# Clinical trial results:
# An Open-Label, Multi-Center, Single Arm Study to Evaluate the Safety and Tolerability of Intravenous Zanamivir in the Treatment of Hospitalized Adult, Adolescent and Pediatric Subjects with Confirmed Influenza Infection

## Summary

| | |
|---|---|
| EudraCT number | 2009-016035-35 |
| Trial protocol | FR ES DE GB Outside EU/EEA |
| Global end of trial date | 13 February 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 July 2016 |
| First version publication date | 10 July 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | NAI113678 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001318-PIP01-12 |
| 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 | 24 June 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 February 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and tolerability of IV zanamivir in the treatment of hospitalized adult, adolescent and pediatric subjects with influenza infection.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 November 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 32 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | France: 36 |
| Country: Number of subjects enrolled | Thailand: 12 |
| Country: Number of subjects enrolled | Australia: 9 |
| Country: Number of subjects enrolled | South Africa: 1 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | United States: 95 |
| Country: Number of subjects enrolled | Japan: 3 |
| Worldwide total number of subjects | 201 |
| EEA total number of subjects | 74 |

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 | 18 |

| | |
|---|---|
| months) | |
| Children (2-11 years) | 36 |
| Adolescents (12-17 years) | 17 |
| Adults (18-64 years) | 106 |
| From 65 to 84 years | 23 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Male or female participants who were >= 6 months of age, hospitalized with laboratory-confirmed influenza, and able to receive study drug within 7 days of influenza symptom onset were enrolled in the study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 6: Adults (18 years and older) |

Arm description:

Participants >=18 years of age received 600 milligrams (mg) zanamivir by intravenous (IV) infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

600 mg twice daily, adjusted for renal function

| | |
|---|---|
| **Arm title** | Cohort 1: Infants (6 months to <1 year of age) |

Arm description:

Participants 6 months to <1 year of age received 14 mg per kilogram (mg/kg) zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

14 mg/kg twice daily, adjusted for renal function

| | |
|---|---|
| **Arm title** | Cohort 2: Children (1 to <2 years of age) |

Arm description:

Participants 1 year to <2 years of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

14 mg/kg twice daily, adjusted for renal function

| | |
|---|---|
| **Arm title** | Cohort 3: Children (2 to <6 years of age) |

Arm description:

Participants 2 years to <6 years of age received 14 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

14 mg/kg twice daily, adjusted for renal function

| | |
|---|---|
| **Arm title** | Cohort 4: Children (6 to <13 years of age) |

Arm description:

Participants 6 years to <13 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

12 mg/kg (maximum dose of 600 mg) twice daily, adjusted for renal function

| | |
|---|---|
| **Arm title** | Cohort 5: Adolescents (13 to <18 years of age) |

Arm description:

Participants 13 to <18 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | zanamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

12 mg/kg (maximum dose of 600 mg) twice daily, adjusted for renal function

| **Number of subjects in period 1** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|
| Started | 130 | 7 | 11 |
| Completed | 107 | 7 | 9 |
| Not completed | 23 | 0 | 2 |
| Adverse event, serious fatal | 20 | - | 1 |
| Consent withdrawn by subject | 1 | - | - |
| Physician decision | 1 | - | - |
| Lost to follow-up | 1 | - | 1 |

| **Number of subjects in period 1** | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) |
|---|---|---|---|
| Started | 12 | 27 | 14 |
| Completed | 12 | 26 | 11 |
| Not completed | 0 | 1 | 3 |
| Adverse event, serious fatal | - | 1 | 3 |
| Consent withdrawn by subject | - | - | - |
| Physician decision | - | - | - |
| Lost to follow-up | - | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 6: Adults (18 years and older) |
| Reporting group description: | |
| Participants >=18 years of age received 600 milligrams (mg) zanamivir by intravenous (IV) infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |
| Reporting group title | Cohort 1: Infants (6 months to <1 year of age) |
| Reporting group description: | |
| Participants 6 months to <1 year of age received 14 mg per kilogram (mg/kg) zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |
| Reporting group title | Cohort 2: Children (1 to <2 years of age) |
| Reporting group description: | |
| Participants 1 year to <2 years of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |
| Reporting group title | Cohort 3: Children (2 to <6 years of age) |
| Reporting group description: | |
| Participants 2 years to <6 years of age received 14 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |
| Reporting group title | Cohort 4: Children (6 to <13 years of age) |
| Reporting group description: | |
| Participants 6 years to <13 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |
| Reporting group title | Cohort 5: Adolescents (13 to <18 years of age) |
| Reporting group description: | |
| Participants 13 to <18 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment. | |

| Reporting group values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|
| Number of subjects | 130 | 7 | 11 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 48.3 | 0.76 | 1.33 |
| standard deviation | ± 16.19 | ± 0.127 | ± 0.22 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 56 | 1 | 4 |
| Male | 74 | 6 | 7 |
| Race, Customized<br>Units: Subjects | | | |
| African American/African Heritage | 10 | 1 | 4 |

| | | | |
|---|---|---|---|
| American Indian or Alaska Native | 1 | 0 | 0 |
| Asian - East Asian Heritage | 4 | 0 | 0 |
| Asian - South East Asian Heritage | 10 | 0 | 0 |
| Asian - Japanese Heritage | 0 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White - Arabic/North African Heritage | 6 | 0 | 0 |
| White - White/Caucasian/European Heritage | 97 | 5 | 7 |
| Unknown | 2 | 0 | 0 |
| Mixed Race | 0 | 0 | 0 |

| **Reporting group values** | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) |
|---|---|---|---|
| Number of subjects | 12 | 27 | 14 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 3.74 | 8.67 | 15.36 |
| standard deviation | ± 1.201 | ± 1.861 | ± 1.151 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 9 | 6 |
| Male | 8 | 18 | 8 |
| Race, Customized | | | |
| Units: Subjects | | | |
| African American/African Heritage | 1 | 4 | 3 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian - East Asian Heritage | 0 | 0 | 0 |
| Asian - South East Asian Heritage | 0 | 0 | 0 |
| Asian - Japanese Heritage | 2 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| White - Arabic/North African Heritage | 1 | 1 | 0 |
| White - White/Caucasian/European Heritage | 7 | 18 | 11 |
| Unknown | 0 | 1 | 0 |
| Mixed Race | 1 | 2 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 201 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 80 | | |
| Male | 121 | | |
| Race, Customized<br>Units: Subjects | | | |
| African American/African Heritage | 23 | | |
| American Indian or Alaska Native | 1 | | |
| Asian - East Asian Heritage | 4 | | |
| Asian - South East Asian Heritage | 10 | | |
| Asian - Japanese Heritage | 3 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| White - Arabic/North African Heritage | 8 | | |
| White - White/Caucasian/European Heritage | 145 | | |
| Unknown | 3 | | |
| Mixed Race | 3 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 6: Adults (18 years and older) |

Reporting group description:

Participants >=18 years of age received 600 milligrams (mg) zanamivir by intravenous (IV) infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 1: Infants (6 months to <1 year of age) |

Reporting group description:

Participants 6 months to <1 year of age received 14 mg per kilogram (mg/kg) zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 2: Children (1 to <2 years of age) |

Reporting group description:

Participants 1 year to <2 years of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 3: Children (2 to <6 years of age) |

Reporting group description:

Participants 2 years to <6 years of age received 14 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 4: Children (6 to <13 years of age) |

Reporting group description:

Participants 6 years to <13 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 5: Adolescents (13 to <18 years of age) |

Reporting group description:

Participants 13 to <18 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Subject analysis set title | Cohort 6: Adults (18 years and older) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants >=18 years of age received 600 mg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Subject analysis set title | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 6 months to <18 years of age received 14 mg/kg zanamivir (participants from 6 months to <6 years of age) or 12 mg/kg zanamivir (participants from 6 years to <18 years of age) with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function for 5 days. Treatment could be extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Subject analysis set title | Cohort 6: Adults (18 years and older); zanamivir <=5 days |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants >=18 years of age received 600 mg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days.

| | |
|---|---|
| Subject analysis set title | Cohort 6: Adults (18 years and older); zanamivir >5 days |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants >=18 years of age received 600 mg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for >5 days and up to 10 days if viral shedding or clinical symptoms warranted further treatment.

| Subject analysis set title | Cohort 1: Infants (6 months to <1 year of age) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 6 months to <1 year of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| Subject analysis set title | Cohort 2: Children (1 to <2 years of age) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 1 year to <2 years of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| Subject analysis set title | Cohort 3: Children (2 to <6 years of age) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 2 years to <6 years of age received 14 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| Subject analysis set title | Cohort 4: Children (6 to <13 years of age) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 6 years to <13 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| Subject analysis set title | Cohort 5: Adolescents (13 to <18 years of age) |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Participants 13 to <18 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

## Primary: Number of participants with any adverse event (AE) considered to be related to study treatment

| End point title | Number of participants with any adverse event (AE) considered to be related to study treatment[1] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. All AEs were assesed by the Investigateor as related or not related to the study treatment.

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[2] | 71[3] | | |
| Units: Participants | 28 | 5 | | |

Notes:

[2] - Safety Population: participants who received >=1 dose of study medication.

[3] - Safety Population: participants who received >=1 dose of study medication.

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with any severe or Grade 3/4 AEs

| End point title | Number of participants with any severe or Grade 3/4 AEs[4] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. AEs that occured during the study were evaluated by the Investigator and graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) table for grading the severity of adult and pediatric AEs. Grade 3=severe; Grade 4=potentially life threatening.

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[5] | 71[6] | | |
| Units: Participants | 57 | 23 | | |

Notes:

[5] - Safety Population

[6] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with any severe or Grade 3/4 treatment-related AE

| End point title | Number of participants with any severe or Grade 3/4 treatment-related AE[7] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or

disease (new or exacerbated) temporally associated with the use of a medicinal product. AEs that occured during the study were evaluated by the Investigator and graded according to the DAIDS table for grading the severity of adult and pediatric AEs. Grade 3=severe; Grade 4=potentially life threatening. All AEs were assesed by the Investigator as related or not related to the study treatment.

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[8] | 71[9] | | |
| Units: Participants | 16 | 2 | | |

Notes:

[8] - Safety Population

[9] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants who permanently discontinued the study treatment due to an AE

| End point title | Number of participants who permanently discontinued the study treatment due to an AE[10] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

| End point type | Primary |
|---|---|

End point timeframe:

Up to 10 days

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[11] | 71[12] | | |
| Units: Participants | 17 | 2 | | |

Notes:

[11] - Safety Population

[12] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants who were permanently discontinued from the study due to an AE

| End point title | Number of participants who were permanently discontinued from the study due to an AE[13] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[14] | 71[15] | | |
| Units: Participants | 20 | 5 | | |

Notes:

[14] - Safety Population

[15] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with the indicated clinical chemistry values relative to the normal range at Baseline (Day 1) and Day 5

| End point title | Number of participants with the indicated clinical chemistry values relative to the normal range at Baseline (Day 1) and Day 5[16] |
|---|---|

End point description:

Blood samples for laboratory assessments were collected at Baseline (Day [D] 1), Days 3 and 5, and on post-treatment +2 days (if hospitalized) and post-treatment +23 days. Clinical chemistry parameters summarized here include alanine aminotransferase (ALT), direct bilirubin (DB), total bilirubin (TB), and creatinine. The number of participants with values that were high (H)/normal (N)/low (L) relative to the normal range at Baseline (D 1) and D 5 for the indicated clinical chemistry parameters are summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[17] | 71[18] | | |
| Units: Participants | | | | |
| D 1, H ALT, n=129, 71 | 48 | 21 | | |
| D 1, N ALT, n=129, 71 | 79 | 49 | | |
| D 1, L ALT, n=129, 71 | 1 | 1 | | |
| D 5, H ALT, n=102, 45 | 41 | 16 | | |
| D 5, N ALT, n=102, 45 | 60 | 27 | | |
| D 5, L ALT, n=102, 45 | 1 | 1 | | |
| D 1, H DB, n=83, 60 | 17 | 9 | | |
| D 1, N DB, n=83, 60 | 61 | 45 | | |
| D 1, L DB, n=83, 60 | 2 | 3 | | |
| D 5, H DB, n=70, 36 | 20 | 4 | | |
| D 5, N DB, n=70, 36 | 46 | 28 | | |
| D 5, L DB, n=70, 36 | 1 | 1 | | |
| D 1, H TB, n=128, 71 | 11 | 13 | | |
| D 1, N TB, n=128, 71 | 110 | 50 | | |
| D 1, L TB, n=128, 71 | 7 | 7 | | |
| D 5, H TB, n=102, 42 | 13 | 6 | | |
| D 5, N TB, n=102, 42 | 85 | 32 | | |
| D 5, L TB, n=102, 42 | 4 | 2 | | |
| D 1, H Creatinine, n=128, 71 | 27 | 6 | | |
| D 1, N Creatinine, n=128, 71 | 50 | 56 | | |
| D 1, L Creatinine, n=128, 71 | 51 | 9 | | |
| D 5, H Creatinine, n=111, 46 | 31 | 7 | | |
| D 5, N Creatinine, n=111, 46 | 46 | 34 | | |
| D 5, L Creatinine, n=111, 46 | 34 | 5 | | |

Notes:

[17] - Safety Population

[18] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with the indicated hematology values relative to the normal range at Baseline (Day 1) and Day 5

| End point title | Number of participants with the indicated hematology values relative to the normal range at Baseline (Day 1) and Day 5[19] |
|---|---|

End point description:

Blood samples for laboratory assessments were collected at Baseline (Day [D] 1), Days 3 and 5, and on post-treatment +2 days (if hospitalized) and post-treatment +23 days. Hematology parameters summarized here include hemoglobin, total neutrophils (TN), and white blood cell (WBC) count. The number of participants with values that were high (H)/normal (N)/low (L) relative to the normal range at Baseline (D 1) and D 5 for the indicated hematology parameters are summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[20] | 71[21] | | |
| Units: Participants | | | | |
| D 1, H Hemoglobin, n=130, 71 | 0 | 1 | | |
| D 1, N Hemoglobin, n=130, 71 | 48 | 30 | | |
| D 1, L Hemoglobin, n=130, 71 | 82 | 40 | | |
| D 5, H Hemoglobin, n=114, 47 | 1 | 0 | | |
| D 5, N Hemoglobin, n=114, 47 | 25 | 16 | | |
| D 5, L Hemoglobin, n=114, 47 | 88 | 31 | | |
| D 1, H TN, n=123, 70 | 51 | 34 | | |
| D 1, N TN, n=123, 70 | 59 | 29 | | |
| D 1, L TN, n=123, 70 | 13 | 7 | | |
| D 5, H TN, n=106, 45 | 49 | 20 | | |
| D 5, N TN, n=106, 45 | 49 | 18 | | |
| D 5, L TN, n=106, 45 | 8 | 7 | | |
| D 1, H WBC Count, n=130, 71 | 29 | 9 | | |
| D 1, N WBC Count, n=130, 71 | 71 | 42 | | |
| D 1, L WBC Count, n=130, 71 | 30 | 20 | | |
| D 5, H WBC Count, n=114, 47 | 50 | 12 | | |
| D 5, N WBC Count, n=114, 47 | 49 | 30 | | |
| D 5, L WBC Count, n=114, 47 | 15 | 5 | | |

Notes:

[20] - Safety Population

[21] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with the indicated treatment-emergent (TE) Grade 3/4 clinical chemistry toxicities

| End point title | Number of participants with the indicated treatment-emergent (TE) Grade 3/4 clinical chemistry toxicities[22] |
|---|---|

End point description:

A toxicity was considered to be TE if it was greater than the Baseline grade, and if it had developed or increased post-Baseline in intensity (and prior to the last dose of investigational product). Clinical chemistry parameters summarized here include ALT, TB, and creatinine. Per the DAIDS table for grading the severity of adult and pediatric AEs, Grade 3=severe and Grade 4=potentially life threatening. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[23] | 71[24] | | |
| Units: Participants | | | | |
| ALT, Grade 3, n=128, 68 | 10 | 1 | | |
| ALT, Grade 4, n=128, 68 | 5 | 0 | | |
| TB, Grade 3, n=127, 68 | 3 | 1 | | |
| TB, Grade 4, n=127, 68 | 3 | 4 | | |
| Creatinine, Grade 3, n=129, 68 | 6 | 3 | | |
| Creatinine, Grade 4, n=129, 68 | 5 | 2 | | |

Notes:

[23] - Safety Population

[24] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with the indicated treatment-emergent (TE) Grade 3/4 hematology toxicities

| End point title | Number of participants with the indicated treatment-emergent (TE) Grade 3/4 hematology toxicities[25] |
|---|---|

End point description:

A toxicity was considered to be TE if it was greater than the Baseline grade, and if it had developed or increased post-Baseline in intensity (and prior to the last dose of investigational product). The hematology parameters summarized here include hemoglobin, TN, and WBC count. Per the DAIDS table for grading the severity of adult and pediatric AEs, Grade 3=severe and Grade 4=potentially life threatening. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Up to post-treatment (PT) + 23 days

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | Cohorts 1-5: Pediatrics/adolescents (6 months to <18 years) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 130[26] | 71[27] | | |
| Units: Participants | | | | |
| Hemoglobin, Grade 3, n=129, 68 | 40 | 12 | | |
| Hemoglobin, Grade 4, n=129, 68 | 9 | 2 | | |
| TN, Grade 3, n=122, 66 | 0 | 3 | | |

| | | | | |
|---|---|---|---|---|
| TN, Grade 4, n=122, 66 | 1 | 2 | | |
| WBC count, Grade 3, n=129, 68 | 2 | 1 | | |
| WBC count, Grade 4, n=129, 68 | 2 | 0 | | |

Notes:

[26] - Safety Population

[27] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Median heart rate at Baseline (Day 1) and Day 5

| End point title | Median heart rate at Baseline (Day 1) and Day 5[28] |
|---|---|

End point description:

Heart rate was measured at Baseline (Day 1); Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. Heart rate was assessed once daily during inpatient or outpatient follow-up visits. Heart rate values at Baseline (Day 1) and Day 5 are summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[29] | 43[30] | 7[31] | 11[32] |
| Units: Beats per minute (bpm) | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 93 (58 to 143) | 95 (50 to 140) | 119 (95 to 156) | 144 (121 to 195) |
| Day 5, n=73, 42, 7, 6, 9, 15, 10 | 87 (50 to 140) | 93.5 (60 to 134) | 127 (93 to 152) | 122.5 (98 to 146) |

Notes:

[29] - Safety Population

[30] - Safety Population

[31] - Safety Population

[32] - Safety Population

| End point values | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[33] | 27[34] | 14[35] | |
| Units: Beats per minute (bpm) | | | | |
| median (full range (min-max)) | | | | |

| | | | | |
|---|---|---|---|---|
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 115.5 (92 to 160) | 112 (59 to 185) | 99 (74 to 134) | |
| Day 5, n=73, 42, 7, 6, 9, 15, 10 | 112 (85 to 123) | 102 (67 to 128) | 79.5 (58 to 113) | |

Notes:

[33] - Safety Population

[34] - Safety Population

[35] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Median systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Baseline (Day 1) and Day 5

| End point title | Median systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Baseline (Day 1) and Day 5[36] |
|---|---|

End point description:

SBP and DBP were measured at Baseline (Day 1), Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. SBP and DBP were assessed once daily during inpatient or outpatient follow-up visits. SBP and DBP values at Baseline (Day 1) and Day 5 are summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[37] | 43[38] | 7[39] | 11[40] |
| Units: Millimeters of mercury (mmHg) | | | | |
| median (full range (min-max)) | | | | |
| SBP, Day 1, n=87, 43, 7, 11, 12, 27, 14 | 126 (70 to 175) | 118 (80 to 180) | 102 (83 to 116) | 100 (77 to 144) |
| SBP, Day 5, n=73, 43, 7, 5, 9, 15, 10 | 128 (51 to 182) | 132 (88 to 220) | 103 (86 to 130) | 98 (87 to 120) |
| DBP, Day 1, n=87, 43, 7, 11, 12, 27, 14 | 68 (32 to 96) | 63 (40 to 97) | 53 (42 to 64) | 60 (39 to 78) |
| DBP, Day 5, n=73, 43, 7, 5, 9, 15, 10 | 70 (29 to 106) | 66 (50 to 100) | 60 (42 to 83) | 60 (45 to 73) |

Notes:

[37] - Safety Population

[38] - Safety Population

[39] - Safety Population

[40] - Safety Population

| End point values | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|

| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
|---|---|---|---|---|
| Number of subjects analysed | 12[41] | 27[42] | 14[43] | |
| Units: Millimeters of mercury (mmHg) | | | | |
| median (full range (min-max)) | | | | |
| SBP, Day 1, n=87, 43, 7, 11, 12, 27, 14 | 105.5 (82 to 124) | 108 (70 to 136) | 107 (95 to 137) | |
| SBP, Day 5, n=73, 43, 7, 5, 9, 15, 10 | 117 (83 to 140) | 110 (96 to 135) | 108.5 (95 to 121) | |
| DBP, Day 1, n=87, 43, 7, 11, 12, 27, 14 | 58 (37 to 86) | 57 (41 to 82) | 62 (36 to 74) | |
| DBP, Day 5, n=73, 43, 7, 5, 9, 15, 10 | 67 (43 to 89) | 68 (47 to 80) | 54.5 (35 to 72) | |

Notes:

[41] - Safety Population

[42] - Safety Population

[43] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Median oxygen saturation measured via transcutaneous oximetry (TCPO2) at Baseline (Day 1) and Day 5

| End point title | Median oxygen saturation measured via transcutaneous oximetry (TCPO2) at Baseline (Day 1) and Day 5[44] |
|---|---|

End point description:

TCPO2 is a noninvasive test that directly measures the oxygen level of tissue beneath the skin. Because oxygen is carried to tissues by blood flow in the arteries, TCPO2 is an indirect measure of blood flow. The percent (%) oxygen saturation was measured at Baseline (Day 1), Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; and post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. Oxygen saturation was assessed once daily during inpatient follow-up visits. The median oxygen saturation values at Baseline (Day 1) and Day 5 are summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[44] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[45] | 43[46] | 7[47] | 11[48] |
| Units: Percentage of oxygen level in blood | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 97 (82 to 100) | 96 (70 to 100) | 98 (76 to 100) | 100 (93 to 100) |
| Day 5, n=70, 43, 7, 6, 9, 15, 9 | 97 (73 to 100) | 96 (45 to 100) | 100 (96 to 100) | 95.5 (85 to 100) |

Notes:

[45] - Safety Population

[46] - Safety Population

[47] - Safety Population

[48] - Safety Population

| End point values | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[49] | 27[50] | 14[51] | |
| Units: Percentage of oxygen level in blood | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 98 (93 to 100) | 98 (91 to 100) | 97.5 (94 to 100) | |
| Day 5, n=70, 43, 7, 6, 9, 15, 9 | 97 (95 to 100) | 97 (50 to 100) | 96 (70 to 100) | |

Notes:

[49] - Safety Population

[50] - Safety Population

[51] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Median respiration rate at Baseline (Day 1) and Day 5

| End point title | Median respiration rate at Baseline (Day 1) and Day 5[52] |
|---|---|

End point description:

Respiration rate was measured at Baseline (Day 1), Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; and post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. Respiration rate was assessed once daily during inpatient or outpatient follow-up visits. The median respiration rate at Baseline (Day 1) and Day 5 is summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[53] | 43[54] | 7[55] | 11[56] |
| Units: Breaths per minute | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 23 (6 to 47) | 22 (10 to 40) | 32 (28 to 46) | 34 (20 to 40) |
| Day 5, n=67, 42, 7, 6, 9, 15, 10 | 20 (10 to 42) | 23.5 (8 to 41) | 40 (28 to 48) | 31 (10 to 50) |

Notes:

[53] - Safety Population

[54] - Safety Population

[55] - Safety Population

[56] - Safety Population

| End point values | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[57] | 27[58] | 14[59] | |
| Units: Breaths per minute | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 29.5 (22 to 66) | 20 (4 to 49) | 21 (0 to 98) | |
| Day 5, n=67, 42, 7, 6, 9, 15, 10 | 30 (22 to 44) | 23 (8 to 48) | 19 (0 to 28) | |

Notes:

[57] - Safety Population

[58] - Safety Population

[59] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Median body temperature at Baseline (Day 1) and Day 5

| End point title | Median body temperature at Baseline (Day 1) and Day 5[60] |
|---|---|

End point description:

Body temperature was recorded at Baseline (Day 1), Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; and post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. Body temperature was recorded once daily during inpatient or outpatient follow-up visits. Median body temperature at Baseline (Day 1) and Day 5 is summarized. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[60] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[61] | 43[62] | 7[63] | 11[64] |
| Units: Degrees centigrade | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 37.3 (33.4 to 40.1) | 37.3 (35.3 to 40.4) | 36.8 (36 to 40) | 37.3 (34 to 40) |
| Day 5, n=73, 42, 7, 6, 9, 15, 10 | 37 (35.3 to 38.8) | 37.15 (34.5 to 39.8) | 37 (36 to 38) | 36.8 (36 to 38) |

Notes:

[61] - Safety Population

[62] - Safety Population

[63] - Safety Population

[64] - Safety Population

| End point values | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[65] | 27[66] | 14[67] | |
| Units: Degrees centigrade | | | | |
| median (full range (min-max)) | | | | |
| Day 1, n=87, 43, 7, 11, 12, 27, 14 | 37.5 (36 to 39) | 37.3 (33 to 39) | 37.5 (36 to 40) | |
| Day 5, n=73, 42, 7, 6, 9, 15, 10 | 37.3 (37 to 38) | 37.1 (37 to 39) | 37.1 (37 to 39) | |

Notes:

[65] - Safety Population

[66] - Safety Population

[67] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants assessed as normal/abnormal (clinically significant [CS] and not clinically significant [NCS]) for 12-lead electrocardiogram (ECG) at Baseline (Day 1)

| End point title | Number of participants assessed as normal/abnormal (clinically significant [CS] and not clinically significant [NCS]) for 12-lead electrocardiogram (ECG) at Baseline (Day 1)[68] |
|---|---|

End point description:

The number of participants with an ECG status of normal and abnormal CS or NCS, as determined by the Investigator, is reported. Normal=all ECG parameters within the accepted normal ranges. Abnormal=ECG findings outside of normal ranges. CS=ECG with a CS abnormality that meets exclusion criteria. NCS=ECG with an abnormality that is not CS nor meets exclusion criteria, per Investigator, based on reasonable standards of clinical judgment. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X in the category titles).

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1)

Notes:

[68] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[69] | 7[70] | 11[71] | 12[72] |
| Units: Participants | | | | |
| Normal, n=128, 7, 10, 12, 25, 13 | 68 | 5 | 7 | 8 |
| Abnormal NCS, n=128, 7, 10, 12, 25, 13 | 57 | 2 | 2 | 4 |
| Abnormal CS, n=128, 7, 10, 12, 25, 13 | 7 | 0 | 1 | 0 |

Notes:

[69] - Safety Population

[70] - Safety Population

[71] - Safety Population

[72] - Safety Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[73] | 14[74] | | |
| Units: Participants | | | | |
| Normal, n=128, 7, 10, 12, 25, 13 | 20 | 8 | | |
| Abnormal NCS, n=128, 7, 10, 12, 25, 13 | 5 | 5 | | |
| Abnormal CS, n=128, 7, 10, 12, 25, 13 | 0 | 0 | | |

Notes:

[73] - Safety Population

[74] - Safety Population

### Statistical analyses

No statistical analyses for this end point

## Primary: Median corrected QT interval (QTc) for heart rate by Fridericia's formula (QTcF) and Bazett's formula (QTcB) at Baseline (Day 1) and Day 5

| End point title | Median corrected QT interval (QTc) for heart rate by Fridericia's formula (QTcF) and Bazett's formula (QTcB) at Baseline (Day 1) and Day 5[75] |
|---|---|

End point description:

Twelve-lead ECGs were recorded for the parameters of QTcF and QTcB. The first set of pre-dose ECG values at Baseline (Day 1) and the pre-dose ECG values at Day 5 are presented. Baseline is defined as the last pre-treatment value collected. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X, X in the category titles). "99999" indicates that data are not available/analysis was not performed.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Day 1) and Day 5

Notes:

[75] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not conducted for this endpoint; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older); zanamivir <=5 days | Cohort 6: Adults (18 years and older); zanamivir >5 days | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87[76] | 43[77] | 7[78] | 11[79] |
| Units: Milliseconds | | | | |
| median (full range (min-max)) | | | | |
| QTcF, Baseline, n=87, 42, 6, 9, 11, 24, 13 | 400.6 (204 to 584) | 413.5 (285 to 502) | 356 (0 to 465) | 362 (331 to 426) |

| | | | | |
|---|---|---|---|---|
| QTcF, Day 5, n=68, 40, 0, 1, 3, 3, 5 | 406.6 (298 to 610) | 405.5 (339 to 555) | 99999 (99999 to 99999) | 373 (373 to 373) |
| QTcB, Baseline, n=87, 42, 6, 9, 11, 24, 13 | 424 (231 to 642) | 432 (310 to 514) | 412 (0 to 443) | 422 (389 to 502) |
| QTcB, Day 5, n=68, 40, 0, 1, 3, 3, 5 | 422 (325 to 649) | 434 (334 to 535) | 99999 (99999 to 99999) | 416 (416 to 416) |

Notes:

[76] - Safety Population

[77] - Safety Population

[78] - Safety Population

[79] - Safety Population

| **End point values** | Cohort 3: Children (2 to <6 years of age) | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[80] | 27[81] | 14[82] | |
| Units: Milliseconds | | | | |
| median (full range (min-max)) | | | | |
| QTcF, Baseline, n=87, 42, 6, 9, 11, 24, 13 | 365 (297 to 483) | 387.5 (267 to 544) | 387 (271 to 424) | |
| QTcF, Day 5, n=68, 40, 0, 1, 3, 3, 5 | 394 (291 to 411) | 353 (310 to 392) | 389 (179 to 409) | |
| QTcB, Baseline, n=87, 42, 6, 9, 11, 24, 13 | 410 (330 to 493) | 422.5 (264 to 497) | 415 (316 to 467) | |
| QTcB, Day 5, n=68, 40, 0, 1, 3, 3, 5 | 444 (321 to 475) | 380 (350 to 410) | 399 (189 to 422) | |

Notes:

[80] - Safety Population

[81] - Safety Population

[82] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median time to virologic improvement

| End point title | Median time to virologic improvement |
|---|---|

End point description:

Time to virologic improvement is defined as a 2-log drop in viral load or undetectable viral ribonucleic acid (RNA) as measured by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal samples (PCR positive at Baseline). Only those participants available at the specified time points were analyzed.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 76[83] | 5[84] | 7[85] | 9[86] |
| Units: Days | | | | |
| median (full range (min-max)) | 3 (1 to 26) | 4 (2 to 9) | 4 (3 to 25) | 3 (3 to 7) |

Notes:

[83] - ITT-E Population

[84] - ITT-E Population

[85] - ITT-E Population

[86] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13[87] | 7[88] | | |
| Units: Days | | | | |
| median (full range (min-max)) | 5 (3 to 6) | 4 (2 to 13) | | |

Notes:

[87] - ITT-E Population

[88] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median change from Baseline (Influenza A or B quantitative PCR, as appropriate) in viral load at the indicated time points

| End point title | Median change from Baseline (Influenza A or B quantitative PCR, as appropriate) in viral load at the indicated time points |
|---|---|

End point description:

Change from Baseline in viral load was measured from nasopharyngeal swab samples, as determined by RT-PCR (PCR positive at Baseline). Nasopharyngeal swab samples were collected at Baseline (Day 1); Day 2, Day 3, Day 4, Day 5, Day 7, and Day 10; and, only if the participants had continued symptoms and were hospitalized, post-treatment (PT) samples were collected at +2 days, +5 days, +9 days, +16 days, and +23 days. 'PT +23 days' also comprises viral load values at early study withdrawal. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X in the category titles). "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Baseline (Day 1); Days 2, 3, 4, 5, 7, and 10; and post-treatment +2, +5, +9, +16, +23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[89] | 7[90] | 11[91] | 12[92] |
| Units: Log10 copies per milliliter | | | | |
| median (full range (min-max)) | | | | |

| | | | | |
|---|---|---|---|---|
| Day 2, n=89, 0, 0, 2, 3, 2 | -0.92 (-4 to 2) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | -3.75 (-3.87 to 3.63) |
| Day 3, n=82, 4, 7, 10, 15, 7 | -1.42 (-3.38 to 1.08) | -1.655 (-3.15 to -0.94) | -1.93 (-4.36 to 0.55) | -2.215 (-6.16 to -0.49) |
| Day 4, n=84, 0, 0, 2, 2, 1 | -1.59 (-5.4 to 1.38) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | -4.895 (-5.01 to -4.78) |
| Day 5, n=75, 5, 4, 8, 12, 5 | -1.57 (-5.06 to 2.05) | -2.72 (-4.92 to -0.12) | -3.705 (-6.2 to 0.24) | -3.285 (-6.16 to -1.81) |
| Day 7, n=23, 1, 1, 1, 3, 1 | -1.58 (-3.52 to 3.02) | -1.82 (-1.82 to -1.82) | -6.2 (-6.2 to -6.2) | -3.03 (-3.03 to -3.03) |
| Day 10, n=19, 0, 2, 1, 4, 1 | -1.75 (-4 to 2.04) | 99999 (99999 to 99999) | -5.385 (-6.2 to -4.57) | -6.43 (-6.43 to -6.43) |
| PT +2 days, n=32, 0, 1, 2, 6, 3 | -1.38 (-4.86 to 0.46) | 99999 (99999 to 99999) | -6.2 (-6.2 to -6.2) | -2.495 (-2.91 to -2.08) |
| PT +5 days, n=26, 0, 2, 0, 5, 2 | -1.84 (-5.21 to -0.4) | 99999 (99999 to 99999) | -5.385 (-6.2 to -4.57) | 99999 (99999 to 99999) |
| PT +9 days, n=27, 0, 1, 0, 3, 2 | -2.58 (-5.21 to -0.41) | 99999 (99999 to 99999) | -6.2 (-6.2 to -6.2) | 99999 (99999 to 99999) |
| PT +16 days, n=21, 0, 1, 0, 4, 1 | -2.48 (-5.21 to -0.41) | 99999 (99999 to 99999) | -2.95 (-2.95 to -2.95) | 99999 (99999 to 99999) |
| PT +23 days, n=21, 2, 4, 0, 4, 0 | -2.89 (-5.21 to -0.46) | -4.455 (-4.92 to -3.99) | -4.67 (-6.2 to -2.95) | 99999 (99999 to 99999) |

Notes:

[89] - ITT-E Population

[90] - ITT-E Population

[91] - ITT-E Population

[92] - ITT-E Population

| **End point values** | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[93] | 14[94] | | |
| Units: Log10 copies per milliliter | | | | |
| median (full range (min-max)) | | | | |
| Day 2, n=89, 0, 0, 2, 3, 2 | -1.16 (-1.87 to 0.5) | -2.28 (-2.55 to -2.01) | | |
| Day 3, n=82, 4, 7, 10, 15, 7 | -1.33 (-5.19 to 0.62) | -2.55 (-4.01 to -0.29) | | |
| Day 4, n=84, 0, 0, 2, 2, 1 | -2.06 (-2.06 to -1.52) | -2.55 (-2.55 to -2.55) | | |
| Day 5, n=75, 5, 4, 8, 12, 5 | -2.93 (-6.71 to -1.53) | -2.55 (-4.01 to -1.4) | | |
| Day 7, n=23, 1, 1, 1, 3, 1 | -3.04 (-3.46 to -1.26) | -1.61 (-1.61 to -1.61) | | |
| Day 10, n=19, 0, 2, 1, 4, 1 | -4.76 (-5.42 to -2.48) | -1.67 (-1.67 to -1.67) | | |
| PT +2 days, n=32, 0, 1, 2, 6, 3 | -3.825 (-5.42 to -1.6) | -3.06 (-4.61 to -1.63) | | |
| PT +5 days, n=26, 0, 2, 0, 5, 2 | -4.19 (-5.42 to -1.6) | -3.275 (-3.43 to -3.12) | | |
| PT +9 days, n=27, 0, 1, 0, 3, 2 | -4.19 (-5.42 to -1.6) | -3.865 (-4.61 to -3.12) | | |
| PT +16 days, n=21, 0, 1, 0, 4, 1 | -3.825 (-4.56 to -1.6) | -4.61 (-4.61 to -4.61) | | |
| PT +23 days, n=21, 2, 4, 0, 4, 0 | -3.825 (-4.56 to -1.6) | 99999 (99999 to 99999) | | |

Notes:

[93] - ITT-E Population

[94] - ITT-E Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean viral susceptibility to zanamivir at Baseline (Day 1) and all Post-Baseline visits collectively

| End point title | Mean viral susceptibility to zanamivir at Baseline (Day 1) and all Post-Baseline visits collectively[95] |
|---|---|

End point description:

Viral susceptibility to zanamivir at Baseline and at all post-Baseline visits collectively was assessed by neuraminidase (NA) enzyme inhibition assay. The mean IC50 data are summarized by subtype (A/H1N1, A/H3N2, B) and by visit. IC50 is defined as the concentration of zanamvir required to inhibit NA activity by 50%. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Baseline and up to post-treatment (PT) + 23 days

Notes:

[95] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not conducted for all arms; there are no data to report.

| **End point values** | Cohort 6: Adults (18 years and older) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 130[96] | | | |
| Units: Nanomolar (nM) | | | | |
| arithmetic mean (standard deviation) | | | | |
| A/H1N1, Day 1, n=22 | 0.2091 (± 0.06886) | | | |
| A/H1N1, All Post-Baseline, n=8 | 0.18 (± 0.04) | | | |
| A/H3N2, Day 1, n=5 | 0.266 (± 0.08385) | | | |
| A/H3N2, All Post-Baseline, n=2 | 0.23 (± 0.01414) | | | |
| B, Day 1, n=2 | 1.61 (± 0.35355) | | | |
| B, All Post-Baseline, n=0 | 99999 (± 99999) | | | |

Notes:

[96] - ITT-E Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with treatment-emergent (TE) mutations

| End point title | Number of participants with treatment-emergent (TE) mutations[97] |
|---|---|

End point description:

Viral RNA isolated from participants at Baseline (Day 1) and post-Baseline visits were sequenced to determine the presence of TE neuraminidase (NA) and hemagglutinin (HA) mutations resulting from selective pressure. A mutation was considered to be TE if it was not present at Baseline and was present in the post-Baseline sample analyzed.These mutations were classified as either known to confer zanamvir resistance or novel mutations with unknown clinical significance.

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

End point timeframe:

Baseline and up to post-treatment (PT) + 23 days

Notes:

[97] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not conducted for all arms; there are no data to report.

| End point values | Cohort 6: Adults (18 years and older) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 130[98] | | | |
| Units: Participants | | | | |
| Known Zanamivir-Resistant NA Mutations | 0 | | | |
| Novel NA Mutations | 5 | | | |
| Resistant HA Mutations | 2 | | | |
| Novel HA Mutations | 4 | | | |

Notes:

[98] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median time to resolution of individual vital signs

| End point title | Median time to resolution of individual vital signs |
|---|---|

End point description:

Times to return to afebrile status (normal body temperature), normal respiratory status, normal heart rate, and normal systolic blood pressure were assessed. Afebrile status is defined as a temperature <=36.6 axilla, <=37.2 oral, or <=37.7 rectal, core or typanic, degrees Centigrade. A return to normal respiratory status is defined as either: (a) return to pre-morbid oxygen requirement; or (b) return to no need for supplemental oxygen; or (c) respiratory rate <=60, <=40, <=34, <=30, <=24 or <=24 breaths/minute (without supplemental oxygen) for Cohorts 1-6 respectively . A normal HR is defined as <=160, <=150, <=140, <=120, <=100 or <=100 bpm for Cohorts 1-6 respectively, and a normal SBP is defined as >=70, >=74, >=76, >=80, >=90 or >=90 mmHg for Cohorts 1-6 respectively. Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X, X in the category titles).

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[99] | 7[100] | 11[101] | 12[102] |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Afebrile Status, n=120, 7, 11, 7, 24, 13 | 3 (2 to 34) | 4 (2 to 26) | 2 (1 to 30) | 25 (2 to 32) |
| Respiratory Status, n=89, 7, 10, 12, 23, 9 | 8 (2 to 36) | 5 (2 to 16) | 2 (1 to 21) | 3.5 (2 to 21) |
| HR, n=121, 7, 11, 12, 27, 13 | 2 (2 to 22) | 2 (2 to 2) | 2 (1 to 25) | 2 (2 to 3) |
| SBP, n=128, 7, 11, 12, 27, 14 | 2 (2 to 3) | 2 (2 to 2) | 2 (1 to 3) | 2 (2 to 3) |

Notes:

[99] - ITT-E Population

[100] - ITT-E Population

[101] - ITT-E Population

[102] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[103] | 14[104] | | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Afebrile Status, n=120, 7, 11, 7, 24, 13 | 3 (2 to 26) | 3 (2 to 15) | | |
| Respiratory Status, n=89, 7, 10, 12, 23, 9 | 3 (2 to 33) | 2 (2 to 20) | | |
| HR, n=121, 7, 11, 12, 27, 13 | 2 (2 to 31) | 2 (2 to 5) | | |
| SBP, n=128, 7, 11, 12, 27, 14 | 2 (2 to 24) | 2 (2 to 3) | | |

Notes:

[103] - ITT-E Population

[104] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated ventilation status: modality of supplemental oxygen delivery and mechanical ventilation

| End point title | Number of participants with the indicated ventilation status: modality of supplemental oxygen delivery and mechanical ventilation |
|---|---|

End point description:

Ventilation status was measured at Baseline (Day 1); Days 2, 3, 4, 5, 6, 7, 8, 9, and 10; and post-treatment +2 days, +5 days, +9 days, +16 days (assessments to be done if participant remained hospitalized), and +23 days. Ventilation status was assessed once daily during inpatient follow-up visits. The number of participants reported for machine-assisted: extracorporeal membrane oxygenation (ECMO), endotracheal mechanical ventilation, and supplemental oxygen delivery (SOD) at "any time (AT) on study" and at Baseline (Day 1) are summarized.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[105] | 7[106] | 11[107] | 12[108] |
| Units: Participants | | | | |
| AT on Study, Machine-Assisted: ECMO | 4 | 0 | 1 | 0 |
| AT on Study, Machine-Assisted: Endotracheal | 74 | 3 | 5 | 4 |
| AT on Study, SOD | 91 | 3 | 5 | 7 |
| Day 1, Machine-Assisted: ECMO | 3 | 0 | 1 | 0 |
| Day 1, Machine-Assisted: Endotracheal | 60 | 2 | 3 | 4 |
| Day 1, SOD | 46 | 1 | 3 | 1 |

Notes:

[105] - ITT-E Population

[106] - ITT-E Population

[107] - ITT-E Population

[108] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[109] | 14[110] | | |
| Units: Participants | | | | |
| AT on Study, Machine-Assisted: ECMO | 2 | 1 | | |
| AT on Study, Machine-Assisted: Endotracheal | 14 | 4 | | |
| AT on Study, SOD | 13 | 5 | | |
| Day 1, Machine-Assisted: ECMO | 2 | 1 | | |
| Day 1, Machine-Assisted: Endotracheal | 11 | 4 | | |
| Day 1, SOD | 6 | 1 | | |

Notes:

[109] - ITT-E Population

[110] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of mechanical ventilation and supplemental oxygen use

| End point title | Duration of mechanical ventilation and supplemental oxygen use |
|---|---|

End point description:

Due to the conditional nature of data collection post treatment, the duration of mechanical ventilation and supplemental oxygen use were not determined.

