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '9999' indicates that the geomentric mean and geometric coefficient of variation was not estimable as no subjects were analysed for the given category.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: IV Decitabine	MDS or CMML: ASTX727	AML: IV Decitabine	AML: ASTX727
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	119	127	70	78
Units: nanograms*hours per millilitres(ng*h/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=119,127,70,78)	174 (± 40.8)	102 (± 54.8)	175 (± 54.9)	118 (± 54.4)
Day 2 (n=0,126,0,74)	9999 (± 9999)	186 (± 55.3)	9999 (± 9999)	193 (± 59.6)
Day 5 (n=119,123,70,75)	170 (± 41.7)	178 (± 52.7)	181 (± 58.1)	187 (± 57.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Decitabine, Cedazuridine, and Cedazuridine-epimer

End point title	Maximum Observed Plasma Concentration (Cmax) of Decitabine, Cedazuridine, and Cedazuridine-epimer

End point description:

Summarized data of Cmax on Day 1, 2 and 5 respectively for Cycle 1 and 2 has been reported for ASTX727. Similarly, summarized data of Cmax on Day 1 and 5 respectively for Cycle 1 and 2 has been reported for IV Decitabine. Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine, cedazuridine, and cedazuridine-epimer. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '9999' indicates that the geomentric mean and geometric coefficient of variation was not estimable as no subjects were analysed for the given category.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: IV Decitabine	MDS or CMML: ASTX727	AML: IV Decitabine	AML: ASTX727
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	122	128	72	79
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Decitabine: Day 1 (n=122,128,72,78)	184 (± 48.1)	83.1 (± 66.1)	187 (± 64.7)	85.9 (± 56.6)
Decitabine: Day 2 (n=0,128,0,76)	9999 (± 9999)	145 (± 54.7)	9999 (± 9999)	139 (± 58.5)
Decitabine: Day 5 (n=122,124,70,76)	180 (± 49.2)	140 (± 62.8)	192 (± 62.4)	139 (± 62.7)
Cedazuridine: Day 1 (n=0,128,0,78)	9999 (± 9999)	321 (± 53.8)	9999 (± 9999)	313 (± 47.7)
Cedazuridine: Day 2 (n=0,128,0,78)	9999 (± 9999)	349 (± 49.1)	9999 (± 9999)	343 (± 43.4)
Cedazuridine: Day 5 (n=0,126,0,77)	9999 (± 9999)	371 (± 51.8)	9999 (± 9999)	350 (± 42.7)

Cedazuridine-epimer: Day 1 (n=0,128,0,79)	9999 (± 9999)	150 (± 65.7)	9999 (± 9999)	182 (± 60.0)
Cedazuridine-epimer: Day 2 (n=0,128,0,78)	9999 (± 9999)	155 (± 64.6)	9999 (± 9999)	204 (± 59.2)
Cedazuridine-epimer: Day 5 (n=0,126,0,77)	9999 (± 9999)	169 (± 65.9)	9999 (± 9999)	191 (± 58.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (Tmax) of Decitabine, Cedazuridine and Cedazuridine-epimer

End point title	Time to Reach Maximum Plasma Concentration (Tmax) of Decitabine, Cedazuridine and Cedazuridine-epimer

End point description:

Summarized data of Tmax on Day 1, 2 and 5 respectively for Cycle 1 and 2 has been reported for ASTX727. Similarly, summarized data of Tmax on Day 1 and 5 respectively for Cycle 1 and 2 has been reported for IV Decitabine. Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine, cedazuridine, and cedazuridine-epimer. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '9999' indicates that the geomentric mean and geometric coefficient of variation was not estimable as no subjects were analysed for the given category.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: IV Decitabine	MDS or CMML: ASTX727	AML: IV Decitabine	AML: ASTX727
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	122	128	72	79
Units: hours				
median (full range (min-max))				
Decitabine: Day 1 (n=122,128,72,78)	0.98 (0.23 to 1.27)	1.00 (0.48 to 3.00)	0.98 (0.25 to 2.00)	1.00 (0.25 to 2.02)
Decitabine: Day 2 (n=0,128,0,76)	9999 (9999 to 9999)	1.00 (0.47 to 2.00)	9999 (9999 to 9999)	1.00 (0.25 to 3.00)
Decitabine: Day 5 (n=122,124,70,76)	0.97 (0.25 to 1.62)	1.00 (0.25 to 3.00)	0.98 (0.00 to 1.17)	1.00 (0.47 to 3.00)
Cedazuridine: Day 1 (n=0,128,0,78)	9999 (9999 to 9999)	3.00 (1.50 to 7.97)	9999 (9999 to 9999)	3.98 (1.47 to 8.00)
Cedazuridine: Day 2 (n=0,128,0,78)	9999 (9999 to 9999)	3.01 (0.52 to 7.88)	9999 (9999 to 9999)	4.00 (1.00 to 7.88)
Cedazuridine: Day 5 (n=0,126,0,77)	9999 (9999 to 9999)	3.00 (1.50 to 6.12)	9999 (9999 to 9999)	3.98 (1.00 to 8.00)
Cedazuridine-epimer: Day 1 (n=0,128,0,79)	9999 (9999 to 9999)	3.08 (1.50 to 7.97)	9999 (9999 to 9999)	4.00 (1.50 to 8.03)

Cedazuridine-epimer: Day 2 (n=0,128,0,78)	9999 (9999 to 9999)	3.03 (0.52 to 7.88)	9999 (9999 to 9999)	4.00 (1.50 to 7.88)
Cedazuridine-epimer: Day 5 (n=0,126,0,77)	9999 (9999 to 9999)	3.08 (1.00 to 8.05)	9999 (9999 to 9999)	4.00 (1.53 to 8.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance (CL/F) of Oral Decitabine and Cedazuridine

End point title	Apparent Oral Clearance (CL/F) of Oral Decitabine and Cedazuridine

End point description:

Oral CL/F for oral decitabine was measured only on Day 1 and oral CL/F for oral cedazuridine was measured on Days 1, 2 and 5. Summarized data of Oral CL/F for oral decitabine on Day 1 for Cycle 1 and 2 and for oral cedazuridine on Day 1, 2 and 5 respectively for Cycle 1 and 2 has been reported for ASTX727. Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine, and cedazuridine. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '99999' indicates that geometric coefficient of variation could not be calculated as data for only one subject was available for analysis.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: ASTX727	AML: ASTX727		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	78		
Units: hours				
geometric mean (geometric coefficient of variation)				
Decitabine: Day 1 (n=127,78)	342 (± 54.8)	297 (± 54.4)		
Cedazuridine: Day 1 (n=109,52)	30.6 (± 46.4)	28.6 (± 55.5)		
Cedazuridine: Day 2 (n=121,74)	25.6 (± 159)	27.4 (± 45.4)		
Cedazuridine: Day 5 (n=2,1)	16.8 (± 15.9)	86.8 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Elimination Half Life (t1/2) of Decitabine, Cedazuridine and Cedazuridine-epimer

End point title	Apparent Elimination Half Life (t1/2) of Decitabine, Cedazuridine and Cedazuridine-epimer

End point description:

Summarized data of t1/2 on Day 1, 2 and 5 respectively for Cycle 1 and 2 has been reported for ASTX727 and on Day 1 and 5 respectively for Cycle 1 and 2 for IV Decitabine. Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine, cedazuridine, and cedazuridine-epimer. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '9999' indicates that geomentric mean & geometric coefficient of variation was not estimable as no subjects were analysed for given category. '99999' indicates that geometric coefficient of variation could not be calculated as data for only 1 subject was available for analysis.

End point type	Secondary

End point timeframe:

ASTX727: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2; Decitabine: Pre-dose, 0.25, 0.5, 1, 1.08, 1.5, 2, 3, 4, 6, 8 hours post-dose on Days 1 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: IV Decitabine	MDS or CMML: ASTX727	AML: IV Decitabine	AML: ASTX727
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	119	127	70	78
Units: hours				
geometric mean (geometric coefficient of variation)				
Decitabine: Day 1 (n=119,127,70,78)	0.967 (± 46.8)	1.18 (± 22.8)	1.16 (± 56.7)	1.07 (± 31.6)
Decitabine: Day 2 (n=0,126,0,74)	9999 (± 9999)	1.38 (± 24.7)	9999 (± 9999)	1.36 (± 35.0)
Decitabine: Day 5 (n=119,123,70,75)	1.14 (± 44.9)	1.47 (± 26.9)	1.18 (± 49.0)	1.45 (± 34.0)
Cedazuridine: Day 1 (n=0,109,0,52)	9999 (± 9999)	6.33 (± 18.1)	9999 (± 9999)	6.68 (± 18.5)
Cedazuridine: Day 2 (n=0,115,0,56)	9999 (± 9999)	6.70 (± 18.9)	9999 (± 9999)	7.05 (± 17.6)
Cedazuridine: Day 5 (n=0,2,0,1)	9999 (± 9999)	2.59 (± 5.43)	9999 (± 9999)	2.41 (± 99999)
Cedazuridine-epimer: Day 1 (n=0,107,0,49)	9999 (± 9999)	5.50 (± 21.8)	9999 (± 9999)	6.22 (± 17.4)
Cedazuridine-epimer: Day 2 (n=0,105,0,45)	9999 (± 9999)	5.90 (± 23.2)	9999 (± 9999)	6.15 (± 22.8)
Cedazuridine-epimer: Day 5 (n=0,9,0,1)	9999 (± 9999)	2.58 (± 5.16)	9999 (± 9999)	2.57 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of Oral Decitabine and Cedazuridine

End point title	Apparent Volume of Distribution (Vz/F) of Oral Decitabine and Cedazuridine

End point description:

Summarized data of Vz/F on Day 1, 2 and 5 respectively for Cycle 1 and 2 has been reported for ASTX727. Overall PK Analysis Set included subjects who may not have been included in the Primary Endpoint PK Analysis Set and received any amount of study treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended and provided sufficient samples to measure available plasma concentrations for decitabine, and cedazuridine. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point. '99999' indicates that geometric coefficient of variation could not be

calculated as data for only one subject was available for analysis.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours post-dose on Days 1, 2 and 5 of Cycle 1 and 2 (each cycle= 28 days)

End point values	MDS or CMML: ASTX727	AML: ASTX727		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	78		
Units: Litres				
geometric mean (geometric coefficient of variation)				
Decitabine: Day 1 (n=127,78)	585 (± 55.0)	434 (± 60.4)		
Decitabine: Day 2 (n=126,74)	369 (± 59.0)	337 (± 67.6)		
Decitabine: Day 5 (n=123,75)	417 (± 54.3)	373 (± 68.9)		
Cedazuridine: Day 1 (n=109,52)	280 (± 50.9)	272 (± 59.9)		
Cedazuridine: Day 2 (n=118,56)	296 (± 51.3)	278 (± 49.8)		
Cedazuridine: Day 5 (n=2,1)	62.8 (± 10.4)	302 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Percentage of Subjects With Complete Response (CR), Marrow CR (mCR), Partial Response (PR), Hematologic Improvement (HI) Based on International Working Group (IWG) 2006 Myelodysplastic Syndromes (MDS) Response Criteria

End point title	MDS/CMML: Percentage of Subjects With Complete Response (CR), Marrow CR (mCR), Partial Response (PR), Hematologic Improvement (HI) Based on International Working Group (IWG) 2006 Myelodysplastic Syndromes (MDS) Response Criteria[6]

End point description:

CR:normal peripheral,persistent granulocyte count≥1.0x10^9/liter(L),platelet≥100x10^9/L,Hemoglobin(Hgb)≥11g/dL,normal bone marrow with persistent marrow blasts≤5%.mCR:reduction of bone marrow blasts to≤5%,decrease by 50% or more with/without normalization of peripheral counts.PR:normal peripheral counts,granulocyte count ≥1.0x10^9/L,platelet count≥100x10^9/L,Hgb≥11 g/dL,normal bone marrow,marrow blasts>5%,reduced by 50% or more for atleast 4 weeks.HI: HI-E:Hb increase≥1.5 g/dL in absence of RBC transfusions.HI-P:Absolute increase of platelet count from<20 to>20X10^9/L by at least 100%,if more than 20x10^9/L,by absolute increase of at least 30x10^9/L in absence of platelet transfusions.HI-N:granulocyte increase≥100%,by an absolute increase≥0.5x10^9/L for atleast 8 weeks.Efficacy Analysis Set included all subjects who received any amount of study treatment.'9999' indicates that

End point type	Secondary

End point timeframe:

Up to approximately 2.7 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the MDS/CMML arm was applicable for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: percentage of subjects				
number (confidence interval 95%)				
Complete Response (CR)	21.8 (15.1 to 29.8)			
Marrow Complete Response (mCR)	32.3 (24.5 to 41.0)			
Partial Response (PR)	0 (0 to 0)			
HI: Erythroid Response (HI-E)	1.5 (0.2 to 5.3)			
HI: Platelet Response (HI-P)	5.3 (2.1 to 10.5)			
HI: Neutrophil Response (HI-N)	0.8 (0.0 to 4.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Percentage of Subjects With CR, CR With Incomplete Platelet Recovery (CRp), CR Plus CRp, and CR With Incomplete Blood Count Recovery (CRi) Based on IWG 2003 AML Response Criteria

End point title	AML: Percentage of Subjects With CR, CR With Incomplete Platelet Recovery (CRp), CR Plus CRp, and CR With Incomplete Blood Count Recovery (CRi) Based on IWG 2003 AML Response Criteria

End point description:

CR was defined as absolute neutrophil content (ANC) ≥1000/ microliter (µL), platelets ≥100,000/µL, independence from red blood cell (RBC) and platelet transfusions over the past week, no leukemic blasts and <5% leukemic blasts. CRp was defined as CR criteria except platelets <100,000/µL.and platelet transfusion over the past week. CRi was defined as CR criteria except ANC <1000/µL or platelets <100,000/µL. Percentage of subjects with CR, CRi, CRp, and CR Plus CRp based on IWG 2003 AML response criteria are reported. Intent-to-Treat (ITT) Analysis Set included data from all subjects who were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 2.4 years

End point values	Arm: AML: ASTX727 or IV Decitabine			
Subject group type	Subject analysis set			
Number of subjects analysed	89			
Units: percentage of subjects				
number (confidence interval 95%)				
Complete Response (CR)	21.3 (13.4 to 31.3)			
CR with Incomplete Platelet Recovery (CRp)	2.2 (0.3 to 7.9)			

CR with Incomplete Blood Count Recovery (CRi) CR Plus CRp	5.6 (1.8 to 12.6) 23.6 (15.2 to 33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Percentage of Subjects With CR With Partial Hematologic Recovery (CRh) Based on IWG 2003 AML Response Criteria

End point title	AML: Percentage of Subjects With CR With Partial Hematologic Recovery (CRh) Based on IWG 2003 AML Response Criteria[7]

End point description:

CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/µL and ANC >500/µL), independence from RBC and platelet transfusions within 7 days of bone marrow evaluation, and peripheral blast ≤1%. Percentage of subjects with CRh based on IWG 2003 AML response criteria are reported. Efficacy Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 3 up to approximately 2.4 years (each cycle= 28 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: percentage of subjects				
number (confidence interval 95%)	24.1 (15.6 to 34.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Time to First Response, Best Response and Complete Response Based on IWG 2003 AML Response Criteria

End point title	AML: Time to First Response, Best Response and Complete Response Based on IWG 2003 AML Response Criteria[8]

End point description:

Time to first response: Time in months from date of first treatment to first date when any response is achieved. Time to best response: Months from date of first treatment to first date when a subject's best response,in the order of CR,CRi(or CRp or CRh), orPR,was achieved. Time to CR: Months from date of first treatment to first date when CR is achieved. CR:ANC ≥1000/ microliter (µL),platelets ≥100,000/µL, independence from RBC and platelet transfusions over past week,no leukemic blasts,and <5% leukemic blasts.CRp: CR criteria except ANC ≥1000/µL, platelets < 100,000/µL.and platelet transfusion over the past week. CRi:CR criteria except ANC <1000/µL or platelets <100,000/µL.CRh: <5% of blasts in the bone marrow,platelets >50,000/µL and ANC >500/µL, independence from RBC and platelet transfusions

within 7 days and peripheral blast ≤1%. PR: CR criteria except decrease of ≥50% in leukemic blasts. Efficacy Analysis Set included all participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 2.4 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: months				
median (full range (min-max))				
Time to First Response	2.91 (1.9 to 6.5)			
Time to Best Response	3.45 (1.9 to 7.5)			
Time to Complete Response	3.02 (1.9 to 7.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Duration of Complete Response and Combined CR and CRh Based on IWG 2003 AML Response Criteria

End point title	AML: Duration of Complete Response and Combined CR and CRh Based on IWG 2003 AML Response Criteria[9]

End point description:

Duration of CR was defined as the time interval from the first CR to time of relapse. Duration of combined CR and CRh was defined as the time interval from the first CR or CRh to time of relapse. Duration of CR and combined CR and CRh was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 2.4 years

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: months				
median (confidence interval 95%)				
Duration of Complete Response	6.9 (3.4 to 11.5)			

Duration of Combined CR and CRh	9.0 (3.4 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Percentage of Subjects With Red Blood Cell (RBC) and Platelet Transfusion Independence (TI)

End point title	MDS/CMML: Percentage of Subjects With Red Blood Cell (RBC) and Platelet Transfusion Independence (TI)[10]

End point description:

Transfusion independence was defined as no transfusion for 56 consecutive days or more (84 and 112 days) after the first dose of study treatment while maintaining hemoglobin ≥8 grams/deciliter (g/dL) (RBC TI) or maintaining platelets ≥20×109/L (platelet TI). Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint in specified category.

End point type	Secondary

End point timeframe:

Up to approximately 2.7 years

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the MDS/CMML arm was applicable for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: percentage of subjects				
number (confidence interval 95%)				
RBC TI: ≥56 Days (n=54)	51.9 (37.8 to 65.7)			
RBC TI: ≥84 Days (n=54)	40.7 (27.6 to 55.0)			
RBC TI: ≥112 Days (n=54)	33.3 (21.1 to 47.5)			
Platelet TI: ≥56 Days (n=12)	50.0 (21.1 to 78.9)			
Platelet TI: ≥84 Days (n=12)	33.3 (9.9 to 65.1)			
Platelet TI: ≥112 Days (n=12)	33.3 (9.9 to 65.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Percentage of Subjects With Red Blood Cell (RBC) and Platelet Transfusion Independence (TI)

End point title	AML: Percentage of Subjects With Red Blood Cell (RBC) and Platelet Transfusion Independence (TI)[11]

End point description:

Transfusion independence was defined as no transfusion for 56 consecutive days or more (112 days) after the first dose of study treatment while maintaining hemoglobin ≥8 grams/deciliter (g/dL) (RBC TI) or maintaining platelets ≥20×109/L (platelet TI). Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint. 'n' signifies those subjects who were evaluable for this endpoint at specified time point.

End point type	Secondary

End point timeframe:

Up to approximately 2.4 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of subjects				
number (confidence interval 95%)				
RBC TI ≥56 Days (n=37)	37.8 (22.5 to 55.2)			
RBC TI ≥112 Days (n=37)	24.3 (11.8 to 41.2)			
Platelet TI ≥56 Days (n=14)	35.7 (12.8 to 64.9)			
Platelet TI ≥112 Days (n=14)	28.6 (8.4 to 58.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Leukemia-free Survival (LFS)

End point title	MDS/CMML: Leukemia-free Survival (LFS)[12]

End point description:

LFS was defined as time from the date of randomisation to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause. Subjects who hadn't reached AML at the time of the analysis were censored at the date of the last follow-up. Leukemia-free survival was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint. '9999999' indicates that the upper limit of the 95% Confidence Interval (CI) was not reached at time of data cut-off due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

From randomisation up to approximately 2.7 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the MDS/CMML arm was applicable for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: days				
median (confidence interval 95%)	889.0 (674.0 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: MDS/CMML: Overall Survival (OS)

End point title	MDS/CMML: Overall Survival (OS)[13]

End point description:

OS was defined as time from the date of randomisation to the date of death from any cause. Subjects without documented death at the time of the analysis were censored at the date of the last follow-up. Overall survival was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint. '9999999' indicates that the upper limit of the 95% CI was not reached at time of data cut-off due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

From randomisation up to approximately 2.7 years

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the MDS/CMML arm was applicable for this endpoint.

End point values	MDS or CMML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: days				
number (confidence interval 95%)	966.0 (809.0 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Overall Survival (OS)

End point title	AML: Overall Survival (OS)[14]

End point description:

OS was defined as time from the date of randomisation to the date of death from any cause. Subjects without documented death at the time of the analysis were censored at the date of the last follow-up. Overall survival was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomisation up to approximately 2.4 years

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: months				
number (confidence interval 95%)	8.9 (5.9 to 13.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Survival Rates at 6 Months, 1 Year, and 2 Years

End point title	AML: Survival Rates at 6 Months, 1 Year, and 2 Years[15]

End point description:

One-year survival rate was defined as the survival rate at the end of the first year from the date of randomisation. The survival rates at 6 months and at 2 years were calculated similarly. Efficacy Analysis Set included all subjects who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Month 6, Years 1 and 2

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: percentage of subjects				
number (confidence interval 95%)				
Month 6	61 (50 to 71)			

Year 1 Year 2	44 (33 to 54) 16 (8 to 26)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Event-free Survival (EFS)

End point title	AML: Event-free Survival (EFS)[16]

End point description:

EFS was defined as time from the date of randomisation to the date of treatment failure [disease progression/relapse (due to confirmed reappearance of leukemic blasts in peripheral blood or ≥5% leukemic blasts in bone marrow (including relapse), discontinue treatment due to disease progression or treatment-related AE, or alternative anti-leukemia therapy except for HCT] or death from any cause, whichever occurs first. Subjects without documented treatment failure at the time of the analysis were censored at the date of the last follow-up. Event-free survival was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomisation up to approximately 2.4 years

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: months				
median (confidence interval 95%)	5.9 (3.8 to 8.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: AML: Progression-free Survival (PFS)

End point title	AML: Progression-free Survival (PFS)[17]

End point description:

PFS was defined as time from the date of randomisation to the date disease progression due to confirmed reappearance of leukemic blasts in peripheral blood or ≥5% leukemic blasts in bone marrow (including relapse) or death from any cause, whichever occurs first. Participants without documented disease progression/relapse or death at the time of the analysis were censored at the date of the last follow-up. Progression-free survival was presented using a Kaplan-Meier estimate. Efficacy Analysis Set included all subjects who received any amount of study treatment. Number of Subjects analysed signifies those who were evaluable for this endpoint

End point type	Secondary

End point timeframe:

From randomization up to approximately 2.4 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the AML arm was applicable for this endpoint.

End point values	AML: ASTX727 or IV Decitabine			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: months				
median (confidence interval 95%)	6.1 (4.0 to 8.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

CMML: From randomisation up to 2.7 years; AML: From randomisation up to 2.4 years

Adverse event reporting additional description:

Safety Analysis Set included all subjects who received any amount of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	MDS or CMML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with MDS or CMML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (1 cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study.

Reporting group title	AML: ASTX727 or IV Decitabine

Reporting group description:

Subjects with AML received ASTX727 tablet, containing the fixed-dose combination of 35 mg decitabine and 100 mg cedazuridine, orally, once daily, on Days 1 to 5 in cycle 1 (1 cycle = 28 days), followed by IV infusion of decitabine 20 mg/m^2, once daily, on Days 1 to 5 in cycle 2 or the converse. A washout period of 23 days was maintained between the 2 cycles. From cycle 3, all subjects enrolled in cycles 1 and 2 received ASTX727 tablet, once daily, on Days 1 to 5 of each 28-day cycle until disease progression, unacceptable toxicity, participant discontinued treatment, or was withdrawn from the study.

Serious adverse events	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 133 (68.42%)	70 / 87 (80.46%)	
number of deaths (all causes)	58	67	
number of deaths resulting from adverse events	15	31	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	3 / 133 (2.26%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation Blood			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 133 (2.26%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 133 (2.26%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 133 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fatigue			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal Inflammation			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 133 (1.50%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 133 (0.75%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Influenza A virus test positive			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Exposure to communicable disease			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Fractures			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 133 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	4 / 133 (3.01%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Dizziness			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Suicide attempt			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	39 / 133 (29.32%)	22 / 87 (25.29%)	
occurrences causally related to treatment / all	12 / 39	8 / 22	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			
subjects affected / exposed	4 / 133 (3.01%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 133 (1.50%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 133 (1.50%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia pure red cell			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 133 (1.50%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Perforation			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis chronic			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma gangrenosum			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 133 (0.75%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	22 / 133 (16.54%)	18 / 87 (20.69%)	
occurrences causally related to treatment / all	5 / 22	6 / 18	
deaths causally related to treatment / all	1 / 3	0 / 8	
Sepsis			
subjects affected / exposed	10 / 133 (7.52%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	3 / 10	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 2	
Cellulitis			
subjects affected / exposed	7 / 133 (5.26%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	2 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 133 (2.26%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 133 (1.50%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 133 (0.75%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Escherichia coli			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillitis			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 133 (1.50%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 2	
Sinusitis fungal			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 133 (0.75%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	0 / 133 (0.00%)	5 / 87 (5.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 133 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	0 / 133 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Bacteraemia			
subjects affected / exposed	0 / 133 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 133 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 133 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Abscess			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Infective			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona Virus Infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			

subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis aspergillus			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 133 (2.26%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 133 (0.75%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 133 (0.75%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MDS or CMML: ASTX727 or IV Decitabine	AML: ASTX727 or IV Decitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 133 (100.00%)	79 / 87 (90.80%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	16 / 133 (12.03%)	2 / 87 (2.30%)	
occurrences (all)	16	2	
Hypertension			
subjects affected / exposed	10 / 133 (7.52%)	8 / 87 (9.20%)	
occurrences (all)	10	8	
Haematoma			
subjects affected / exposed	4 / 133 (3.01%)	9 / 87 (10.34%)	
occurrences (all)	4	9	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	68 / 133 (51.13%)	9 / 87 (10.34%)	
occurrences (all)	68	9	
Oedema peripheral			

subjects affected / exposed	36 / 133 (27.07%)	16 / 87 (18.39%)	
occurrences (all)	36	16	
Asthenia			
subjects affected / exposed	29 / 133 (21.80%)	20 / 87 (22.99%)	
occurrences (all)	29	20	
Pyrexia			
subjects affected / exposed	27 / 133 (20.30%)	18 / 87 (20.69%)	
occurrences (all)	27	18	
Chills			
subjects affected / exposed	13 / 133 (9.77%)	2 / 87 (2.30%)	
occurrences (all)	13	2	
Non-cardiac chest pain			
subjects affected / exposed	9 / 133 (6.77%)	1 / 87 (1.15%)	
occurrences (all)	9	1	
Pain			
subjects affected / exposed	8 / 133 (6.02%)	4 / 87 (4.60%)	
occurrences (all)	8	4	
Peripheral swelling			
subjects affected / exposed	7 / 133 (5.26%)	1 / 87 (1.15%)	
occurrences (all)	7	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	45 / 133 (33.83%)	5 / 87 (5.75%)	
occurrences (all)	45	5	
Cough			
subjects affected / exposed	40 / 133 (30.08%)	9 / 87 (10.34%)	
occurrences (all)	40	9	
Oropharyngeal pain			
subjects affected / exposed	27 / 133 (20.30%)	1 / 87 (1.15%)	
occurrences (all)	27	1	
Epistaxis			
subjects affected / exposed	17 / 133 (12.78%)	7 / 87 (8.05%)	
occurrences (all)	17	7	
Nasal congestion			

subjects affected / exposed	15 / 133 (11.28%)	1 / 87 (1.15%)	
occurrences (all)	15	1	
Dyspnoea exertional			
subjects affected / exposed	7 / 133 (5.26%)	2 / 87 (2.30%)	
occurrences (all)	7	2	
Rhinitis allergic			
subjects affected / exposed	7 / 133 (5.26%)	0 / 87 (0.00%)	
occurrences (all)	7	0	
Rhinorrhoea			
subjects affected / exposed	7 / 133 (5.26%)	0 / 87 (0.00%)	
occurrences (all)	7	0	
Pleural effusion			
subjects affected / exposed	3 / 133 (2.26%)	6 / 87 (6.90%)	
occurrences (all)	3	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 133 (14.29%)	9 / 87 (10.34%)	
occurrences (all)	19	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	20 / 133 (15.04%)	6 / 87 (6.90%)	
occurrences (all)	20	6	
Blood creatinine increased			
subjects affected / exposed	17 / 133 (12.78%)	6 / 87 (6.90%)	
occurrences (all)	17	6	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 133 (10.53%)	5 / 87 (5.75%)	
occurrences (all)	14	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 133 (8.27%)	3 / 87 (3.45%)	
occurrences (all)	11	3	
Blood bilirubin increased			
subjects affected / exposed	10 / 133 (7.52%)	0 / 87 (0.00%)	
occurrences (all)	10	0	
Weight decreased			

subjects affected / exposed	10 / 133 (7.52%)	4 / 87 (4.60%)	
occurrences (all)	10	4	
C-reactive protein increased			
subjects affected / exposed	0 / 133 (0.00%)	8 / 87 (9.20%)	
occurrences (all)	0	8	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 133 (37.59%)	6 / 87 (6.90%)	
occurrences (all)	50	6	
Dizziness			
subjects affected / exposed	42 / 133 (31.58%)	8 / 87 (9.20%)	
occurrences (all)	42	8	
Anxiety			
subjects affected / exposed	11 / 133 (8.27%)	1 / 87 (1.15%)	
occurrences (all)	11	1	
Depression			
subjects affected / exposed	10 / 133 (7.52%)	2 / 87 (2.30%)	
occurrences (all)	10	2	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	92 / 133 (69.17%)	50 / 87 (57.47%)	
occurrences (all)	92	50	
Neutropenia			
subjects affected / exposed	80 / 133 (60.15%)	27 / 87 (31.03%)	
occurrences (all)	80	27	
Anaemia			
subjects affected / exposed	74 / 133 (55.64%)	42 / 87 (48.28%)	
occurrences (all)	74	42	
Leukopenia			
subjects affected / exposed	37 / 133 (27.82%)	9 / 87 (10.34%)	
occurrences (all)	37	9	
Lymphopenia			
subjects affected / exposed	8 / 133 (6.02%)	0 / 87 (0.00%)	
occurrences (all)	8	0	
Febrile Neutropenia			

subjects affected / exposed	7 / 133 (5.26%)	7 / 87 (8.05%)	
occurrences (all)	7	7	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	7 / 133 (5.26%)	1 / 87 (1.15%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	64 / 133 (48.12%)	17 / 87 (19.54%)	
occurrences (all)	64	17	
Nausea			
subjects affected / exposed	64 / 133 (48.12%)	17 / 87 (19.54%)	
occurrences (all)	64	17	
Diarrhoea			
subjects affected / exposed	54 / 133 (40.60%)	17 / 87 (19.54%)	
occurrences (all)	54	17	
Vomiting			
subjects affected / exposed	26 / 133 (19.55%)	10 / 87 (11.49%)	
occurrences (all)	26	10	
Stomatitis			
subjects affected / exposed	23 / 133 (17.29%)	2 / 87 (2.30%)	
occurrences (all)	23	2	
Abdominal pain			
subjects affected / exposed	21 / 133 (15.79%)	2 / 87 (2.30%)	
occurrences (all)	21	2	
Haemorrhoids			
subjects affected / exposed	9 / 133 (6.77%)	6 / 87 (6.90%)	
occurrences (all)	9	6	
Toothache			
subjects affected / exposed	9 / 133 (6.77%)	1 / 87 (1.15%)	
occurrences (all)	9	1	
Dyspepsia			
subjects affected / exposed	8 / 133 (6.02%)	2 / 87 (2.30%)	
occurrences (all)	8	2	
Skin and subcutaneous tissue disorders			

Rash maculo-papular			
subjects affected / exposed	17 / 133 (12.78%)	3 / 87 (3.45%)	
occurrences (all)	17	3	
Rash			
subjects affected / exposed	16 / 133 (12.03%)	3 / 87 (3.45%)	
occurrences (all)	16	3	
Alopecia			
subjects affected / exposed	13 / 133 (9.77%)	0 / 87 (0.00%)	
occurrences (all)	13	0	
Petechiae			
subjects affected / exposed	12 / 133 (9.02%)	2 / 87 (2.30%)	
occurrences (all)	12	2	
Pruritus			
subjects affected / exposed	9 / 133 (6.77%)	3 / 87 (3.45%)	
occurrences (all)	9	3	
Skin lesion			
subjects affected / exposed	8 / 133 (6.02%)	0 / 87 (0.00%)	
occurrences (all)	8	0	
Night sweats			
subjects affected / exposed	7 / 133 (5.26%)	2 / 87 (2.30%)	
occurrences (all)	7	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	10 / 133 (7.52%)	2 / 87 (2.30%)	
occurrences (all)	10	2	
Pollakiuria			
subjects affected / exposed	7 / 133 (5.26%)	2 / 87 (2.30%)	
occurrences (all)	7	2	
Acute kidney injury			
subjects affected / exposed	5 / 133 (3.76%)	5 / 87 (5.75%)	
occurrences (all)	5	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 133 (24.06%)	8 / 87 (9.20%)	
occurrences (all)	32	8	
Back Pain			

subjects affected / exposed	26 / 133 (19.55%)	9 / 87 (10.34%)	
occurrences (all)	26	9	
Myalgia			
subjects affected / exposed	21 / 133 (15.79%)	1 / 87 (1.15%)	
occurrences (all)	21	1	
Pain in extremity			
subjects affected / exposed	18 / 133 (13.53%)	1 / 87 (1.15%)	
occurrences (all)	18	1	
Bone pain			
subjects affected / exposed	11 / 133 (8.27%)	1 / 87 (1.15%)	
occurrences (all)	11	1	
Musculoskeletal pain			
subjects affected / exposed	8 / 133 (6.02%)	2 / 87 (2.30%)	
occurrences (all)	8	2	
Neck pain			
subjects affected / exposed	8 / 133 (6.02%)	1 / 87 (1.15%)	
occurrences (all)	8	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 133 (12.03%)	3 / 87 (3.45%)	
occurrences (all)	16	3	
Urinary tract infection			
subjects affected / exposed	16 / 133 (12.03%)	8 / 87 (9.20%)	
occurrences (all)	16	8	
Cellulitis			
subjects affected / exposed	11 / 133 (8.27%)	6 / 87 (6.90%)	
occurrences (all)	11	6	
Nasopharyngitis			
subjects affected / exposed	10 / 133 (7.52%)	3 / 87 (3.45%)	
occurrences (all)	10	3	
Pneumonia			
subjects affected / exposed	10 / 133 (7.52%)	7 / 87 (8.05%)	
occurrences (all)	10	7	
Corona Virus Infection			
subjects affected / exposed	0 / 133 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	5	

Contusion			
subjects affected / exposed	24 / 133 (18.05%)	0 / 87 (0.00%)	
occurrences (all)	24	0	
Fall			
subjects affected / exposed	16 / 133 (12.03%)	9 / 87 (10.34%)	
occurrences (all)	16	9	
Procedural pain			
subjects affected / exposed	7 / 133 (5.26%)	0 / 87 (0.00%)	
occurrences (all)	7	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 133 (32.33%)	12 / 87 (13.79%)	
occurrences (all)	43	12	
Hypokalaemia			
subjects affected / exposed	27 / 133 (20.30%)	15 / 87 (17.24%)	
occurrences (all)	27	15	
Hyperglycaemia			
subjects affected / exposed	14 / 133 (10.53%)	3 / 87 (3.45%)	
occurrences (all)	14	3	
Hypocalcaemia			
subjects affected / exposed	14 / 133 (10.53%)	1 / 87 (1.15%)	
occurrences (all)	14	1	
Hyponatraemia			
subjects affected / exposed	12 / 133 (9.02%)	2 / 87 (2.30%)	
occurrences (all)	12	2	
Hypoalbuminaemia			
subjects affected / exposed	9 / 133 (6.77%)	0 / 87 (0.00%)	
occurrences (all)	9	0	
Hypomagnesaemia			
subjects affected / exposed	9 / 133 (6.77%)	5 / 87 (5.75%)	
occurrences (all)	9	5	
Dehydration			
subjects affected / exposed	7 / 133 (5.26%)	2 / 87 (2.30%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2021	The following changes were made as part of Amendment 2: 1.Addition of information on marketing approval of ASTX727 as INQOVI® (35 mg decitabine/100 mg cedazuridine). 2.Addition of language describing modifications to study conduct implemented due to current coronavirus disease 2019 (COVID-19) health emergency. 3.Removal of restriction on ingestion of medication that may affect gastric pH for 4 hours before and 4 hours after ASTX727 dosing because PK results have shown this is not required. 4.Description of informed consent is changed from "written informed consent" to "legally effective informed consent." 5.Further details and guidance on antibiotic prophylaxis are provided at request of health authority. 6.Exclusion criterion for "Hypersensitivity to decitabine, cedazuridine, or any of the excipients in ASTX727 tablets or IV decitabine" is added at request of health authority. 7.Brief summary of PK results from MDS subjects in this study is added at request of health authority. 8.Paragraph emphasizing importance of multiple cycles of treatment after completion of Cycles 1 and 2 is added at request of health authority. 9.An explanation that assessment of efficacy and safety is independent of PK endpoints is added at request of health authority. 10.Instructions regarding what to do in event of vomited dose are added at request of health authority. 11.Instructions that dosing should be delayed in presence of certain non-hematologic toxicities are added at request of health authority. 12. Prohibition of nucleosides or drugs metabolized by cytidine deaminase (CDA) is extended from days that ASTX727 is administered to entire duration of study treatment at request of health authority. 13.ASTX727 is identified as genotoxic, based on current INQOVI Prescribing Information. 14.Description of AE reporting is updated to align with current practice. 15.SAE reporting requirements are updated to align with current practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported