



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 |
|-----------------------|---------|

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 |
|------------------------------|-----|

| | |
|------------------|-------------------------|
| Arm title | Placebo plus Cytarabine |
|------------------|-------------------------|

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 |
|------------------|-----------------------------|

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 |
|-----------------|---|

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) | 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

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

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) |
|-----------------|--|

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 | 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 |
|-----------------|---|

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 | 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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|----------------------------|

End point description:

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

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 |
|-----------------|-----------------------------------|

End point description:

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

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 |
|-----------------|------------------------------------|

End point description:

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

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 |
|-----------------|----------------------|

End point description:

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

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 |
|-----------------|----------------------------|

End point description:

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

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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|-----------------------------------|

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: 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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|---|

End point description:

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

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 (Cmax) of Idasanutlin

| | |
|-----------------|--|
| End point title | Maximum Concentration Observed (Cmax) of Idasanutlin |
|-----------------|--|

End point description:

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

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 (Ctrough) of Idasanutlin

| | |
|-----------------|---|
| End point title | Steady-State Concentration (Ctrough) of Idasanutlin |
|-----------------|---|

End point description:

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

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 |
|-----------------|--|

End point description:

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

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 |
|-----------------|---|

End point description:

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

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 |
|-----------------|----------------------------------|

End point description:

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

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 |
|-----------------|------------------------------------|

End point description:

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

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 |
|-----------------|---|

End point description:

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

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 |
|-----------------|--|

End point description:

Due to the study termination, no 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

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 |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo-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-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

| 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 | | | |

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|--|-----------------|-----------------|--|
| 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 | |

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| 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 | |

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| 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 | |

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| 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 | |

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|---|-----------------|-----------------|--|
| 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 | | | |

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

| | | | |
|--|-------------------------|---------------------------|--|
| 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