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

End point timeframe:

Up to discharge from the hospital

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0[111] | 0[112] | 0[113] | 0[114] |
| Units: Days | | | | |
| median (full range (min-max)) | ( to ) | ( to ) | ( to ) | ( to ) |

Notes:

[111] - ITT-E Population

[112] - ITT-E Population

[113] - ITT-E Population

[114] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0[115] | 0[116] | | |
| Units: Days | | | | |
| median (full range (min-max)) | ( to ) | ( to ) | | |

Notes:

[115] - ITT-E Population

[116] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median time to return to pre-morbid functional status

| End point title | Median time to return to pre-morbid functional status |
|---|---|

End point description:

Time to return to pre-morbid functional status was assessed on a 3-point scale (bed rest, limited ambulation, or unrestricted). Only those participants available at the specified time points were analyzed.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 76[117] | 7[118] | 9[119] | 11[120] |
| Units: Days | | | | |
| median (full range (min-max)) | 10 (2 to 48) | 8 (2 to 27) | 3 (2 to 27) | 5 (2 to 28) |

Notes:
[117] - ITT-E Population
[118] - ITT-E Population
[119] - ITT-E Population
[120] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22[121] | 9[122] | | |
| Units: Days | | | | |
| median (full range (min-max)) | 5.5 (2 to 34) | 4 (2 to 8) | | |

Notes:
[121] - ITT-E Population
[122] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated mortality status at Day 14 and Day 28

| End point title | Number of participants with the indicated mortality status at Day 14 and Day 28 |
|---|---|

End point description:

The number of participants who died on or before Study Day 14 and Study Day 28 was summarized. Only those participants available at the specified time points were analyzed.

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

End point timeframe:

Day 14 and Day 28

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[123] | 7[124] | 11[125] | 12[126] |
| Units: Participants | | | | |
| Died on or before Study Day 14, No | 113 | 7 | 11 | 12 |
| Died on or before Study Day 14, Yes | 17 | 0 | 0 | 0 |
| Died on or before Study Day 28, No | 108 | 7 | 10 | 12 |
| Died on or before Study Day 28, Yes | 22 | 0 | 1 | 0 |

Notes:
[123] - ITT-E Population
[124] - ITT-E Population
[125] - ITT-E Population
[126] - ITT-E Population

| End point values | Cohort 4: Children (6 to | Cohort 5: Adolescents | | |
|---|---|---|---|---|

| | <13 years of age) | (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[127] | 14[128] | | |
| Units: Participants | | | | |
| Died on or before Study Day 14, No | 26 | 12 | | |
| Died on or before Study Day 14, Yes | 1 | 2 | | |
| Died on or before Study Day 28, No | 26 | 11 | | |
| Died on or before Study Day 28, Yes | 1 | 3 | | |

Notes:

[127] - ITT-E Population

[128] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median time to clinical response (sustained resolution) of all vital signs (composite)

| End point title | Median time to clinical response (sustained resolution) of all vital signs (composite) |
|---|---|

End point description:

Sustained resolution of the following vital signs (composite) was assessed: afebrile status, normal oxygen saturation, normal respiratory status, normal HR, and normal BP. Clinical response is defined as the resolution of at least four of five vital signs within the following resolution criteria, maintained for 24 hours or hospital discharge, whichever occurred first: Temperature in degrees Centigrade (<=36.6 axilla, <=37.2 oral, <=37.7 rectal, core or tympanic); oxygen saturation (>=95%, without supplemental oxygen); respiratory status (return to pre-morbid oxygen requirement, or no need for supplemental oxygen, or respiratory rate <=60, <=40, <=34, <=30, <=24 or <=24 breaths/minute without supplemental oxygen for Cohorts 1-6 respectively); HR (<=160, <=150, <=140, <=120, <=100 or <=100 bpm for Cohorts 1-6 respectively); SBP (>=70, >=74, >=76, >=80, >=90 or >=90 mmHg for Cohorts 1-6 respectively). Only those participants available at the specified time points were analyzed.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| **End point values** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 81[129] | 7[130] | 10[131] | 12[132] |
| Units: Days | | | | |
| median (full range (min-max)) | 9 (2 to 32) | 7 (2 to 23) | 3.5 (1 to 21) | 6.5 (2 to 37) |

Notes:

[129] - ITT-E Population

[130] - ITT-E Population

[131] - ITT-E Population

[132] - ITT-E Population

| **End point values** | Cohort 4: Children (6 to <13 years of | Cohort 5: Adolescents (13 to <18 | | |
|---|---|---|---|---|

| | age) | years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25[133] | 11[134] | | |
| Units: Days | | | | |
| median (full range (min-max)) | 4 (1 to 42) | 5 (2 to 32) | | |

Notes:

[133] - ITT-E Population

[134] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with any AE categorized as an influenza complication

| End point title | Number of participants with any AE categorized as an influenza complication |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[135] | 7[136] | 11[137] | 12[138] |
| Units: Participants | 45 | 4 | 4 | 3 |

Notes:

[135] - ITT-E Population

[136] - ITT-E Population

[137] - ITT-E Population

[138] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[139] | 14[140] | | |
| Units: Participants | 8 | 3 | | |

Notes:

[139] - ITT-E Population

[140] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants who used any concomitant antibiotic medications for complications of influenza

| End point title | Number of participants who used any concomitant antibiotic medications for complications of influenza |
|---|---|

End point description:

Concomitant medications (prescription and non-prescription) were permitted during the course of the study at the Investigator's discretion (except for prohibited medications: during the treatment period with IV zanamivir, other influenza antiviral drugs were not permitted). The number of participants who were treated with antibiotics for influenza complications was summarized.

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

End point timeframe:

Up to post-treatment (PT) + 23 days

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[141] | 7[142] | 11[143] | 12[144] |
| Units: Participants | 63 | 5 | 7 | 7 |

Notes:

[141] - ITT-E Population

[142] - ITT-E Population

[143] - ITT-E Population

[144] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[145] | 14[146] | | |
| Units: Participants | 12 | 6 | | |

Notes:

[145] - ITT-E Population

[146] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median duration of hospitalization and intensive care unit (ICU) stays

| End point title | Median duration of hospitalization and intensive care unit (ICU) stays |
|---|---|

End point description:

The duration of hospitalization (H) reflects the number of hospitalization days between the date of the first dose of investigational product and the date of discharge. ICU stay includes total duration in ICU and may include days in ICU before entry into the study. For participants with a missing discharge date who were not discharged at the end of the study, the date of discharge was imputed to the last follow-up visit (post-treatment +23 days). Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

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

End point timeframe:

Up to discharge from hospital

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[147] | 7[148] | 11[149] | 12[150] |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Duration of H, n=130, 7, 11, 12, 27, 14 | 15 (1 to 133) | 7 (2 to 23) | 4 (2 to 44) | 6.5 (3 to 37) |
| Duration of H-ICU, n=108, 4, 6, 8, 19, 9 | 11.5 (1 to 104) | 7.5 (5 to 24) | 5 (3 to 19) | 5.5 (2 to 26) |

Notes:

[147] - ITT-E Population

[148] - ITT-E Population

[149] - ITT-E Population

[150] - ITT-E Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27[151] | 14[152] | | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Duration of H, n=130, 7, 11, 12, 27, 14 | 6 (1 to 45) | 6.5 (2 to 42) | | |
| Duration of H-ICU, n=108, 4, 6, 8, 19, 9 | 8 (2 to 50) | 8 (4 to 39) | | |

Notes:

[151] - ITT-E Population

[152] - ITT-E Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean maximum serum concentration (Cmax) of zanamivir at the end of infusion

| End point title | Geometric mean maximum serum concentration (Cmax) of zanamivir at the end of infusion |
|---|---|

End point description:

The Cmax of zanamivir was evaluated at the end of infusion. Serial blood samples for pharmacokinetic (PK) analysis were collected if possible in conjunction with the initial dose on Day 1 (5-7 serial samples) and over a dosing interval during repeat dosing on Days 3, 4, or 5 (5 serial samples). PK data for all participants with available blood samples were analyzed. PK data for those participants who were neither on extracorporeal membrane oxygenation (ECMO) nor on continuous renal replacement therapy (CRRT), who had CLcr >=80 mL/minutes (>=80mL/minute/1.73m^2 for cohorts 1-4) and who received an initial dose (ID) and a maintenance dose (MD) of 14 mg/kg (6 months to <6 years of age), 12 mg/kg, not to exceed 600 mg (6 to <18 years of age) or 600 mg zanamivir (>=18 years of age) (represented by n=X in the category titles) were summarized. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Days 3, 4, or 5

| **End point values** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[153] | 7[154] | 6[155] | 12[156] |
| Units: Micrograms per mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=67, 0, 0, 0, 0, 6 | 32.77 (± 34) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 9, 3 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 14 mg/kg, CLcr>=80, n=0, 4, 5, 9, 0, 0 | 99999 (± 99999) | 36.21 (± 21) | 37.78 (± 24) | 41.54 (± 23) |
| MD, 600 mg, CLcr>=80, n=72, 0, 0, 0, 0, 2 | 35.3 (± 32) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | 38.01 (± 99999) | 43.19 (± 9) |

Notes:

[153] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

[154] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

[155] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

[156] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

| **End point values** | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[157] | 13[158] | | |
| Units: Micrograms per mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=67, 0, 0, 0, 0, 6 | 99999 (± 99999) | 34.47 (± 27) | | |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 9, 3 | 44.16 (± 47) | 4.99 (± 3997) | | |
| ID, 14 mg/kg, CLcr>=80, n=0, 4, 5, 9, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |
| MD, 600 mg, CLcr>=80, n=72, 0, 0, 0, 0, 2 | 99999 (± 99999) | 25.73 (± 52) | | |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 45.18 (± 48) | 99999 (± 99999) | | |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |

Notes:

[157] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

[158] - PK Parameter Population: participants with one or more estimated zanamivir PK parameters

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean area under the serum drug concentration-time curve (AUC) over a 12-hour dosing interval (AUC[0-tau]) and AUC extrapolated to infinity (AUC[0-inf]) of zanamivir

| End point title | Geometric mean area under the serum drug concentration-time curve (AUC) over a 12-hour dosing interval (AUC[0-tau]) and AUC extrapolated to infinity (AUC[0-inf]) of zanamivir |
|---|---|

End point description:

The AUC(0-tau) during the repeat dose interval and AUC(0-inf) for the initial dose were evaluated. Serial blood samples for PK analysis were collected if possible in conjunction with the initial dose on Day 1 (5-7 serial samples) and over a dosing interval during repeat dosing on Days 3, 4, or 5 (5 serial samples). PK data for all participants with available blood samples were analyzed. PK data for those participants not on ECMO or CRRT with a CLcr >=80 mL/minutes (>=80 mL/minute/1.73m^2 for cohorts 1-4) and who received an ID and a MD of 14 mg/kg (6 months to <6 years of age), 12 mg/kg, not to exceed 600 mg (6 to <18 years of age) or 600 mg zanamivir (>=18 years of age) (represented by n=X in the category titles) were summarized. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Days 3, 4, or 5

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[159] | 7[160] | 6[161] | 12[162] |
| Units: Micrograms per hour per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC(0-inf), ID, 600 mg, CLcr>=80, n=63,0,0,0,0,5 | 82.86 (± 36) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| AUC(0-inf), ID, 12 mg/kg, CLcr>=80, n=0,0,0,0,8,1 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| AUC(0-inf), ID, 14 mg/kg, CLcr>=80, n=0,3,4,9,0,0 | 99999 (± 99999) | 75.31 (± 23) | 72.42 (± 14) | 80.28 (± 38) |
| AUC(0-tau), MD, 600 mg, CLcr>=80, n=65,0,0, 0,0,2 | 90.33 (± 36) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| AUC(0-tau), MD, 12 mg/kg, CLcr>=80, n=0,0,0,0,4,0 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| AUC(0-tau), MD, 14 mg/kg, CLcr>=80, n=0,0,1,4,0,0 | 99999 (± 99999) | 99999 (± 99999) | 68.2 (± 99999) | 81.02 (± 28) |

Notes:

[159] - PK Parameter Population

[160] - PK Parameter Population

[161] - PK Parameter Population

[162] - PK Parameter Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[163] | 13[164] | | |

| | | | | |
|---|---|---|---|---|
| Units: Micrograms per hour per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| AUC(0-inf), ID, 600 mg, CLcr>=80, n=63,0,0,0,0,5 | 99999 (± 99999) | 91.07 (± 27) | | |
| AUC(0-inf), ID, 12 mg/kg, CLcr>=80, n=0,0,0,0,8,1 | 107.21 (± 41) | 135.22 (± 99999) | | |
| AUC(0-inf), ID, 14 mg/kg, CLcr>=80, n=0,3,4,9,0,0 | 99999 (± 99999) | 99999 (± 99999) | | |
| AUC(0-tau), MD, 600 mg, CLcr>=80, n=65,0,0, 0,0,2 | 99999 (± 99999) | 64.52 (± 30) | | |
| AUC(0-tau), MD, 12 mg/kg, CLcr>=80, n=0,0,0,0,4,0 | 90.33 (± 45) | 99999 (± 99999) | | |
| AUC(0-tau), MD, 14 mg/kg, CLcr>=80, n=0,0,1,4,0,0 | 99999 (± 99999) | 99999 (± 99999) | | |

Notes:

[163] - PK Parameter Population

[164] - PK Parameter Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean terminal half life (t1/2) of zanamivir

| End point title | Geometric mean terminal half life (t1/2) of zanamivir |
|---|---|

End point description:

The t1/2 of zanamivir was evaluated. Terminal half life is defined as the time it takes for a substance to lose half of its pharmacologic, physiologic, or radiologic activity. Serial blood samples for PK analysis were collected if possible in conjunction with the initial dose on Day 1 (5-7 serial samples) and over a dosing interval during repeat dosing on Day 3, 4, or 5 (5 serial samples). PK data for all participants with available blood samples were analyzed. PK data for those participants not on ECMO or CRRT with a CLcr>=80 mL/minutes (>=80 mL/minute/1.73m^2 for cohorts 1-4) and who received an ID and a MD of 14 mg/kg (6 months to <6 years of age), 12 mg/kg, not to exceed 600 mg (6 to <18 years of age) or 600 mg zanamivir (>=18 years of age) (represented by n=X in the category titles) were summarized. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Days 3, 4, or 5

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[165] | 7[166] | 6[167] | 12[168] |
| Units: Hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=67, 0, 0, 0, 0, 5 | 2.39 (± 31) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 5, 9, 0, 0 | 99999 (± 99999) | 1.84 (± 19) | 2.49 (± 118) | 1.6 (± 34) |
| MD, 600 mg, CLcr>=80, n=68, 0, 0, 0, 0, 2 | 2.56 (± 34) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |

| | | | | |
|---|---|---|---|---|
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | 1.68 (± 99999) | 1.76 (± 20) |

Notes:

[165] - PK Parameter Population

[166] - PK Parameter Population

[167] - PK Parameter Population

[168] - PK Parameter Population

| **End point values** | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[169] | 13[170] | | |
| Units: Hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=67, 0, 0, 0, 0, 5 | 99999 (± 99999) | 2.06 (± 47) | | |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 2.57 (± 55) | 2.16 (± 99999) | | |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 5, 9, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |
| MD, 600 mg, CLcr>=80, n=68, 0, 0, 0, 0, 2 | 99999 (± 99999) | 1.73 (± 21) | | |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 1.81 (± 41) | 99999 (± 99999) | | |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |

Notes:

[169] - PK Parameter Population

[170] - PK Parameter Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean serum clearance of zanamivir

| End point title | Geometric mean serum clearance of zanamivir |
|---|---|

End point description:

The serum clearance of zanamivir was evaluated. Clearance is defined as the volume of zanamivir per unit time eliminated from serum. Serial blood samples for PK analysis were collected if possible in conjunction with the initial dose on Day 1 (5-7 serial samples) and over a dosing interval during repeat dosing on Days 3, 4, or 5 (5 serial samples). PK data for all participants with available blood samples were analyzed. PK data for those participants not on ECMO or CRRT with a CLcr >=80 mL/minutes (>=80 mL/minute/1.73m^2 for cohorts 1-4) and who received an ID and a MD 14 mg/kg (6 months to <6 years of age), 12 mg/kg, not to exceed 600 mg (6 to <18 years of age) or 600 mg zanamivir (>=18 years of age) (represented by n=X in the category titles) were summarized. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Days 3, 4, or 5

| End point values | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[171] | 7[172] | 6[173] | 12[174] |
| Units: mL per minutes | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=63, 0, 0, 0, 0, 5 | 120.68 (± 36) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 4, 9, 0, 0 | 99999 (± 99999) | 27.31 (± 32) | 31 (± 12) | 41.95 (± 37) |
| MD, 600 mg, CLcr>=80, n=65, 0, 0, 0, 0, 2 | 110.71 (± 36) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | 31.78 (± 99999) | 40.35 (± 35) |

Notes:

[171] - PK Parameter Population

[172] - PK Parameter Population

[173] - PK Parameter Population

[174] - PK Parameter Population

| End point values | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[175] | 13[176] | | |
| Units: mL per minutes | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=63, 0, 0, 0, 0, 5 | 99999 (± 99999) | 109.83 (± 27) | | |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 46.7 (± 47) | 53.7 (± 99999) | | |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 4, 9, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |
| MD, 600 mg, CLcr>=80, n=65, 0, 0, 0, 0, 2 | 99999 (± 99999) | 155.03 (± 30) | | |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 4, 0 | 68.61 (± 34) | 99999 (± 99999) | | |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |

Notes:

[175] - PK Parameter Population

[176] - PK Parameter Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean volume of distribution (Vd) of zanamivir

| End point title | Geometric mean volume of distribution (Vd) of zanamivir |
|---|---|

End point description:

TThe Vd of zanamivir was evaluated. Volume of distribution is defined as the apparent volume in which zanamivir is distributed. Serial blood samples for PK analysis were collected if possible in conjunction with the initial dose on Day 1 (5-7 serial samples) and over a dosing interval during repeat dosing on Days 3, 4, or 5 (5 serial samples). PK data for all participants with available blood samples were analyzed. PK data for those participants not on ECMO or CRRT with a CLcr >= 80 mL/minutes (>=80 mL/minute/1.73m^2 for cohorts 1-4) and who received an ID and a MD of 14 mg/kg (6 months to <6 years of age), 12 mg/kg, not to exceed 600 mg (6 to <18 years of age) or 600 mg zanamivir (>=18 years of age) (represented by n=X in the category titles) were summarized. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Days 3, 4, or 5

| **End point values** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) | Cohort 3: Children (2 to <6 years of age) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 130[177] | 7[178] | 6[179] | 12[180] |
| Units: Liters (L) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=63, 0, 0, 0, 0, 5 | 22.02 (± 30) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 4, 9, 0, 0 | 99999 (± 99999) | 3.77 (± 12) | 3.94 (± 29) | 5.15 (± 20) |
| MD, 600 mg, CLcr>=80, n=65, 0, 0, 0, 0, 2 | 21.61 (± 33) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 0 | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | 3.77 (± 99999) | 5.23 (± 32) |

Notes:

[177] - PK Parameter Population

[178] - PK Parameter Population

[179] - PK Parameter Population

[180] - PK Parameter Population

| **End point values** | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[181] | 13[182] | | |
| Units: Liters (L) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| ID, 600 mg, CLcr>=80, n=63, 0, 0, 0, 0, 5 | 99999 (± 99999) | 18.57 (± 26) | | |
| ID, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 1 | 9.21 (± 48) | 10.09 (± 99999) | | |
| ID, 14 mg/kg, CLcr>=80, n=0, 3, 4, 9, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |

| | | | | |
|---|---|---|---|---|
| MD, 600 mg, CLcr>=80, n=65, 0, 0, 0, 0, 2 | 99999 (± 99999) | 23.2 (± 25) | | |
| MD, 12 mg/kg, CLcr>=80, n=0, 0, 0, 0, 8, 0 | 9.82 (± 8) | 99999 (± 99999) | | |
| MD, 14 mg/kg, CLcr>=80, n=0, 0, 1, 4, 0, 0 | 99999 (± 99999) | 99999 (± 99999) | | |

Notes:

[181] - PK Parameter Population

[182] - PK Parameter Population

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events (AEs) were collected from the start of study medication until follow-up (up to 33 days). Serious adverse events (SAEs) assessed as related to study participation were recorded from time of consent until any follow-up contact.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 6: Adults (18 years and older) |

Reporting group description:

Participants >=18 years of age received 600 milligrams (mg) zanamivir by intravenous (IV) infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 1: Infants (6 months to <1 year of age) |

Reporting group description:

Participants 6 months to <1 year of age received 14 mg per kilogram (mg/kg) zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 2: Children (1 to <2 years of age) |

Reporting group description:

Participants 1 year to <2 years of age received 14 mg/kg zanamivir by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 3: Children (2 to <6 years of age |

Reporting group description:

Participants 2 years to <6 years of age received 14 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 4: Children (6 to <13 years of age) |

Reporting group description:

Participants 6 years to <13 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| | |
|---|---|
| Reporting group title | Cohort 5: Adolescents (13 to <18 years of age) |

Reporting group description:

Participants 13 to <18 years of age received 12 mg/kg zanamivir with a maximum dose of 600 mg by IV infusion over 30 minutes twice daily, adjusted for renal function, for 5 days. Treatment could have been extended for up to 5 additional days if viral shedding or clinical symptoms warranted further treatment.

| **Serious adverse events** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 44 / 130 (33.85%) | 1 / 7 (14.29%) | 2 / 11 (18.18%) |
| number of deaths (all causes) | 33 | 0 | 1 |
| number of deaths resulting from adverse events | | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 7 / 130 (5.38%) | 1 / 7 (14.29%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 1 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Cyclic vomiting syndrome | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 130 (5.38%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acinetobacter bacteraemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superinfection bacterial | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pericarditis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 3: Children (2 to <6 years of age | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 8 / 27 (29.63%) | 4 / 14 (28.57%) |
| number of deaths (all causes) | 0 | 1 | 3 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Cyclic vomiting syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Toxic skin eruption | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acinetobacter bacteraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superinfection bacterial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pericarditis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Cohort 6: Adults (18 years and older) | Cohort 1: Infants (6 months to <1 year of age) | Cohort 2: Children (1 to <2 years of age) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 100 / 130 (76.92%) | 4 / 7 (57.14%) | 7 / 11 (63.64%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 15 / 130 (11.54%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 26 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 11 / 130 (8.46%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 19 | 0 | 1 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Thrombophlebitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Arterial thrombosis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoperfusion | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Poor peripheral circulation | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 130 (10.77%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 14 | 1 | 0 |
| Oedema | | | |
| subjects affected / exposed | 7 / 130 (5.38%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Facial pain | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site reaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Unintentional medical device removal | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Reproductive system and breast disorders | | | |
| Perineal rash | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 130 (4.62%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Respiratory distress | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stridor | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 2 / 7 (28.57%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Interstitial lung disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thoracic haemorrhage | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 12 / 130 (9.23%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 12 | 0 | 0 |

| | | | |
|---|---|---|---|
| Insomnia | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Mental status changes | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Agitation | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conduct disorder | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Drug dependence | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 11 / 130 (8.46%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 11 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 130 (3.85%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Blood creatinine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Hepatic enzyme increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood sodium increased | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chest X-ray abnormal | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastric occult blood positive | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematrocrit decreased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pseudomonas test positive | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Troponin I increased | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Contusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Overdose | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 6 / 130 (4.62%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Bundle branch block right | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dilatation ventricular | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Right atrial dilatation | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Critical illness polyneuropathy | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neuromyopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Aphasia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Apraxia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Brain injury | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness exertional | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 11 / 130 (8.46%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 12 | 0 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 7 (14.29%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 1 | 2 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Agranulocytosis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bandaemia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphpenia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Normochromic normocytic anaemia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Keratopathy | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pupillary disorder | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 10 / 130 (7.69%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 130 (7.69%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 16 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 6 / 130 (4.62%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Impaired gastic emptying | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral disorder | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rectal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Volvulus | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Cholestasis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 5 / 130 (3.85%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 2 / 7 (28.57%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Drug eruption | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prurigo | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash vesicular | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|---|---|---|---|
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Polyuria | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperparathyroidism secondary | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Muscle atrophy | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myositis ossificans | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 7 (28.57%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|---|---|---|---|
| Bronchopneumonia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Lung infection | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Croup infectious | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Empyema | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Penile infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia necrotising | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory moniliasis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 16 / 130 (12.31%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 17 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 7 / 130 (5.38%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 6 / 130 (4.62%) | 0 / 7 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 7 | 0 | 1 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 130 (3.08%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 6 / 130 (4.62%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 130 (3.85%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Acidosis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Metabolic alkalosis | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypochloraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperchloraemia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 7 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| **Non-serious adverse events** | Cohort 3: Children (2 to <6 years of age | Cohort 4: Children (6 to <13 years of age) | Cohort 5: Adolescents (13 to <18 years of age) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 12 (66.67%) | 20 / 27 (74.07%) | 9 / 14 (64.29%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 27 (7.41%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoperfusion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Poor peripheral circulation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Venous thrombosis limb | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 27 (14.81%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 4 | 1 |
| Oedema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 27 (7.41%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infusion site extravasation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Facial pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Unintentional medical device removal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Perineal rash | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Stridor | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea exertional | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thoracic haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Agitation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conduct disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Drug dependence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatinine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest X-ray abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastric occult blood positive | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematrocrit decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pseudomonas test positive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Troponin I increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Excoriation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bundle branch block right | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dilatation ventricular | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Right atrial dilatation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Critical illness polyneuropathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Neuromyopathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Apraxia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Brain injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness exertional | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 27 (11.11%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 3 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bandaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphpenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Normochromic normocytic anaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Keratopathy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pupillary disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 27 (11.11%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 27 (7.41%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal compartment syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ileus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Impaired gastic emptying | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 27 (7.41%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 27 (7.41%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Prurigo | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash vesicular | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin exfoliation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 2 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Polyuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hyperparathyroidism secondary | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle atrophy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myositis ossificans | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchiolitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Otitis media acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Penile infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia necrotising | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory moniliasis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 1 | 1 |
| Acidosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolic alkalosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Food intolerance | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 27 (7.41%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypochloraemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 27 (3.70%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperchloraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 27 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 February 2010 | Protocol Amendment 03 was written to i) modify pediatric/adolescent dose selection in response to recommendations from EU regulators, ii) add an inclusion criterion to include only subjects who have severe or progressive influenza illness on approved (fully licensed) influenza antiviral agents or who are considered unsuitable or inappropriate for treatment with approved influenza antivirals. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Two participants who withdrew consent prior to receiving intravenous zanamivir have not been captured in any of the tables.

Notes: