



Clinical trial results:

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase III Study of Idasanutlin, an MDM2 Antagonist, with Cytarabine Versus Cytarabine Plus Placebo in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

Summary

EudraCT number	2014-003065-15
Trial protocol	AT FI GB NO BE NL ES FR IT
Global end of trial date	03 July 2020

Results information

Result version number	v1 (current)
This version publication date	07 May 2021
First version publication date	07 May 2021

Trial information

Trial identification

Sponsor protocol code	WO29519
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann- La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann- La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann- La Roche AG, +41 61 6878333, global-roche-genentech-trials@gene.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	03 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare OS in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) who had been randomized to idasanutlin in combination with cytarabine versus those who had been randomized to cytarabine and placebo

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) guidelines according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2015
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	Australia: 23
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Spain: 82
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 76
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Panama: 3
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	United States: 13

Worldwide total number of subjects	447
EEA total number of subjects	310

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)	252
From 65 to 84 years	195
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 612 participants were screened, of which 447 patients were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo plus Cytarabine
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Arm description:

Participants will receive induction therapy idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or CRi, up to 28 additional days are allowed for blood count recovery, if needed.

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

Dosage and administration details:

Idasanutlin matching placebo for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days).

Arm title	Idasanutlin plus Cytarabine
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Arm description:

Participants will receive induction therapy idasanutlin and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRi), up to 28 additional days are allowed for blood count recovery, if needed.

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

Dosage and administration details:

Idasanutlin and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days).

Number of subjects in period 1	Placebo plus Cytarabine	Idasanutlin plus Cytarabine
Started	149	298
Completed	0	0
Not completed	149	298
Consent withdrawn by subject	5	9
Study Terminated By Sponsor	33	71
Death	109	211
Lost to follow-up	2	4
(Give reason)	-	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo plus Cytarabine
Reporting group description:	
Participants will receive induction therapy idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or CRi, up to 28 additional days are allowed for blood count recovery, if needed.	
Reporting group title	Idasanutlin plus Cytarabine
Reporting group description:	
Participants will receive induction therapy idasanutlin and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRi), up to 28 additional days are allowed for blood count recovery, if needed.	

Reporting group values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine	Total
Number of subjects	149	298	447
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	83	169	252
From 65-84 years	66	129	195
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	59.9	59.4	
standard deviation	± 12.1	± 13.1	-
Sex/Gender, Customized Units: Participants			
Male	86	163	249
Female	63	135	198
Ethnicity Units: Subjects			
Hispanic or Latino	8	11	19
Not Hispanic or Latino	112	231	343
Not Stated	18	36	54
Unknown	11	20	31
Race Units: Subjects			
Asian	11	20	31

Black or African America	2	4	6
Native Hawaiian or other	0	1	1
White	111	222	333
Unknown	25	51	76

End points

End points reporting groups

Reporting group title	Placebo plus Cytarabine
Reporting group description: Participants will receive induction therapy idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or CRi, up to 28 additional days are allowed for blood count recovery, if needed.	
Reporting group title	Idasanutlin plus Cytarabine
Reporting group description: Participants will receive induction therapy idasanutlin and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRi), up to 28 additional days are allowed for blood count recovery, if needed.	

Primary: Overall Survival in TP53 WT Population

End point title	Overall Survival in TP53 WT Population
End point description:	
End point type	Primary
End point timeframe: From randomization to death from any cause (up to approximately 5.5 years)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Months				
median (confidence interval 95%)	9.13 (7.59 to 10.64)	8.28 (6.67 to 10.87)		

Statistical analyses

Statistical analysis title	Hazard Ratio Superiority Statistical Analysis
Comparison groups	Placebo plus Cytarabine v Idasanutlin plus Cytarabine
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5752
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.45

Secondary: Percentage of Participants in Complete Response (CR) at the End of Induction According to Hematologic Malignancy Response Assessment (HMRA) in TP53 WT Population

End point title	Percentage of Participants in Complete Response (CR) at the End of Induction According to Hematologic Malignancy Response Assessment (HMRA) in TP53 WT Population
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End point description:

End point type	Secondary
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End point timeframe:

At the end of induction (up to Day 56)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Percentage of Participants				
number (not applicable)	20.3	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) According to HMRA in TP53 WT Population

End point title	Event-Free Survival (EFS) According to HMRA in TP53 WT Population
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End point description:

Event Free Survival (EFS) is defined as the time from the date of randomization to whichever occurs first:

treatment failure (failure to achieve CR, set as day of final response assessment), relapse from CR, or death from any cause.

End point type	Secondary
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End point timeframe:

From randomization up to treatment failure, relapse, or death from any cause (up to approximately 5.5 years)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Weeks				
median (confidence interval 95%)	6.29 (5.86 to 8.00)	4.36 (4.14 to 5.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Overall Remission (CR, CRp, and CRi) at the End of Induction According to HMRA in TP53 WT Population

End point title	Percentage of Participants with Overall Remission (CR, CRp, and CRi) at the End of Induction According to HMRA in TP53 WT Population
End point description:	
End point type	Secondary
End point timeframe:	
At the end of induction (up to Day 56)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Percentage of Participants				
number (not applicable)	38.8	22.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Remission Following CR (DOR) in TP53 WT Population

End point title	Duration of Remission Following CR (DOR) in TP53 WT Population
End point description:	
Duration of Remission Following CR (DOR) in TP53 WT Population is based on any patients with CR observed after study treatment or HSCT or further salvage therapy.	
End point type	Secondary
End point timeframe:	
From achieving CR until relapse or death from any cause (up to approximately 5.5 years)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	59		
Units: Months				
median (confidence interval 95%)	18.73 (5.26 to 999)	16.76 (7.82 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Undergoing HSCT Following Complete Response (CR), in TP53 WT Population

End point title	Percentage of Participants Undergoing HSCT Following Complete Response (CR), in TP53 WT Population
End point description:	
End point type	Secondary
End point timeframe:	
Baseline up to approximately 5.5 years	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Percentage of Participants				
number (not applicable)	10.6	11.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Complete Response (CR) in Clinically Actionable Mutation-Defined Subpopulation (FLT3, IDH1 and IDH2) in TP53 WT Population

End point title	Percentage of Participants with Complete Response (CR) in Clinically Actionable Mutation-Defined Subpopulation (FLT3, IDH1 and IDH2) in TP53 WT Population
End point description:	
End point type	Secondary

End point timeframe:

At the end of induction (up to Day 56)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Percentage of Participants				
number (not applicable)				
IDH2	23.1	29.5		
IDH1	11.1	34.8		
FLT3	12.5	15.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Clinically Actionable Mutation-Defined Subpopulation (FLT3, IDH1 and IDH2) in TP53 WT Population

End point title	Overall Survival in Clinically Actionable Mutation-Defined Subpopulation (FLT3, IDH1 and IDH2) in TP53 WT Population
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End point description:

End point type	Secondary
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End point timeframe:

From randomization to death from any cause (up to approximately 5.5 years)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Months				
median (confidence interval 95%)				
IDH2	11.37 (8.02 to 999)	11.01 (6.87 to 999)		
IDH1	9.13 (2.50 to 16.69)	8.25 (4.27 to 37.29)		
FLT3	4.76 (1.97 to 13.04)	5.55 (4.50 to 8.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experienced at Least One Adverse Event by Severity, According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Participants who Experienced at Least One Adverse Event by Severity, According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI-CTCAE v4.03)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.5 years

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	232		
Units: Participants	149	232		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events Leading to Discontinuation

End point title	Number of Participants with Adverse Events Leading to Discontinuation
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End point description:

End point type	Secondary
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End point timeframe:

Baseline up to approximately 5.5 years

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events Leading to Death up to Day 30

End point title	Number of Participants with Adverse Events Leading to Death up to Day 30
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End point description:

End point type	Secondary
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End point timeframe:

Up to Day 30

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Participants	9	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events Leading to Death up to Day 60

End point title	Number of Participants with Adverse Events Leading to Death up to Day 60
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End point description:

End point type	Secondary
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End point timeframe:

Up to Day 60

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Participants	60	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinical Laboratory Abnormalities in Biochemistry Tests at the Greatest Severity, According to NCI-CTCAE v4.03

End point title	Number of Participants with Clinical Laboratory Abnormalities in Biochemistry Tests at the Greatest Severity, According to NCI-CTCAE v4.03
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End point description:

Laboratory parameters for blood biochemistry will be measured and compared with a standard reference range. Values outside the standard reference range are considered abnormalities. Not every laboratory abnormality qualifies as an adverse event. A laboratory test result will be reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment or a medical intervention; or is clinically significant in the investigator's judgment.

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 2, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinical Laboratory Abnormalities in Hematology Tests at the Greatest Severity, According to NCI-CTCAE v4.03

End point title	Number of Participants with Clinical Laboratory Abnormalities in Hematology Tests at the Greatest Severity, According to NCI-CTCAE v4.03
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End point description:

Laboratory parameters for hematology will be measured and compared with a standard reference range. Values outside the standard reference range are considered abnormalities. Not every laboratory abnormality qualifies as an adverse event. A laboratory test result will be reported as an adverse event if it meets any of the following criteria: is accompanied by clinical symptoms; results in a change in study treatment or a medical intervention; or is clinically significant in the investigator's judgment.

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 2, 8, 15, 22, and 28 (1 cycle is 28 days); and, 30 Days after CR or CRp in Cycle 1, or if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	232		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Body Temperature Over Time

End point title	Body Temperature Over Time
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End point description:

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: C, Celsius degree				
arithmetic mean (standard deviation)				
Baseline	36.49 (± 0.59)	36.52 (± 0.51)		
Cycle 1 Day 8	0.07 (± 0.82)	0.32 (± 0.72)		
Cycle 1 Day 15	0.30 (± 0.91)	0.46 (± 0.92)		
Cycle 1 Day 22	0.22 (± 0.74)	0.36 (± 0.86)		
Cycle 1 Day 28	0.06 (± 0.65)	0.23 (± 0.87)		
Cycle 1 Day 29-42	0.08 (± 0.69)	0.00 (± 0.71)		
Cycle 1 Day 43-56	-0.02 (± 0.53)	0.07 (± 0.80)		
Cycle 2 Day 1	0.11 (± 0.60)	-0.10 (± 0.47)		
Cycle 2 Day 8	-0.08 (± 0.51)	0.07 (± 0.56)		
Cycle 2 Day 15	0.17 (± 0.76)	0.34 (± 0.83)		
Cycle 2 Day 22	0.04 (± 0.72)	0.10 (± 0.59)		
Cycle 2 Day 28	-0.22 (± 0.65)	0.04 (± 0.62)		
Cycle 2 Day 29-56	-0.06 (± 0.36)	-0.09 (± 0.55)		
Cycle 3 Day 1	-0.25 (± 0.54)	-0.19 (± 0.51)		
Cycle 3 Day 8	0.10 (± 0.60)	-0.04 (± 0.59)		
Cycle 3 Day 15	-0.09 (± 0.76)	0.29 (± 0.65)		
Cycle 3 Day 22	-0.07 (± 0.64)	0.04 (± 0.49)		
Cycle 3 Day 28	-0.26 (± 0.63)	-0.15 (± 0.52)		
Cycle 3 Day 29-56	0.27 (± 0.47)	-0.25 (± 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure Over Time

End point title	Systolic Blood Pressure Over Time
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End point description:

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline	120.6 (± 17.2)	122.1 (± 16.2)		
Cycle 1 Day 8	-3.7 (± 20.0)	-6.9 (± 18.6)		
Cycle 1 Day 15	-2.8 (± 19.2)	-0.1 (± 18.7)		
Cycle 1 Day 22	0.7 (± 20.3)	-1.5 (± 19.6)		
Cycle 1 Day 28	1.2 (± 21.7)	-0.5 (± 17.6)		
Cycle 1 Day 29-42	4.4 (± 17.8)	3.4 (± 17.7)		
Cycle 1 Day 43-56	9.8 (± 17.4)	3.8 (± 20.9)		
Cycle 2 Day 1	6.9 (± 15.6)	0.6 (± 15.2)		
Cycle 2 Day 8	5.3 (± 18.6)	-5.1 (± 16.2)		
Cycle 2 Day 15	-1.7 (± 17.7)	-0.2 (± 19.6)		
Cycle 2 Day 22	5.5 (± 19.8)	2.5 (± 17.0)		
Cycle 2 Day 28	5.8 (± 22.2)	5.0 (± 17.9)		
Cycle 2 Day 29-56	-1.0 (± 18.2)	6.6 (± 16.3)		
Cycle 3 Day 1	11.2 (± 18.9)	2.3 (± 18.2)		
Cycle 3 Day 8	6.0 (± 23.5)	-1.7 (± 13.4)		
Cycle 3 Day 15	3.3 (± 22.5)	0.2 (± 21.7)		
Cycle 3 Day 22	13.9 (± 22.8)	-1.1 (± 17.7)		
Cycle 3 Day 28	5.3 (± 23.0)	7.1 (± 18.0)		
Cycle 3 Day 29-56	27.7 (± 28.3)	5.1 (± 18.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Blood Pressure Over Time

End point title	Diastolic Blood Pressure Over Time
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End point description:

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline	70.2 (± 9.9)	71.5 (± 10.6)		
Cycle 1 Day 8	-1.5 (± 12.6)	-3.1 (± 12.7)		
Cycle 1 Day 15	-1.3 (± 11.3)	-1.3 (± 12.3)		
Cycle 1 Day 22	-0.5 (± 11.1)	-1.4 (± 12.9)		
Cycle 1 Day 28	1.0 (± 13.2)	-0.7 (± 12.6)		
Cycle 1 Day 29-42	3.8 (± 10.5)	0.6 (± 12.4)		
Cycle 1 Day 43-56	1.7 (± 11.8)	0.9 (± 13.5)		
Cycle 2 Day 1	1.1 (± 13.5)	0.9 (± 12.9)		
Cycle 2 Day 8	0.4 (± 13.5)	-2.2 (± 13.2)		
Cycle 2 Day 15	-0.6 (± 14.8)	-1.5 (± 15.4)		
Cycle 2 Day 22	3.1 (± 11.6)	1.7 (± 11.3)		
Cycle 2 Day 28	4.6 (± 13.9)	3.9 (± 12.7)		
Cycle 2 Day 29-56	-2.9 (± 12.4)	3.2 (± 15.8)		
Cycle 3 Day 1	5.0 (± 8.4)	0.3 (± 10.7)		
Cycle 3 Day 8	2.0 (± 15.5)	-3.3 (± 11.8)		
Cycle 3 Day 15	0.7 (± 11.1)	-1.8 (± 11.1)		
Cycle 3 Day 22	10.1 (± 14.3)	-2.1 (± 9.3)		
Cycle 3 Day 28	2.3 (± 14.7)	1.3 (± 10.1)		
Cycle 3 Day 29-56	5.0 (± 21.8)	2.6 (± 13.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pulse Rate Over Time

End point title	Pulse Rate Over Time
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End point description:

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Beats per Minute				
arithmetic mean (standard deviation)				
Baseline	78.4 (± 14.4)	79.2 (± 12.9)		
Cycle 1 Day 8	-4.3 (± 15.9)	3.4 (± 15.6)		
Cycle 1 Day 15	1.5 (± 16.0)	1.1 (± 17.2)		
Cycle 1 Day 22	0.2 (± 16.2)	4.1 (± 15.8)		
Cycle 1 Day 28	4.8 (± 15.8)	4.0 (± 16.8)		
Cycle 1 Day 29-42	2.0 (± 13.5)	5.1 (± 16.4)		
Cycle 1 Day 43-56	5.5 (± 18.6)	6.8 (± 14.0)		
Cycle 2 Day 1	2.0 (± 16.6)	-0.9 (± 12.0)		
Cycle 2 Day 8	-3.3 (± 18.6)	2.4 (± 14.9)		
Cycle 2 Day 15	-0.4 (± 12.7)	1.7 (± 18.4)		
Cycle 2 Day 22	2.3 (± 15.5)	0.3 (± 15.4)		
Cycle 2 Day 28	-2.3 (± 14.6)	1.2 (± 12.2)		
Cycle 2 Day 29-56	1.8 (± 11.8)	4.0 (± 14.8)		
Cycle 3 Day 1	0.4 (± 18.4)	1.0 (± 9.8)		
Cycle 3 Day 8	1.3 (± 21.5)	2.4 (± 16.2)		
Cycle 3 Day 15	2.5 (± 16.9)	1.9 (± 11.9)		
Cycle 3 Day 22	4.8 (± 19.7)	3.4 (± 13.6)		
Cycle 3 Day 28	0.4 (± 16.1)	0.9 (± 13.7)		
Cycle 3 Day 29-56	-5.0 (± 1.7)	5.2 (± 11.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory Rate Over Time

End point title	Respiratory Rate Over Time
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End point description:

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-3 Days 1, 8, 15, 22, and 28 (1 cycle is 28 days); and, if incomplete blood count recovery, Cycle 1 Days 29-42, Days 43-56, Cycles 2 and 3 Days 29-56 (max delay between cycles is 56 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Breaths per Minute				
arithmetic mean (standard deviation)				
Baseline	16.3 (± 2.7)	16.6 (± 2.7)		
Cycle 1 Day 8	-0.1 (± 2.7)	0.0 (± 2.8)		
Cycle 1 Day 15	0.7 (± 2.9)	0.4 (± 2.8)		
Cycle 1 Day 22	0.6 (± 3.2)	0.7 (± 4.1)		
Cycle 1 Day 28	0.4 (± 2.9)	0.6 (± 2.9)		
Cycle 1 Day 29-42	0.7 (± 2.1)	0.5 (± 2.7)		
Cycle 1 Day 43-56	0.3 (± 1.0)	0.0 (± 2.9)		
Cycle 2 Day 1	-0.3 (± 2.8)	-0.2 (± 3.2)		
Cycle 2 Day 8	-0.2 (± 2.9)	0.1 (± 3.3)		
Cycle 2 Day 15	0.5 (± 2.4)	0.0 (± 2.5)		
Cycle 2 Day 22	0.8 (± 2.3)	0.4 (± 1.4)		
Cycle 2 Day 28	-0.3 (± 2.3)	0.5 (± 3.5)		
Cycle 2 Day 29-56	0.2 (± 1.8)	0.3 (± 2.5)		
Cycle 3 Day 1	1.1 (± 2.5)	0.2 (± 2.1)		
Cycle 3 Day 8	0.2 (± 2.5)	-1.0 (± 3.1)		
Cycle 3 Day 15	1.5 (± 3.6)	0.9 (± 2.2)		
Cycle 3 Day 22	1.1 (± 2.7)	0.8 (± 1.6)		
Cycle 3 Day 28	0.3 (± 1.2)	0.8 (± 1.8)		
Cycle 3 Day 29-56	0.7 (± 4.6)	0.1 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Heart Rate, as Measured by Electrocardiogram

End point title	Change from Baseline in Heart Rate, as Measured by Electrocardiogram
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Days 1, 2, and 5 of Cycle 1, Days 1, 2 of Cycles 2 and 3 (1 cycle is 28 days), Treatment Discontinuation Visit (28 days after last dose of study drug)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Beats per Minute				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Electrocardiogram Parameters: PQ, PR, RR, QRS, QT and QTcF Intervals

End point title	Change from Baseline in Electrocardiogram Parameters: PQ, PR, RR, QRS, QT and QTcF Intervals
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Days 1, 2, and 5 of Cycle 1, Days 1, 2 of Cycles 2 and 3 (1 cycle is 28 days), Treatment Discontinuation Visit (28 days after last dose of study drug)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Millisecond (msec)				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Duration of Study Treatment

End point title	Total Duration of Study Treatment
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End point description:

End point type	Secondary
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End point timeframe:

Up to 3 cycles (1 cycle is 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Days				
arithmetic mean (standard deviation)	17.6 (± 28.25)	16.5 (± 28.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment Cycles Started

End point title	Number of Treatment Cycles Started
End point description:	
End point type	Secondary
End point timeframe:	
Up to 3 cycles (1 cycle is 28 days)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Numbers				
arithmetic mean (standard deviation)	1.3 (± 0.63)	1.2 (± 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Dose of Idasanutlin and Cytarabine

End point title	Cumulative Dose of Idasanutlin and Cytarabine
End point description:	
End point type	Secondary
End point timeframe:	
Up to 3 cycles (1 cycle is 28 days)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Milligram (mg) and Gram (g)				
arithmetic mean (standard deviation)				
Idasanutlin/Placebo cumulative dose (mg)	0 (± 0)	3340.1 (± 896.35)		
Cytarabine cumulative dose (g)	11.5 (± 5.85)	11.2 (± 5.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Idasanutlin

End point title	Apparent Clearance (CL/F) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 hour [Hr]), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vd/F) of Idasanutlin

End point title	Apparent Volume of Distribution (Vd/F) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration Observed (C_{max}) of Idasanutlin

End point title	Maximum Concentration Observed (C _{max}) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-State Concentration (C_{trough}) of Idasanutlin

End point title	Steady-State Concentration (C _{trough}) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC) During One Dosing Interval (AUCtau) of Idasanutlin

End point title	Area Under the Concentration-Time Curve (AUC) During One Dosing Interval (AUCtau) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC from Time Zero to 24 Hours Post Dose (AUC0-24) of Idasanutlin

End point title	AUC from Time Zero to 24 Hours Post Dose (AUC0-24) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life (t 1/2) of Idasanutlin

End point title	Half-Life (t 1/2) of Idasanutlin
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Predose (0 Hr), end of 1-3 Hr cytarabine infusion, 6 Hr postdose on Days 1, 5; Predose (0 Hr) on Day 2; at Days 8, 10; Cycle 2, 3: predose (0 Hr) on Days 2, 5 (predose/postdose: relative to idasanutlin morning dose; cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Clearance (CL) of Cytarabine

End point title	Total Clearance (CL) of Cytarabine
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Number	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vd) of Cytarabine

End point title	Volume of Distribution (Vd) of Cytarabine
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End point description:

End point type	Secondary
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End point timeframe:

Cycle 1: Within 2 Hr pre-cytarabine dose, end of 1-3 Hr cytarabine infusion, 6 Hr post idasanutlin morning dose on Days 1, 5; Within 2 Hr pre-cytarabine dose on Day 2; Cycle 2, 3: Within 2 Hr pre-cytarabine dose on Day 2 (Cycle length= 28 days)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	292		
Units: Milliliter				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Score

End point title	Change from Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Score
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End point description:

Due to the study termination, no data derived

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Score on a Scale				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire Score

End point title	Change from Baseline in EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire Score
End point description: Due to the study termination, no result data derived.	
End point type	Secondary
End point timeframe: Cycle 1 Day 1 (Baseline), Days 8, 15, 28 of Cycle 1, Days 1, 8, 15, 28 of Cycles 2, 3, 28 days after last dose (last dose on Cycle 3 Day 5), thereafter every 3 months until relapse (maximum up to 3.5 years)	

End point values	Placebo plus Cytarabine	Idasanutlin plus Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	232		
Units: Score on a Scale				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 5.5 years. The study was pre-maturely terminated, therefore did not reach the planned end of study.

Adverse event reporting additional description:

Reported: Safety Population. During the Safety Follow-up Period, non-Serious Adverse Events occurred at the 5% frequency threshold.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo-Cytarabine
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Reporting group description:

Participants will receive induction therapy idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin matching placebo and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or CRi, up to 28 additional days are allowed for blood count recovery, if needed.

Reporting group title	Idasanutlin-Cytarabine
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Reporting group description:

Participants will receive induction therapy idasanutlin and cytarabine for 5 days followed by 23 days of rest in Cycle 1 (treatment cycle length=28 days). Responding participants may continue with consolidation therapy for a maximum of 2 additional cycles including idasanutlin and cytarabine for 5 days followed by 23 days of rest in each cycle (treatment cycle length=28 days). After each cycle, for participants achieving CRp or complete remission with incomplete blood count recovery (CRi), up to 28 additional days are allowed for blood count recovery, if needed

Serious adverse events	Placebo-Cytarabine	Idasanutlin-Cytarabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 149 (48.32%)	173 / 292 (59.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 149 (0.00%)	5 / 292 (1.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 149 (0.67%)	6 / 292 (2.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site extravasation			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (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	2 / 149 (1.34%)	6 / 292 (2.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 149 (0.67%)	6 / 292 (2.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in intestine			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	1 / 149 (0.67%)	4 / 292 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 149 (0.67%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (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	1 / 149 (0.67%)	0 / 292 (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 / 149 (1.34%)	4 / 292 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Anaphylactic transfusion reaction			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bundle branch block right			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	2 / 149 (1.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 149 (1.34%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial mass			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Cytopenia			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	13 / 149 (8.72%)	28 / 292 (9.59%)	
occurrences causally related to treatment / all	0 / 16	0 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 149 (0.00%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 149 (1.34%)	4 / 292 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 149 (0.67%)	8 / 292 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue haematoma			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 149 (0.67%)	6 / 292 (2.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular icterus			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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			
Erythema			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 149 (0.67%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 149 (0.67%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 149 (0.00%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
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			
Back pain			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspergillus infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 149 (0.67%)	4 / 292 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 149 (0.67%)	2 / 292 (0.68%)	
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	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 149 (0.67%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 149 (0.67%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fusobacterium infection			

subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	2 / 149 (1.34%)	5 / 292 (1.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 149 (8.72%)	21 / 292 (7.19%)	
occurrences causally related to treatment / all	0 / 13	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 149 (5.37%)	34 / 292 (11.64%)	
occurrences causally related to treatment / all	0 / 8	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	8 / 149 (5.37%)	11 / 292 (3.77%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 149 (0.67%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginitis			

subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 149 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 149 (0.67%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo-Cytarabine	Idasanutlin-Cytarabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 149 (98.66%)	290 / 292 (99.32%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 149 (8.05%)	26 / 292 (8.90%)	
occurrences (all)	12	34	
Hypotension			
subjects affected / exposed	16 / 149 (10.74%)	44 / 292 (15.07%)	
occurrences (all)	16	53	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	19 / 149 (12.75%)	56 / 292 (19.18%)	
occurrences (all)	24	70	
Chest pain			
subjects affected / exposed	9 / 149 (6.04%)	19 / 292 (6.51%)	
occurrences (all)	9	25	
Fatigue			
subjects affected / exposed	13 / 149 (8.72%)	28 / 292 (9.59%)	
occurrences (all)	15	30	
Mucosal inflammation			
subjects affected / exposed	10 / 149 (6.71%)	46 / 292 (15.75%)	
occurrences (all)	11	50	
Oedema			
subjects affected / exposed	5 / 149 (3.36%)	22 / 292 (7.53%)	
occurrences (all)	6	24	
Oedema peripheral			
subjects affected / exposed	26 / 149 (17.45%)	65 / 292 (22.26%)	
occurrences (all)	34	88	
Pyrexia			
subjects affected / exposed	49 / 149 (32.89%)	108 / 292 (36.99%)	
occurrences (all)	67	174	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 149 (8.05%)	40 / 292 (13.70%)	
occurrences (all)	13	45	
Dyspnoea			
subjects affected / exposed	7 / 149 (4.70%)	28 / 292 (9.59%)	
occurrences (all)	8	34	
Epistaxis			
subjects affected / exposed	26 / 149 (17.45%)	29 / 292 (9.93%)	
occurrences (all)	37	39	
Hiccups			
subjects affected / exposed	6 / 149 (4.03%)	15 / 292 (5.14%)	
occurrences (all)	6	17	
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	24 / 149 (16.11%) 26	24 / 292 (8.22%) 24	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	12 / 149 (8.05%) 12	15 / 292 (5.14%) 20	
Blood creatinine increased subjects affected / exposed occurrences (all)	9 / 149 (6.04%) 10	10 / 292 (3.42%) 12	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	9 / 149 (6.04%) 9	15 / 292 (5.14%) 16	
Weight increased subjects affected / exposed occurrences (all)	6 / 149 (4.03%) 7	16 / 292 (5.48%) 16	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 11	14 / 292 (4.79%) 21	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	6 / 149 (4.03%) 8	15 / 292 (5.14%) 20	
Tachycardia subjects affected / exposed occurrences (all)	3 / 149 (2.01%) 3	16 / 292 (5.48%) 17	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	5 / 149 (3.36%) 6	17 / 292 (5.82%) 19	
Headache subjects affected / exposed occurrences (all)	33 / 149 (22.15%) 39	49 / 292 (16.78%) 67	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	49 / 149 (32.89%)	79 / 292 (27.05%)	
occurrences (all)	71	131	
Febrile neutropenia			
subjects affected / exposed	63 / 149 (42.28%)	136 / 292 (46.58%)	
occurrences (all)	79	178	
Neutropenia			
subjects affected / exposed	13 / 149 (8.72%)	35 / 292 (11.99%)	
occurrences (all)	19	36	
Thrombocytopenia			
subjects affected / exposed	69 / 149 (46.31%)	120 / 292 (41.10%)	
occurrences (all)	104	175	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 149 (12.08%)	54 / 292 (18.49%)	
occurrences (all)	19	68	
Abdominal pain upper			
subjects affected / exposed	6 / 149 (4.03%)	24 / 292 (8.22%)	
occurrences (all)	6	28	
Constipation			
subjects affected / exposed	76 / 149 (51.01%)	53 / 292 (18.15%)	
occurrences (all)	99	76	
Diarrhoea			
subjects affected / exposed	49 / 149 (32.89%)	251 / 292 (85.96%)	
occurrences (all)	65	404	
Dry mouth			
subjects affected / exposed	3 / 149 (2.01%)	15 / 292 (5.14%)	
occurrences (all)	3	15	
Dyspepsia			
subjects affected / exposed	10 / 149 (6.71%)	15 / 292 (5.14%)	
occurrences (all)	12	19	
Haemorrhoids			
subjects affected / exposed	8 / 149 (5.37%)	18 / 292 (6.16%)	
occurrences (all)	8	22	
Nausea			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>47 / 149 (31.54%)</p> <p>56</p> <p>6 / 149 (4.03%)</p> <p>8</p> <p>27 / 149 (18.12%)</p> <p>30</p>	<p>153 / 292 (52.40%)</p> <p>227</p> <p>24 / 292 (8.22%)</p> <p>24</p> <p>89 / 292 (30.48%)</p> <p>145</p>	
<p>Hepatobiliary disorders</p> <p>Hyperbilirubinaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 149 (8.05%)</p> <p>15</p>	<p>52 / 292 (17.81%)</p> <p>56</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Petechiae</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash maculo-papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 149 (5.37%)</p> <p>9</p> <p>7 / 149 (4.70%)</p> <p>8</p> <p>24 / 149 (16.11%)</p> <p>32</p> <p>8 / 149 (5.37%)</p> <p>9</p>	<p>38 / 292 (13.01%)</p> <p>44</p> <p>17 / 292 (5.82%)</p> <p>21</p> <p>55 / 292 (18.84%)</p> <p>62</p> <p>14 / 292 (4.79%)</p> <p>15</p>	
<p>Renal and urinary disorders</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 149 (1.34%)</p> <p>2</p>	<p>17 / 292 (5.82%)</p> <p>26</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 149 (8.72%)</p> <p>15</p> <p>9 / 149 (6.04%)</p> <p>10</p>	<p>27 / 292 (9.25%)</p> <p>28</p> <p>3 / 292 (1.03%)</p> <p>3</p>	

Infections and infestations Bacteraemia subjects affected / exposed occurrences (all)	2 / 149 (1.34%) 2	15 / 292 (5.14%) 15	
Device related infection subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8	16 / 292 (5.48%) 16	
Oral herpes subjects affected / exposed occurrences (all)	11 / 149 (7.38%) 11	22 / 292 (7.53%) 23	
Pneumonia subjects affected / exposed occurrences (all)	7 / 149 (4.70%) 7	18 / 292 (6.16%) 18	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	14 / 149 (9.40%) 14	54 / 292 (18.49%) 58	
Hyperglycaemia subjects affected / exposed occurrences (all)	9 / 149 (6.04%) 9	17 / 292 (5.82%) 23	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	4 / 149 (2.68%) 4	20 / 292 (6.85%) 23	
Hypocalcaemia subjects affected / exposed occurrences (all)	7 / 149 (4.70%) 9	35 / 292 (11.99%) 42	
Hypokalaemia subjects affected / exposed occurrences (all)	48 / 149 (32.21%) 65	129 / 292 (44.18%) 207	
Hypomagnesaemia subjects affected / exposed occurrences (all)	12 / 149 (8.05%) 12	51 / 292 (17.47%) 72	
Hypophosphataemia subjects affected / exposed occurrences (all)	11 / 149 (7.38%) 15	30 / 292 (10.27%) 43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported