



Clinical trial results:

NAI114373: A Phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza

Summary

| | |
|--------------------------|---|
| EudraCT number | 2010-021621-12 |
| Trial protocol | SK DE FR GB HU NL CZ NO DK GR BE PL ES Outside EU/EEA |
| Global end of trial date | 18 March 2015 |

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | NAI114373 |
|-----------------------|-----------|

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 8664357343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, +1 8664357343, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 February 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 March 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of treatment with 600 mg of intravenous (IV) zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily, and 600 mg IV zanamivir compared to 300 mg IV zanamivir twice daily on time to clinical response (TTCR).

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 15 January 2011 |
| 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 | Korea, Republic of: 18 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Norway: 11 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Spain: 146 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Belgium: 24 |
| Country: Number of subjects enrolled | Czech Republic: 13 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | France: 42 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Greece: 19 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Hong Kong: 3 |
| Country: Number of subjects enrolled | India: 44 |
| Country: Number of subjects enrolled | Brazil: 2 |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Mexico: 19 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | New Zealand: 13 |
| Country: Number of subjects enrolled | Canada: 18 |
| Country: Number of subjects enrolled | Australia: 22 |
| Country: Number of subjects enrolled | China: 18 |
| Country: Number of subjects enrolled | United States: 151 |
| Country: Number of subjects enrolled | South Africa: 13 |
| Worldwide total number of subjects | 626 |
| EEA total number of subjects | 285 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 400 |
| From 65 to 84 years | 189 |
| 85 years and over | 32 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male and female adult and adolescent participants ≥ 16 years of age hospitalized with documented influenza or suspected influenza were eligible for enrollment. A total of 626 participants were randomized, and 615 participants were included in the Intent-to-Treat Exposed (ITT-E) Population.

Period 1

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

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | IV zanamivir 300 mg |

Arm description:

Participants ≥ 16 years of age received intravenous (IV) zanamivir 300 milligrams (mg) twice daily, adjusted for renal function for 5–10 days.

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

300 mg twice daily, adjusted for renal function

| | |
|------------------|---------------------|
| Arm title | IV zanamivir 600 mg |
|------------------|---------------------|

Arm description:

Participants ≥ 16 years of age received IV zanamivir 600 mg twice daily, adjusted for renal function for 5–10 days.

| | |
|--|-----------------------|
| 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 | Oral oseltamivir 75 mg |
|------------------|------------------------|

Arm description:

Participants ≥ 16 years of age received oral oseltamivir 75 mg twice daily, adjusted for renal function for 5–10 days.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-------------|
| Investigational medicinal product name | oseltamivir |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

75 mg twice daily, frequency adjusted for renal function

| Number of subjects in period 1^[1] | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg |
|---|---------------------|---------------------|------------------------|
| Started | 201 | 209 | 205 |
| Completed | 175 | 178 | 166 |
| Not completed | 26 | 31 | 39 |
| Adverse event, serious fatal | 12 | 14 | 11 |
| Physician decision | 3 | 5 | 10 |
| Consent withdrawn by subject | 6 | 6 | 8 |
| Adverse event, non-fatal | 2 | 2 | 1 |
| Lost to follow-up | 3 | 4 | 9 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Male and female adult and adolescent participants ≥ 16 years of age hospitalized with documented influenza or suspected influenza were eligible for enrollment. A total of 626 participants were randomized, and 615 participants were included in the Intent-to-Treat Exposed (ITT-E) Population.

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | IV zanamivir 300 mg |
| Reporting group description: Participants ≥ 16 years of age received intravenous (IV) zanamivir 300 milligrams (mg) twice daily, adjusted for renal function for 5–10 days. | |
| Reporting group title | IV zanamivir 600 mg |
| Reporting group description: Participants ≥ 16 years of age received IV zanamivir 600 mg twice daily, adjusted for renal function for 5–10 days. | |
| Reporting group title | Oral oseltamivir 75 mg |
| Reporting group description: Participants ≥ 16 years of age received oral oseltamivir 75 mg twice daily, adjusted for renal function for 5–10 days. | |

| Reporting group values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg |
|------------------------------------|---------------------|---------------------|------------------------|
| Number of subjects | 201 | 209 | 205 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Age continuous Units: years arithmetic mean standard deviation | 55.2 ± 18.88 | 57.3 ± 17.39 | 55.9 ± 18.7 |
| Gender categorical Units: Subjects | | | |
| Female | 82 | 86 | 117 |
| Male | 119 | 123 | 88 |
| Race Units: Subjects | | | |
| African American/African Heritage | 12 | 4 | 10 |
| American Indian or Alaskan Native | 3 | 2 | 4 |
| Asian - Central/South Asian Heritage | 10 | 15 | 13 |
| Asian - East Asian Heritage | 12 | 18 | 13 |
| Asian - South East Asian Heritage | 6 | 4 | 7 |
| Native Hawaiian or Other Pacific Islander | 2 | 1 | 0 |
| White - Arabic/North African Heritage | 4 | 3 | 3 |
| White -White/Caucasian/European Heritage | 150 | 162 | 154 |
| Unknown | 1 | 0 | 1 |
| Mixed Race | 1 | 0 | 0 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 615 | | |

| | | | |
|---|-----|--|--|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 285 | | |
| Male | 330 | | |
| Race Units: Subjects | | | |
| African American/African Heritage | 26 | | |
| American Indian or Alaskan Native | 9 | | |
| Asian - Central/South Asian Heritage | 38 | | |
| Asian - East Asian Heritage | 43 | | |
| Asian - South East Asian Heritage | 17 | | |
| Native Hawaiian or Other Pacific Islander | 3 | | |
| White - Arabic/North African Heritage | 10 | | |
| White -White/Caucasian/European Heritage | 466 | | |
| Unknown | 2 | | |
| Mixed Race | 1 | | |

End points

End points reporting groups

| | |
|--|------------------------|
| Reporting group title | IV zanamivir 300 mg |
| Reporting group description: Participants >=16 years of age received intravenous (IV) zanamivir 300 milligrams (mg) twice daily, adjusted for renal function for 5–10 days. | |
| Reporting group title | IV zanamivir 600 mg |
| Reporting group description: Participants >=16 years of age received IV zanamivir 600 mg twice daily, adjusted for renal function for 5–10 days. | |
| Reporting group title | Oral oseltamivir 75 mg |
| Reporting group description: Participants >=16 years of age received oral oseltamivir 75 mg twice daily, adjusted for renal function for 5–10 days. | |

Primary: Median time to clinical response (TTCR) in participants with confirmed influenza

| | |
|---|--|
| End point title | Median time to clinical response (TTCR) in participants with confirmed influenza |
| End point description: Clinical response is defined as the resolution of at least 4 of the 5 vital signs (temperature, oxygen saturation, respiratory status, heart rate, systolic blood pressure) within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurred first. The ITT-E Population is comprised of all randomized participants who received at least one dose of investigational product. The Influenza Positive Population (IPP) is comprised of all participants in the ITT-E Population with proven influenza infection. "-99999, 99999" indicates that full range data are not available. | |
| End point type | Primary |
| End point timeframe: Up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[1] | 162 ^[2] | 163 ^[3] | |
| Units: Days to success | | | | |
| median (full range (min-max)) | 5.87 (-99999 to 99999) | 5.14 (-99999 to 99999) | 5.63 (-99999 to 99999) | |

Notes:

[1] - IPP Population

[2] - IPP Population

[3] - IPP Population

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | IV zanamivir 300 mg v IV zanamivir 600 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2496 ^[4] |
| Method | Wilcoxon rank-sum test |

Notes:

[4] - Wilcoxon-sum test stratified by the randomization strata

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | IV zanamivir 600 mg v Oral oseltamivir 75 mg |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3912 ^[5] |
| Method | Wilcoxon rank-sum test |

Notes:

[5] - Wilcoxon-sum test stratified by the randomization strata

Primary: Percentage of participants with confirmed influenza achieving a clinical response

| | |
|-----------------|--|
| End point title | Percentage of participants with confirmed influenza achieving a clinical response ^[6] |
|-----------------|--|

End point description:

Clinical response is defined as the resolution of at least 4 of the 5 vital signs (temperature, oxygen saturation, respiratory status, heart rate, systolic blood pressure) within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever occurred first.

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

End point timeframe:

Up to 42 days

Notes:

[6] - 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: There are no statistical data to report.

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[7] | 162 ^[8] | 163 ^[9] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 85 | 87 | 77 | |

Notes:

[7] - IPP Population

[8] - IPP Population

[9] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Combined time to clinical response (TTCR) and TTRI

| | |
|-----------------|--|
| End point title | Combined time to clinical response (TTCR) and TTRI |
|-----------------|--|

End point description:

Respiratory Status (RS) is a component of TTCR. Response criteria included the return to the pre-morbid oxygen requirement (participants with chronic oxygen use), a need for supplemental oxygen (administered by any modality: ventilator, non-invasive ventilation, facemask, facient, nasal canula, etc.) to no need for supplemental oxygen, or a respiratory rate of ≤ 24 breaths/minute (without supplemental oxygen). Data are presented as the percentage of participants achieving respiratory improvement. This analysis utilizes the Wei-Johanson method.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[10] | 162 ^[11] | 163 ^[12] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 77 | 78 | 74 | |

Notes:

[10] - IPP Population

[11] - IPP Population

[12] - IPP Population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | IV zanamivir 600 mg v IV zanamivir 300 mg |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.506 |
| Method | Wei-Johnson method |

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | IV zanamivir 600 mg v Oral oseltamivir 75 mg |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.41 |
| Method | Wei-Johnson method |

Secondary: Number of participants with all cause and attributable mortality at Day 14, at Day 28, and at the End of Study Visit

| | |
|-----------------|--|
| End point title | Number of participants with all cause and attributable mortality at Day 14, at Day 28, and at the End of Study Visit |
|-----------------|--|

End point description:

The number of participants who died on or before Day 14, Day 28, and the End of Study Visit are summarized.

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

End point timeframe:

On or before Day 14, Day 28, End of Study Visit (assessed up to 42 days)

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[13] | 162 ^[14] | 163 ^[15] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Died on or before Study Day 14: all cause | 5 | 8 | 5 | |
| Died on or before Study Day 28: all cause | 8 | 9 | 9 | |
| Died while on-study: all cause | 10 | 12 | 10 | |
| Died on or before Study Day 14: attributable | 3 | 4 | 4 | |
| Died on or before Study Day 28: attributable | 5 | 5 | 5 | |
| Died while on-study: attributable | 5 | 6 | 6 | |

Notes:

[13] - IPP Population

[14] - IPP Population

[15] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Katz Activities of Daily Living (ADL) score and each ADL activity score

| | |
|-----------------|---|
| End point title | Change from Baseline in the Katz Activities of Daily Living (ADL) score and each ADL activity score |
|-----------------|---|

End point description:

The Katz ADL scores were collected for bathing, dressing, toileting, transferring, continence, and feeding activities and were assessed once daily during the treatment period/hospitalization and once at each Post-Treatment Clinic Visit. For the six individual activities, a score of 1 indicates independence, and a score of 0 indicates dependence. The total score is generated by adding the scores of all six activities. A total score of 6 indicates that the participant was independent; a total score of 0 indicates that the participant was very dependent. Baseline is defined as the pre-dose value collected on Study Day 1. Change from Baseline is defined as the difference at each time point (Day 5/6, and Day 10/11, and last day S/R if treatment was extended beyond 5 days) and the end of the study (post-treatment [PT] +28 Days) compared to Baseline. Only those participants available at the specified time points were analyzed.

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[16] | 162 ^[17] | 163 ^[18] | |
| Units: Scores on the scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total Score Day 5/6, n=149, 150, 139 | 1.07 (± 1.959) | 0.93 (± 1.782) | 0.78 (± 1.837) | |
| Total Score Day 10/11, n=16, 6, 12, | 0.88 (± 1.746) | 0.5 (± 0.837) | -0.08 (± 3.029) | |
| Total Score Last Day of S/R, n=5, 2, 8 | 0.2 (± 2.49) | -3 (± 4.243) | 0.75 (± 1.165) | |
| Total Score PT+28 Day, n=138, 134, 120 | 2.13 (± 2.234) | 1.72 (± 2.342) | 1.98 (± 2.142) | |
| Bathing: DAY 5/6, n=149, 150, 139 | 0.24 (± 0.488) | 0.19 (± 0.429) | 0.18 (± 0.438) | |
| Bathing: DAY 10/11, n=16, 6, 12 | 0.19 (± 0.403) | 0 (± 0) | 0 (± 0.426) | |
| Bathing: Last Day of S/R, n=5, 2, 8 | 0.2 (± 0.447) | -0.5 (± 0.707) | 0 (± 0) | |
| Bathing: PT + 28 DAYS, n=138, 134, 120 | 0.43 (± 0.498) | 0.34 (± 0.505) | 0.39 (± 0.507) | |
| Dressing DAY 5/6, n=149, 150, 139 | 0.23 (± 0.481) | 0.21 (± 0.438) | 0.14 (± 0.427) | |
| Dressing: Day 10/11, n=16, 6, 12 | 0.13 (± 0.342) | 0 (± 0) | -0.08 (± 0.515) | |
| Dressing: Last Day of S/R, n=5, 2, 8 | 0.2 (± 0.447) | -0.5 (± 0.707) | 0.13 (± 0.354) | |
| Dressing: PT+28 Day, n=138, 134, 120 | 0.42 (± 0.495) | 0.37 (± 0.515) | 0.41 (± 0.494) | |
| Toileting: DAY 5/6, n=149, 150, 139 | 0.19 (± 0.456) | 0.19 (± 0.439) | 0.14 (± 0.409) | |
| Toileting: Day 10/11, n=16, 6, 12 | 0.13 (± 0.342) | 0.33 (± 0.516) | 0.08 (± 0.515) | |
| Toileting: Last Day of S/R, n=5, 2, 8 | 0.2 (± 0.447) | -0.5 (± 0.707) | 0 (± 0.535) | |
| Toileting: PT+28 Day, n=138, 134, 120 | 0.4 (± 0.491) | 0.32 (± 0.514) | 0.37 (± 0.484) | |
| Transferring: DAY 5/6, n=149, 150, 139 | 0.28 (± 0.505) | 0.23 (± 0.451) | 0.17 (± 0.41) | |
| Transferring: Day 10/11, n=16, 6, 12 | 0.19 (± 0.403) | 0.17 (± 0.408) | 0.08 (± 0.515) | |
| Transferring: Last Day of S/R, n=5, 2, 8 | 0 (± 0.707) | -0.5 (± 0.707) | 0.25 (± 0.463) | |
| Transferring: PT+28 Day, n=138, 134, 120 | 0.45 (± 0.499) | 0.36 (± 0.526) | 0.4 (± 0.492) | |
| Continence: DAY 5/6, n=149, 150, 139 | 0.07 (± 0.322) | 0.05 (± 0.314) | 0.07 (± 0.374) | |
| Continence: Day 10/11, n=16, 6, 12 | 0.13 (± 0.342) | 0 (± 0) | -0.08 (± 0.669) | |
| Continence: Last Day of S/R, n=5, 2, 8 | -0.2 (± 0.447) | -0.5 (± 0.707) | 0.13 (± 0.354) | |
| Continence: PT+28 Day, n=138, 134, 120 | 0.22 (± 0.431) | 0.16 (± 0.422) | 0.23 (± 0.439) | |
| Feeding: Day 5/6, n=149, 150, 139 | 0.07 (± 0.331) | 0.07 (± 0.309) | 0.08 (± 0.382) | |
| Feeding: Day 10/11, n=16, 6, 12 | 0.13 (± 0.342) | 0 (± 0) | -0.08 (± 0.669) | |
| Feeding: Last Day of S/R, n=5, 2, 8 | -0.2 (± 0.447) | -0.5 (± 0.707) | 0.25 (± 0.463) | |
| Feeding: PT+28 Day, n=138, 134, 120 | 0.21 (± 0.409) | 0.17 (± 0.416) | 0.19 (± 0.395) | |

Notes:

[16] - IPP Population

[17] - IPP Population

[18] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to return to pre-morbid functional status as measured by the Katz ADL score and each ADL activity score

| | |
|-----------------|---|
| End point title | Median time to return to pre-morbid functional status as measured by the Katz ADL score and each ADL activity score |
|-----------------|---|

End point description:

Pre-morbid functional status is defined as the best functional status in the 4 weeks prior to enrolment. Median time to return to pre-morbid functional status was assessed via the Katz ADL score (bathing, dressing, toileting, transferring, continence, and feeding activities). For the six individual activities, a score of 1 indicates independence, and a score of 0 indicates dependence. The total score is generated by adding the scores of all six activities. A total score of 6 indicates that the participant was independent; a total score of 0 indicates that the participant was very dependent. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles)

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[19] | 162 ^[20] | 163 ^[21] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Total score; n=139, 138, 130 | 2 (2 to 38) | 2 (2 to 37) | 2.5 (2 to 57) | |
| Bathing; n=135, 133, 126: | 2 (2 to 38) | 2 (2 to 37) | 2 (2 to 57) | |
| Dressing; n=138, 135, 126 | 2 (2 to 38) | 2 (2 to 40) | 2 (2 to 57) | |
| Toileting; n=139, 136, 130 | 2 (2 to 38) | 2 (2 to 31) | 2 (2 to 40) | |
| Transferring; n=140, 140, 133 | 2 (2 to 38) | 2 (2 to 31) | 2 (2 to 40) | |
| Continence; n= 142, 143, 139 | 2 (2 to 35) | 2 (2 to 33) | 2 (2 to 31) | |
| Feeding; n= 145, 148, 144 | 2 (2 to 29) | 2 (2 to 32) | 2 (2 to 36) | |

Notes:

[19] - IPP Population

[20] - IPP Population

[21] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who returned to their pre-morbid functional status as assessed per the Katz ADL score and each ADL activity score at the end of the study

| | |
|-----------------|--|
| End point title | Number of participants who returned to their pre-morbid functional status as assessed per the Katz ADL score and each ADL activity score at the end of the study |
|-----------------|--|

End point description:

Pre-morbid functional status is defined as the best functional status in the 4 weeks prior to enrolment. The number of participants who returned to their pre-morbid functional status at the end of the study assessed per the Katz ADL score (bathing, dressing, toileting, transferring, continence and feeding activities) is summarized

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[22] | 162 ^[23] | 163 ^[24] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Total | 139 | 138 | 130 | |
| Bathing | 135 | 133 | 126 | |
| Dressing | 138 | 135 | 126 | |
| Toileting | 139 | 136 | 130 | |
| Transferring: | 140 | 140 | 133 | |
| Continence | 142 | 143 | 139 | |
| Feeding | 145 | 148 | 144 | |

Notes:

[22] - IPP Population

[23] - IPP Population

[24] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to return to the pre-morbid level of activity as measured by the 3-point scale

| | |
|-----------------|--|
| End point title | Median time to return to the pre-morbid level of activity as measured by the 3-point scale |
|-----------------|--|

End point description:

Median time to return to pre-morbid level of activity was assessed during the study i.e once daily during treatment/hospitalization and once at each post-treatment assessment and was measured using the 3-point scale (bed rest, limited ambulation, or unrestricted). Participants succeeded in pre-morbid functional status were analyzed.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 138 ^[25] | 137 ^[26] | 135 ^[27] | |
| Units: Days | | | | |
| median (full range (min-max)) | 5 (2 to 34) | 4 (2 to 31) | 4 (1 to 57) | |

Notes:

[25] - IPP Population

[26] - IPP Population

[27] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated clinical symptoms of influenza

| | |
|-----------------|--|
| End point title | Number of participants with the indicated clinical symptoms of influenza |
|-----------------|--|

End point description:

Influenza clinical symptoms included nasal symptoms (rhinorrhea, congestion), feverishness, cough, myalgias, fatigue, diarrhea, anorexia, dyspnea, headache, sore throat, nausea, and vomiting. Influenza symptoms were assessed once daily during inpatient/hospitalization and once at each post-treatment assessment

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[28] | 162 ^[29] | 163 ^[30] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Anorexia | 102 | 112 | 123 | |
| Cough | 151 | 150 | 157 | |
| Diarrhea | 64 | 57 | 66 | |
| Dyspnea | 143 | 145 | 152 | |
| Fatigue | 144 | 144 | 148 | |
| Feverishness | 138 | 145 | 136 | |
| Headache | 104 | 102 | 103 | |
| Myalgias | 115 | 117 | 114 | |
| Nasal symptoms (rhinorrhea, congestion) | 118 | 123 | 122 | |
| Nausea | 57 | 51 | 77 | |
| Sore throat | 94 | 115 | 97 | |
| Vomiting | 27 | 23 | 45 | |

Notes:

[28] - IPP Population

[29] - IPP Population

[30] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median duration of clinical symptoms of influenza

| | |
|-----------------|---|
| End point title | Median duration of clinical symptoms of influenza |
|-----------------|---|

End point description:

Influenza clinical symptoms included nasal symptoms (rhinorrhea, congestion), feverishness, cough, myalgias, fatigue, diarrhea, anorexia, dyspnea, headache, sore throat, nausea, and vomiting. Influenza symptoms were assessed once daily during inpatient/hospitalization and once at each post-treatment assessment. Only those participants with clinical symptoms of influenza were analyzed (represented by

n=X, X, X in the category titles)

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[31] | 162 ^[32] | 163 ^[33] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Anorexia; n=102, 112, 123 | 5 (1 to 39) | 3 (1 to 46) | 5 (1 to 55) | |
| Cough; n= 151, 150, 157 | 14 (1 to 39) | 13 (1 to 46) | 15 (1 to 56) | |
| Diarrhea; n=64, 57, 66 | 3 (1 to 29) | 2 (1 to 28) | 3 (1 to 23) | |
| Dyspnea; n=143, 145, 152 | 7 (1 to 40) | 6 (1 to 43) | 8 (1 to 56) | |
| Fatigue; n= 144, 144, 148 | 11 (1 to 41) | 11 (1 to 44) | 12 (1 to 56) | |
| Feverishness; n=138, 145, 136 | 2 (1 to 28) | 2 (1 to 29) | 2.5 (1 to 56) | |
| Headache; n=104, 102, 103 | 3 (1 to 33) | 3 (1 to 33) | 4 (1 to 56) | |
| Myalgias; n=115, 117, 114 | 4 (1 to 39) | 3 (1 to 34) | 4 (1 to 56) | |
| Nasal symptoms; n=118, 123, 122 | 6 (1 to 34) | 4 (1 to 43) | 5.5 (1 to 35) | |
| Nausea; n=57, 51, 77 | 3 (1 to 34) | 2 (1 to 24) | 2 (1 to 28) | |
| Sore throat; n=94, 115, 97 | 3 (1 to 28) | 2 (1 to 36) | 3 (1 to 35) | |
| Vomiting; n=27, 23, 45 | 2 (1 to 19) | 1 (1 to 11) | 1 (1 to 20) | |

Notes:

[31] - IPP Population

[32] - IPP Population

[33] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with complications of influenza and associated antibiotic use

| | |
|--|--|
| End point title | Number of participants with complications of influenza and associated antibiotic use |
| End point description: | |
| The number of participants with complications of influenza and associated antibiotic use is summarized | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|----------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[34] | 162 ^[35] | 163 ^[36] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Associated use of any antibiotic | 22 | 16 | 29 | |
| Any complication of influenza | 34 | 33 | 41 | |

Notes:

[34] - IPP Population

[35] - IPP Population

[36] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated ventilation status: modality of invasive and non-invasive ventilator support and oxygen supplementation

| | |
|-----------------|---|
| End point title | Number of participants with the indicated ventilation status: modality of invasive and non-invasive ventilator support and oxygen supplementation |
|-----------------|---|

End point description:

Ventilation status was assessed three times daily during the treatment period/hospitalization. Ventilation status was assessed once daily during inpatient/hospitalization and once at each post-treatment clinic visit. The number of participants reported for machine-assisted: extracorporeal membrane oxygenation (ECMO), endotracheal mechanical ventilation, and supplemental oxygen delivery (SOD), no supplemental oxygen (O2) or ventilation support, Respiratory support at "any time (AT) on study" and at Baseline (Day 1) are summarized. Data for the "any time (AT) on study" time point was reported.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[37] | 162 ^[38] | 163 ^[39] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Day 1, Machine-Assisted: ECMO | 0 | 0 | 0 | |
| Day 1, Machine-Assisted: Endotracheal | 28 | 25 | 27 | |
| Day 1, SOD | 96 | 103 | 87 | |
| Day 1, No supplemental O2 or ventilation support | 32 | 29 | 37 | |
| Day 1, Respiratory Support | 34 | 29 | 39 | |
| AT on Study, Machine-Assisted: ECMO | 2 | 0 | 1 | |
| AT on Study, Machine-Assisted: Endotracheal | 36 | 31 | 37 | |
| AT on Study, SOD | 137 | 137 | 128 | |
| AT on Study, No supplemental O2 or ventilation sup | 138 | 135 | 131 | |

| | | | | |
|----------------------------------|----|----|----|--|
| AT on Study, Respiratory Support | 46 | 37 | 50 | |
|----------------------------------|----|----|----|--|

Notes:

[37] - IPP Population

[38] - IPP Population

[39] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time duration of invasive and non-invasive ventilator support and oxygen supplementation

| | |
|-----------------|---|
| End point title | Median time duration of invasive and non-invasive ventilator support and oxygen supplementation |
|-----------------|---|

End point description:

Ventilation status was assessed three times daily during the treatment period/hospitalization. Ventilation status was assessed once daily during inpatient/hospitalization and once at each post-treatment clinic visit. Only those participants available with the indicated ventilator support or oxygen supplementation were analyzed (represented by n=X, X, X in the category titles).

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

End point timeframe:

Baseline and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[40] | 162 ^[41] | 163 ^[42] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Ventilator Support, n=46, 37, 50 | 9 (0 to 38) | 5.2 (0 to 36) | 8.2 (0 to 36) | |
| Oxygen Supplementation, n=137, 137, 128 | 4.4 (0 to 38) | 4.2 (0 to 43) | 3.7 (0 to 36) | |

Notes:

[40] - IPP Population

[41] - IPP Population

[42] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time of duration of hospitalization and Intensive Care Unit (ICU) stay

| | |
|-----------------|---|
| End point title | Median time of duration of hospitalization and Intensive Care Unit (ICU) stay |
|-----------------|---|

End point description:

Hospital duration and ICU duration was assessed from the first day of dosing. Hospital duration was calculated as the discharge date minus the admission date + 1. Hospital duration while on study was the earlier of discharge, completion, or withdrawal minus the later of the admission date or the study start date + 1. ICU duration-Modified was calculated as the original ICU duration minus ICU days prior to Study Day 1. Only those participants with the indicated hospitalization or ICU stay were analyzed (represented by n=X, X, X in the category titles)

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to the end of the study (assessed up to 42 days) | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[43] | 162 ^[44] | 163 ^[45] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Hospitalization; n=163, 162, 163 | 10 (1 to 108) | 8 (2 to 64) | 9 (1 to 58) | |
| Hospitalization while on study; n=163, 162, 163 | 8 (1 to 39) | 6 (1 to 43) | 7 (1 to 39) | |
| Hospitalization-ICU; n=72, 56, 71 | 8 (1 to 41) | 7.5 (1 to 36) | 8 (1 to 36) | |
| ICU Duration Modified; n=70, 54, 69 | 7 (1 to 39) | 6 (1 to 36) | 7 (1 to 36) | |

Notes:

[43] - IPP Population

[44] - IPP Population

[45] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to the absence of fever and improved respiratory status, oxygen saturation, heart rate, and systolic blood pressure

| | |
|-----------------|---|
| End point title | Median time to the absence of fever and improved respiratory status, oxygen saturation, heart rate, and systolic blood pressure |
|-----------------|---|

End point description:

The absence of fever is defined as a nonaxillary temperature recording ≤ 36.6 degrees Celsius axillary, ≤ 37.2 degrees Celsius oral or ≤ 37.7 degrees Celsius core. Respiratory Status (RS) response criteria included the return to the pre-morbid oxygen requirement (participants with chronic oxygen use), or the need for supplemental oxygen (administered by any modality: ventilator, non-invasive ventilation, facemask, facient, nasal canula, etc.) to no need for supplemental oxygen, or a respiratory rate ≤ 24 breaths/minute (without supplemental oxygen). Oxygen saturation response criteria: $\geq 95\%$ (without supplemental oxygen). Heart rate response criteria: ≤ 100 beats/minute. Systolic blood pressure response criteria: ≥ 90 millimeters of mercury. Vital signs were assessed three times daily during the treatment period/hospitalization. Vital signs were assessed once daily during inpatient/hospitalization and once at each post-treatment clinic visit.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[46] | 162 ^[47] | 163 ^[48] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Fever | 1.6 (0 to 34) | 0.8 (0 to 14) | 1.5 (0 to 31) | |
| Oxygen Saturation; n=98, 108, 99 | 5.3 (0 to 30) | 5.6 (0 to 32) | 4.5 (0 to 25) | |
| Respiratory status; n=126, 126, 121 | 3.5 (0 to 31) | 3.6 (0 to 32) | 2.8 (0 to 21) | |
| Heart rate; n=156, 148, 155 | 0.4 (0 to 28) | 0.4 (0 to 21) | 0.5 (0 to 24) | |
| Systolic blood pressure; n=156, 156, 154 | 0.3 (0 to 23) | 0.3 (0 to 14) | 0.3 (0 to 16) | |

Notes:

[46] - IPP Population

[47] - IPP Population

[48] - IPP 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:

Virologic improvement is defined as a 2 log drop in viral load or sustained undetectable viral ribonucleic acid (RNA) (on two successive occasions) as measured by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal samples. Nasopharyngeal swabs were collected daily from Baseline through Day 5. If randomized treatment was continued beyond Day 5, samples were taken on Treatment Days 6, 8, 10 and on the last day of randomized treatment. For participants who utilized the Switch (S)/Rescue (R) option, samples were taken on S/R Day 1, S/R Day 3, S/R Day 5, or S/R Day 6, whichever was the last day of S/R treatment. Nasopharyngeal swabs were taken if the participant was symptomatic and continued to be hospitalized on the Post-Treatment +2, +5, +9, +16, and +28 Day assessment. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Data presented is for subjects positive at Baseline.

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

End point timeframe:

Baseline and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|------------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[49] | 162 ^[50] | 163 ^[51] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Influenza A and B; n=116, 122, 129 | 3 (2 to 34) | 3 (2 to 35) | 3 (2 to 34) | |
| Influenza A/H1N1; n=47, 42, 48 | 3 (2 to 13) | 3 (2 to 34) | 3 (2 to 34) | |
| Influenza A/H3N2, n=55, 58, 61 | 3 (2 to 8) | 3 (2 to 35) | 3 (2 to 11) | |
| Influenza B; n=15, 20, 21 | 5 (2 to 34) | 3 (2 to 21) | 3 (2 to 12) | |

Notes:

[49] - IPP Population

[50] - IPP Population

[51] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in quantitative virus culture from nasopharyngeal swabs positive at Baseline

| | |
|-----------------|---|
| End point title | Change from Baseline in quantitative virus culture from nasopharyngeal swabs positive at Baseline |
|-----------------|---|

End point description:

Nasopharyngeal swabs were collected daily from Baseline through Day5. If randomized treatment was continued beyond Day5, samples were taken on Treatment Day6, Day8, Day10, Day11, and the last day of randomized treatment. For participants who utilized the S/R option, samples were taken on S/R Day1, S/R Day3, S/R Day5, or S/R Day6, whichever was the last day of S/R treatment. Samples were taken if the participant was symptomatic and continued to be hospitalized on the Post-Treatment +2, +5, +9, +16 and +28Day assessment. Viral load as measured by RT-PCR was assessed in Quantitative Virus Culture, log₁₀ 50% Tissue Culture Infectious Dose (TCID₅₀)/milliliter (mL). Change from Baseline was calculated as the post-Baseline value minus Baseline value. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). "99999" :data are not available/analysis was not performed. Data presented is for participants positive at Baseline.

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

End point timeframe:

Baseline, Day 3, Day 5, Day 8, Day 10, Day 11 and/or last day of randomized treatment, if randomized treatment was extended beyond 5 days, and S/R Day 5/6 (up to Day 14) if applicable

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---|-------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[52] | 162 ^[53] | 163 ^[54] | |
| Units: log ₁₀ TCID ₅₀ /mL | | | | |
| median (full range (min-max)) | | | | |
| Day 3 n=78, 76, 89 | -2.01 (-5 to 0.8) | -2.01 (-4.8 to 1.3) | -2.01 (-5.3 to 2.8) | |
| Day 5 n=66, 69, 80 | -2.51 (-5.5 to 0) | -2.26 (-5.3 to 0) | -2.26 (-5.3 to 2) | |
| Day 8 n=6, 7, 10 | -1.64 (-5.5 to 0) | -2.01 (-4.3 to 0.3) | -2.26 (-4.3 to 0) | |
| Day 10 n=4, 3, 4 | -3.76 (-5.5 to 0.3) | -0.3 (-1.3 to 0.3) | -2.26 (-3.8 to 1.3) | |
| Day 11 n=3, 3, 4 | -3.01 (-5.5 to 0.3) | -0.3 (-1.3 to 0.3) | -2.26 (-3.8 to 1.3) | |
| S/R Day 5 n=0, 1, 1 | 99999 (-99999 to 99999) | -4.3 (-4.3 to -4.3) | -3 (-3 to -3) | |
| S/R Day 6 n=1, 1, 1 | -2.5 (-2.5 to -2.5) | -4.3 (-4.3 to -4.3) | 0 (0 to 0) | |

Notes:

[52] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline viral load (influenza A or B) from nasopharyngeal swabs positive at Baseline

| | |
|-----------------|---|
| End point title | Change from Baseline viral load (influenza A or B) from nasopharyngeal swabs positive at Baseline |
|-----------------|---|

End point description:

Nasopharyngeal swabs were collected daily from Baseline through Day 5. If randomized treatment was continued beyond Day 5, samples were taken on Treatment Day 6, Day 8, Day 10, Day 11, and the last day of randomized treatment. For participants who utilized the S/R option, samples were taken on S/R Day 1, S/R Day 3, S/R Day 5, or S/R Day 6, whichever was the last day of S/R treatment. Samples were taken if the participant was symptomatic and continued to be hospitalized on the Post-Treatment +2, +5, +9, +16 and +28 Day assessment. Viral load as measured by PCR. Change from Baseline is calculated as the post-Baseline value minus the Baseline value. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). "99999" indicates that data are not available/analysis was not performed. Data presented is for participants positive at Baseline

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

End point timeframe:

Baseline, Day 3, Day 5, Day 8, Day 10, Day 11 and/or last day of randomized treatment, if randomized treatment was extended beyond 5 days, and S/R Day 5/6 (up to Day 14) if applicable

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--------------------------------|-------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[55] | 162 ^[56] | 163 ^[57] | |
| Units: log ₁₀ vp/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 3 n=126, 127, 129 | -1.5 (-5.4 to 2.2) | -1.83 (-4.9 to 2) | -1.75 (-6 to 2.8) | |
| Day 5 n=110, 114, 114 | -2.51 (-5.8 to 3.2) | -2.71 (-6.2 to 3.1) | -2.73 (-6.3 to 2.3) | |
| Day 8 n=15, 12, 16 | -2.38 (-4.4 to 1) | -3.16 (-5.5 to 0.3) | -1.78 (-5.7 to 1.1) | |
| Day 10 n=13, 6, 8 | -2.75 (-6 to -0.9) | -3.03 (-3.5 to 1.5) | -2.63 (-4.6 to 0.9) | |
| Day 11 n=9, 4, 7 | -3.58 (-4.9 to -0.6) | -2.6 (-3.1 to 1.7) | -3.29 (-4.9 to 1) | |
| S/R Day 5 n=0, 1, 1 | 99999 (-99999 to 99999) | -3.8 (-3.8 to -3.8) | -5.7 (-5.7 to -5.7) | |
| S/R Day 6 n=1, 1, 2 | -5.2 (-5.2 to -5.2) | -5.4 (-5.4 to -5.4) | -3.84 (-4 to -3.7) | |

Notes:

[55] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with no detectable viral RNA and the absence of cultivable virus in lower respiratory samples (bronchoalveolar lavage sample [BAL], endotracheal aspirate)

| | |
|-----------------|---|
| End point title | Number of participants with no detectable viral RNA and the absence of cultivable virus in lower respiratory samples (bronchoalveolar lavage sample [BAL], endotracheal aspirate) |
|-----------------|---|

End point description:

Lower respiratory samples included BAL and endotracheal aspirates. Endotracheal aspirates were requested in participants (par.) who were intubated. Samples were collected daily from Baseline/Day 1 through Day 5 and Day 6 (if the last day of randomized treatment [trt]). If trt was continued beyond Day 5, additional samples were taken on Trt Day 6, Day 8, Day 10, and/or the day of the last dose of randomized trt, if applicable, and S/R Day 1, S/R Day 3, S/R Day 5, or S/R Day 6 if the last day of S/R trt. If the par. was symptomatic and hospitalized, samples were taken on the Post-Trt +2, +5, +9, +16 assessment days, and at the Post-Trt [PT]+28 Day assessment. Only those par. available at the specified time points were analyzed (represented by n=X, X, X in the category titles). BAL samples were only collected if the procedure was being carried out for the routine management of the par. Data also presented for par. positive at Baseline.

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[58] | 162 ^[59] | 163 ^[60] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Influenza A and B Day 1; n=21, 17, 21 | 0 | 0 | 0 | |
| Influenza A and B Day 2; n=17, 15, 14 | 0 | 4 | 1 | |
| Influenza A and B Day 3; n=16, 10, 15 | 1 | 2 | 0 | |
| Influenza A and B Day 4; n=16,10, 15 | 2 | 2 | 2 | |
| Influenza A and B Day 5; n=15,10, 15 | 3 | 4 | 2 | |
| Influenza A and B Day 6; n= 14, 5, 9 | 3 | 1 | 3 | |
| Influenza A and B Day 8; n=5, 3, 7 | 2 | 0 | 2 | |
| Influenza A and B Day 10; n=4, 3, 3 | 0 | 0 | 0 | |
| Influenza A and B S/R Day 1; n=0, 0, 1 | 0 | 0 | 0 | |
| Influenza A and B S/R Day 3; n=1, 0, 1 | 0 | 0 | 1 | |
| Influenza A and B S/R Day 5; n=1, 0, 0 | 0 | 0 | 0 | |
| Influenza A and B PT + 2 Days; n= 9, 3, 9 | 4 | 1 | 3 | |
| Influenza A and B PT + 5 Days; n= 11, 2, 6 | 4 | 1 | 0 | |

| | | | | |
|--|---|---|---|--|
| Influenza A and B PT + 9 Days; n= 5, 2, 4 | 4 | 1 | 3 | |
| Influenza A and B PT + 16 Days; n= 4, 1, 3 | 3 | 1 | 2 | |
| Influenza A and B PT + 28 Days; n= 1, 0, 1 | 1 | 0 | 1 | |

Notes:

[58] - IPP Population

[59] - IPP Population

[60] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to no detectable viral RNA and the absence of cultivable virus in any obtained sample (upper and lower respiratory samples)

| | |
|-----------------|---|
| End point title | Median time to no detectable viral RNA and the absence of cultivable virus in any obtained sample (upper and lower respiratory samples) |
|-----------------|---|

End point description:

Upper and lower respiratory samples were collected daily from Baseline/Day 1 through Day 5 and Day 6 (if the last day of randomized treatment). If treatment was continued beyond Day 5, additional samples were taken on Treatment Day 6, Day 8, Day 10, and/or the day of the last dose of randomized treatment, if applicable, and S/R Day 1, S/R Day 3, S/R Day 5, or S/R Day 6 if the last day of S/R treatment. If the participant was symptomatic and hospitalized, samples were taken on the Post-Treatment+2, +5, +9, +16 assessment days, and at the Post-Treatment +28 Day. Assessment of samples was done by quantitative RT-PCR. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Data also presented for participants positive at Baseline.

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---------------------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[61] | 162 ^[62] | 163 ^[63] | |
| Units: Days | | | | |
| median (full range (min-max)) | | | | |
| Influenza A and B, n=114, 118, 115 | 4 (1 to 34) | 3 (1 to 35) | 4 (1 to 57) | |
| Positive at baseline; n=102, 104, 102 | 4 (2 to 34) | 4 (2 to 35) | 4 (2 to 57) | |

Notes:

[61] - IPP Population

[62] - IPP Population

[63] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Resistance-associated mutations events detected in the NA and HA gene of influenza A and B viruses in nasopharyngeal swabs and endotracheal/BAL

samples

| | |
|-----------------|---|
| End point title | Resistance-associated mutations events detected in the NA and HA gene of influenza A and B viruses in nasopharyngeal swabs and endotracheal/BAL samples |
|-----------------|---|

End point description:

Nasopharyngeal swabs and endotracheal /BAL samples were collected for viral susceptibility analysis. Susceptibility analyses consisted of phenotyping and genotyping. Resistance mutations were detected by genotyping. Viral susceptibility to zanamivir and oral oseltamivir at Baseline and throughout treatment determined by NA and HA (gene of influenza A and B viruses) sequence analysis and NA enzyme inhibition. Number of participants with viral mutation events are summarized, this includes all resistance mutations (substitutions) i.e. those present at Baseline and those that emerged during treatment.

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

End point timeframe:

Baseline and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 163 ^[64] | 162 ^[65] | 163 ^[66] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| NA Gene,H3N2: Y155F | 5 | 7 | 5 | |
| NA Gene,H3N2:S245N | 4 | 4 | 0 | |
| NA Gene,H3N2:I222V | 0 | 1 | 2 | |
| NA Gene,H3N2:N294S/N | 2 | 0 | 0 | |
| NA Gene,H3N2:V149A | 0 | 1 | 1 | |
| NA Gene,H3N2:D198D/G | 0 | 0 | 1 | |
| NA Gene,H3N2:G248G/E | 1 | 0 | 0 | |
| NA Gene,H3N2:N294D/N | 0 | 1 | 0 | |
| NA Gene,H3N2:R292R/K | 0 | 0 | 1 | |
| NA Gene,H3N2:T325I | 1 | 0 | 0 | |
| NA Gene,H3N2:Y155H | 0 | 0 | 1 | |
| NA Gene,H1N1: H275H/Y | 0 | 1 | 4 | |
| NA Gene,H1N1:H275Y | 0 | 1 | 3 | |
| NA Gene,H1N1:Q313R | 1 | 0 | 2 | |
| NA Gene,H1N1:D199N | 1 | 0 | 0 | |
| NA Gene,H1N1:E278G/E | 0 | 0 | 1 | |
| NA Gene,H1N1:I223I/K | 0 | 0 | 1 | |
| NA Gene,H1N1:Q136Q/R | 0 | 0 | 1 | |
| NA Gene,H1N1:S247N | 1 | 0 | 0 | |
| NA Gene,H1N1:S247S/I | 1 | 0 | 0 | |
| NA Gene,H1N1:S247S/N | 0 | 1 | 0 | |
| NA Gene,B: E148G | 1 | 0 | 0 | |
| NA Gene,B: G141E | 0 | 0 | 1 | |
| NA Gene,B: M403I | 1 | 0 | 0 | |
| HA Gene, H3N2:R142G | 18 | 21 | 21 | |
| HA Gene, H3N2:S198A | 13 | 8 | 11 | |
| HA Gene, H3N2:A138S | 3 | 1 | 2 | |
| HA Gene, H3N2:R142K | 0 | 0 | 2 | |
| HA Gene, H3N2:A304A/P | 0 | 0 | 1 | |

| | | | | |
|----------------------------|---|---|---|--|
| HA Gene, H3N2:A304D | 0 | 1 | 0 | |
| HA Gene, H3N2:L194P/L | 1 | 0 | 0 | |
| HA Gene, H3N2:Q75H | 0 | 1 | 0 | |
| HA Gene, H3N2:S124G | 0 | 0 | 1 | |
| HA Gene, H3N2:S262N | 0 | 1 | 0 | |
| HA Gene, H3N2:H1N1: S183P | 1 | 0 | 2 | |
| HA Gene, H1N1 :D222D/G | 0 | 0 | 2 | |
| HA Gene, H1N1 :D222D/N | 0 | 2 | 0 | |
| HA Gene, H1N1 :D222N | 0 | 0 | 2 | |
| HA Gene, H1N1 :S162N | 0 | 0 | 2 | |
| HA Gene, H1N1 :D187E | 0 | 1 | 0 | |
| HA Gene, H1N1 :D222G | 1 | 0 | 0 | |
| HA Gene, H1N1 :D222S/D/N/G | 1 | 0 | 0 | |
| HA Gene, H1N1 :L151P/L | 0 | 1 | 0 | |
| HA Gene, H1N1 :V152I | 0 | 0 | 1 | |

Notes:

[64] - IPP Population

[65] - IPP Population

[66] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: 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 |
|-----------------|--|

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse. All AEs were assessed by the Investigator as related or not related to the study treatment. The Safety Population is comprised of all randomized participants who received at least one dose of investigational product and assessed according to their actual treatment received, regardless of the randomization assigned.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[67] | 209 ^[68] | 205 ^[69] | |
| Units: Participants | | | | |
| number (not applicable) | 25 | 22 | 35 | |

Notes:

[67] - Safety Population

[68] - Safety Population

[69] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any severe or Grade 3/4 AE

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

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse. AEs that occurred 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 AEs. Grade 3=severe; Grade 4=potentially life threatening.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[70] | 209 ^[71] | 205 ^[72] | |
| Units: Participants | | | | |
| number (not applicable) | 39 | 45 | 44 | |

Notes:

[70] - Safety Population

[71] - Safety Population

[72] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: 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 |
|-----------------|--|

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[73] | 209 ^[74] | 205 ^[75] | |
| Units: Participants | | | | |
| number (not applicable) | 8 | 10 | 11 | |

Notes:

[73] - Safety Population

[74] - Safety Population

[75] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: 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 |
|-----------------|--|

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.

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

End point timeframe:

Up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[76] | 209 ^[77] | 205 ^[78] | |
| Units: Participants | | | | |
| number (not applicable) | 14 | 16 | 13 | |

Notes:

[76] - Safety Population

[77] - Safety Population

[78] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: 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 |
| 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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse. AEs that occurred 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 assessed by the Investigator as related or not related to the study treatment. | |
| End point type | Secondary |
| End point timeframe: Up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[79] | 209 ^[80] | 205 ^[81] | |
| Units: Participants | | | | |
| number (not applicable) | 5 | 3 | 7 | |

Notes:

[79] - Safety Population

[80] - Safety Population

[81] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated chemistry laboratory values shifts from Baseline (Day 1) and up to 42 days

| | |
|---|--|
| End point title | Number of participants with the indicated chemistry laboratory values shifts from Baseline (Day 1) and up to 42 days |
| End point description: Samples for laboratory assessments were collected at Baseline (Day 1), Day 3, Day 5/6, Day 8, Day 10/11 (or last day of randomized treatment), switch/rescue (S/R) Day 1, S/R Day 3, and S/R Day 5/6 (last day of S/R treatment for those participants who utilized this option), Post-Treatment +2 (if hospitalized), and Post-Treatment +5, +16, and +28 Days. Clinical chemistry parameters included albumin, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, calcium, creatine kinase, chloride, carbon dioxide content (CO2), creatinine, potassium, magnesium, sodium. Per the DAIDS table for grading the severity of adult and pediatric AEs, Grade (G) 1=mild, G2= moderate, G3=severe and G4=potentially life threatening. The number of participants with values that were G1, G2, G3 and G4 relative to the normal range are summarised. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1) and up to 42 days | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|-----------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[82] | 209 ^[83] | 205 ^[84] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Albumin G1, n=194,203,202 | 12 | 18 | 15 | |
| Albumin G2, n=194,203,202 | 32 | 43 | 40 | |
| Albumin G3, n=194,203,202 | 1 | 5 | 0 | |
| Albumin G4, n=194,203,202 | 0 | 0 | 0 | |
| ALP G1, n=194,203,202 | 10 | 15 | 9 | |
| ALP G2, n=194,203,202 | 0 | 4 | 1 | |
| ALP G3, n=194,203,202 | 0 | 2 | 0 | |
| ALP G4, n=194,203,202 | 0 | 0 | 0 | |
| ALT G1, n=194,203,202 | 13 | 10 | 12 | |
| ALT G2, n=194,203,202 | 2 | 1 | 1 | |
| ALT G3, n=194,203,202 | 0 | 0 | 0 | |
| ALT G4, n=194,203,202 | 0 | 0 | 1 | |
| AST G1, n=193,202,202 | 23 | 27 | 19 | |
| AST G2, n=193,202,202 | 8 | 8 | 6 | |
| AST G3, n=193,202,202 | 2 | 0 | 2 | |
| AST G4, n=193,202,202 | 0 | 0 | 1 | |
| Total Bilirubin G1, n=194,203,202 | 5 | 2 | 2 | |
| Total Bilirubin G2, n=194,203,202 | 3 | 2 | 3 | |
| Total Bilirubin G3, n=194,203,202 | 1 | 2 | 0 | |
| Total Bilirubin G4, n=194,203,202 | 0 | 0 | 1 | |
| Creatine Kinase G1, n=194,203,202 | 10 | 11 | 6 | |
| Creatine Kinase G2, n=194,203,202 | 3 | 3 | 6 | |
| Creatine Kinase G3, n=194,203,202 | 1 | 2 | 4 | |
| Creatine Kinase G4, n=194,203,202 | 1 | 1 | 2 | |
| CO2 G1, n=193,202,202 | 34 | 43 | 47 | |
| CO2 G2, n=193,202,202 | 4 | 9 | 6 | |
| CO2 G3, n=193,202,202 | 0 | 0 | 0 | |
| CO2 G4, n=193,202,202 | 0 | 1 | 0 | |
| Creatinine G1, n=194,203,202 | 6 | 5 | 4 | |
| Creatinine G2, n=194,203,202 | 11 | 7 | 4 | |
| Creatinine G3, n=194,203,202 | 8 | 7 | 4 | |
| Creatinine G4, n=194,203,202 | 0 | 0 | 1 | |
| Magnesium G1, n=194,203,202 | 14 | 14 | 15 | |
| Magnesium G2, n=194,203,202 | 7 | 9 | 4 | |
| Magnesium G3, n=194,203,202 | 0 | 0 | 0 | |
| Magnesium G4, n=194,203,202 | 0 | 0 | 0 | |
| Hypercalcemia G1, n=193,202,202 | 0 | 0 | 0 | |
| Hypercalcemia G2, n=193,202,202 | 0 | 0 | 0 | |
| Hypercalcemia G3, n=193,202,202 | 0 | 0 | 0 | |
| Hypercalcemia G4, n=193,202,202 | 0 | 0 | 0 | |
| Hyperkalemia G1, n=193,202,202 | 0 | 1 | 1 | |
| Hyperkalemia G2, n=193,202,202 | 0 | 0 | 0 | |
| Hyperkalemia G3, n=193,202,202 | 0 | 0 | 0 | |
| Hyperkalemia G4, n=193,202,202 | 1 | 0 | 1 | |
| Hypernatremia G1, n=194,203,202 | 4 | 10 | 4 | |

| | | | | |
|---------------------------------|----|----|----|--|
| Hypernatremia G2, n=194,203,202 | 1 | 1 | 0 | |
| Hypernatremia G3, n=194,203,202 | 0 | 1 | 1 | |
| Hypernatremia G4, n=194,203,202 | 0 | 0 | 0 | |
| Hypocalcemia G1, n=193,202,202 | 43 | 48 | 40 | |
| Hypocalcemia G2, n=193,202,202 | 26 | 39 | 42 | |
| Hypocalcemia G3, n=193,202,202 | 7 | 8 | 8 | |
| Hypocalcemia G4, n=193,202,202 | 0 | 1 | 0 | |
| Hypokalemia G1, n=193,202,202 | 16 | 12 | 21 | |
| Hypokalemia G2, n=193,202,202 | 1 | 1 | 1 | |
| Hypokalemia G3, n=193,202,202 | 1 | 0 | 0 | |
| Hypokalemia G4, n=193,202,202 | 0 | 0 | 0 | |
| Hyponatremia G1, n=194,203,202 | 42 | 34 | 26 | |
| Hyponatremia G2, n=194,203,202 | 2 | 2 | 4 | |
| Hyponatremia G3, n=194,203,202 | 0 | 2 | 0 | |
| Hyponatremia G4, n=194,203,202 | 0 | 0 | 1 | |

Notes:

[82] - Safety Population

[83] - Safety Population

[84] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated hematology values shifts from Baseline (Day 1) and up to 42 days

| | |
|-----------------|--|
| End point title | Number of participants with the indicated hematology values shifts from Baseline (Day 1) and up to 42 days |
|-----------------|--|

End point description:

Blood samples for laboratory assessments were collected at Baseline (Day 1), Day 3, Day 5/6, Day 8, Day 10/11 (or last day of randomized treatment), S/R Day 1, S/R Day 3, and S/R Day 5/6 (last day of S/R treatment for those participants who utilized this option), Post-Treatment +2 (if hospitalized), and Post-Treatment +5, +16, and +28 Days. Hematology parameters included hemoglobin, lymphocytes, total neutrophils, platelet count, and white blood cell (WBC) count. Per the DAIDS table for grading the severity of adult and pediatric AEs, Grade (G) 1=mild, G2= moderate, G3=severe and G4=potentially life threatening. The number of participants with values that were G1, G2, G3 and G4 relative to the normal range for the indicated hematology parameters is summarized. Baseline is defined as the pre-dose value collected on Study Day 1.

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|------------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[85] | 209 ^[86] | 205 ^[87] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Hemoglobin G1, n=194,202,200 | 28 | 25 | 28 | |
| Hemoglobin G2, n=194,202,200 | 11 | 19 | 13 | |
| Hemoglobin G3, n=194,202,200 | 14 | 10 | 8 | |

| | | | | |
|-------------------------------|----|----|----|--|
| Hemoglobin G4, n=194,202,200 | 0 | 4 | 1 | |
| Lymphocytes G1, n=186,199,198 | 8 | 18 | 10 | |
| Lymphocytes G2, n=186,199,198 | 11 | 15 | 11 | |
| Lymphocytes G3, n=186,199,198 | 16 | 21 | 18 | |
| Lymphocytes G4, n=186,199,198 | 18 | 19 | 14 | |
| Neutrophils G1, n=193,202,200 | 2 | 2 | 3 | |
| Neutrophils G2, n=193,202,200 | 2 | 0 | 0 | |
| Neutrophils G3, n=193,202,200 | 0 | 1 | 0 | |
| Neutrophils G4, n=193,202,200 | 1 | 0 | 3 | |
| Platelets G1, n=194,200,198 | 8 | 22 | 21 | |
| Platelets G2, n=194,200,198 | 18 | 12 | 16 | |
| Platelets G3, n=194,200,198 | 4 | 3 | 2 | |
| Platelets G4, n=194,200,198 | 2 | 1 | 2 | |
| Leukocytes G1, n=194,202,200 | 3 | 2 | 1 | |
| Leukocytes G2, n=194,202,200 | 3 | 5 | 3 | |
| Leukocytes G3, n=194,202,200 | 0 | 1 | 0 | |
| Leukocytes G4, n=194,202,200 | 1 | 0 | 2 | |

Notes:

[85] - Safety Population

[86] - Safety Population

[87] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

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 included albumin, ALP, ALT, AST, total bilirubin, calcium, creatine kinase, chloride, CO2/bicarbonate, creatinine, potassium, magnesium and sodium. 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 pre-dose value collected on Study Day 1. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|------------------------------|---------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[88] | 209 ^[89] | 205 ^[90] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Albumin, G3; n=194, 203, 202 | 6 | 3 | 4 | |
| Albumin, G4; n=194, 203, 202 | 0 | 0 | 0 | |
| ALP, G3; n=194, 203, 202 | 0 | 2 | 0 | |

| | | | | |
|--------------------------------------|----|---|---|--|
| ALP, G4; n=194, 203, 202 | 1 | 0 | 1 | |
| ALT, G3; n=194, 203, 202 | 2 | 2 | 4 | |
| ALT, G4; n=194, 203, 202 | 0 | 2 | 1 | |
| AST, G3; n=193, 202, 202 | 2 | 4 | 5 | |
| AST, G4; n=193, 202, 202 | 1 | 2 | 1 | |
| Total Bilirubin, G3; n=194, 203, 202 | 2 | 2 | 1 | |
| Total Bilirubin, G4; n=194, 203, 202 | 0 | 0 | 0 | |
| Creatine Kinase, G3; n=194, 203, 202 | 2 | 3 | 2 | |
| Creatine Kinase, G4; n=194, 203, 202 | 3 | 1 | 1 | |
| Carbon Dioxide, G3; n=193, 202, 202 | 0 | 0 | 0 | |
| Carbon Dioxide, G4; n=193, 202, 202 | 1 | 0 | 0 | |
| Creatinine, G3; n=194, 203, 202 | 3 | 6 | 1 | |
| Creatinine, G4; n=194, 203, 202 | 3 | 2 | 0 | |
| Magnesium, G3; n=194, 203, 202 | 1 | 0 | 0 | |
| Magnesium, G4; n=194, 203, 202 | 0 | 0 | 1 | |
| Hypercalcemia, G3; n=194, 202, 202 | 0 | 0 | 0 | |
| Hypercalcemia, G4; n=194, 202, 202 | 0 | 0 | 0 | |
| Hyperkalemia, G3; n=193, 202, 202 | 2 | 0 | 1 | |
| Hyperkalemia, G4; n=193, 202, 202 | 1 | 5 | 3 | |
| Hypernatremia, G3; n=194, 203, 202 | 0 | 1 | 5 | |
| Hypernatremia, G4; n=194, 203, 202 | 0 | 0 | 0 | |
| Hypocalcemia, G3; n=193, 202, 202 | 10 | 7 | 8 | |
| Hypocalcemia, G4; n=193, 202, 202 | 2 | 4 | 4 | |
| Hypokalemia, G3; n=193, 202, 202 | 0 | 0 | 0 | |
| Hypokalemia, G4; n=193, 202, 202 | 0 | 0 | 0 | |
| Hyponatremia, G3; n=194, 203, 202 | 1 | 0 | 0 | |
| Hyponatremia G4, n=194,203,202 | 0 | 0 | 0 | |

Notes:

[88] - Safety Population

[89] - Safety Population

[90] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: 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 |
|-----------------|---|

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 included hemoglobin, lymphocytes, total neutrophils, platelet count, 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 pre-dose value collected on Study Day 1. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

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

End point timeframe:

Baseline (Day 1) and up to 42 days

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 201 ^[91] | 209 ^[92] | 205 ^[93] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Hemoglobin, G3; n=194, 202, 200 | 29 | 24 | 26 | |
| Hemoglobin, G4; n=194, 202, 200 | 2 | 5 | 8 | |
| Lymphocytes, G3; n=186, 199, 198 | 6 | 5 | 11 | |
| Lymphocytes, G4; n=186, 199, 198 | 3 | 14 | 7 | |
| Total Neutrophils, G3; n=193, 202, 200 | 1 | 2 | 2 | |
| Total Neutrophils, G4; n=193, 202, 200 | 4 | 4 | 3 | |
| Platelet count, G3; n=194, 200, 198 | 4 | 4 | 5 | |
| Platelet count, G4; n=194, 200, 198 | 3 | 3 | 2 | |
| Leukocytes Count, G3; n=194, 202, 200 | 1 | 1 | 0 | |
| Leukocytes Count, G4; n=194, 202, 200 | 2 | 1 | 3 | |

Notes:

[91] - Safety Population

[92] - Safety Population

[93] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Median quantity of oxygen delivery measured at Baseline (Day 1) and during the study

| | |
|-----------------|--|
| End point title | Median quantity of oxygen delivery measured at Baseline (Day 1) and during the study |
|-----------------|--|

End point description:

The quantity of oxygen delivery were assessed three times daily at Baseline (Day 1) and at Days 2, 3, 4, and 5/6 and once daily during post-treatment +5 days, +16 days, and +28 days. All assessments were to be made at approximately the same time each day (morning, afternoon, and evening) and ideally at least 6 hours apart. The median quantity of oxygen delivery during the study was not summarized since the data was not collected in a way to accurately calculate values. Baseline is defined as the pre-dose value collected on Study Day 1.

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

End point timeframe:

Baseline (Day 1) and during the study

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[94] | 0 ^[95] | 0 ^[96] | |
| Units: Percentage of oxygen level in blood | | | | |
| median (full range (min-max)) | (to) | (to) | (to) | |

Notes:

[94] - This end point was not analyzed.

[95] - This end point was not analysed

[96] - This end point was not analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants assessed as normal/abnormal (clinically significant [CS] and not clinically significant [NCS]) for 12-lead electrocardiogram (ECG) at Baseline (Day 1) and Day 4

| | |
|-----------------|---|
| 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) and Day 4 |
|-----------------|---|

End point description:

On Baseline/Day 1, a 12-lead ECG was obtained within approximately 24 hours prior to dosing. 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. In the original protocol ECGs were also done on Day 4, however amendment 2 removed this requirement and therefore not all participants had Day 4 ECGs. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline/Day 1 and Day 4 | |

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|---------------------------------------|------------------------|------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 197 ^[97] | 208 ^[98] | 203 ^[99] | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Normal | 100 | 121 | 99 | |
| Abnormal - Not Clinically Significant | 97 | 86 | 102 | |
| Abnormal - Clinically Significant | 5 | 4 | 7 | |

Notes:

[97] - Safety Population

[98] - Safety Population

[99] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of intravenous (IV) zanamivir

| | |
|-----------------|---|
| End point title | Serum concentration of intravenous (IV) zanamivir |
|-----------------|---|

End point description:

Pharmacokinetic samples were collected at four time points to characterize peak concentration (end of infusion; C[EOI]) after the first dose on Day 1 and on Day 4 to characterize the pre-dose concentration (C[0]), the peak concentration C(EOI), and the trough concentration at 11-12 hours post-dose (C[12]) of zanamavir. The PK Population is comprised of all participants who received IV zanamivir and underwent sparse PK sampling during the study from which one or more serum zanamivir concentrations was determined. Data was summarised by Creatinine clearance (CL) Category. The dose on Day 1 is the initial dose (unadjusted) and the dose on Day 4 is the maintenance dose. "99999" indicates that data are not available/analysis was not performed.

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

End point timeframe:

Day 1 and Day 4

| End point values | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg | |
|--------------------------------------|-------------------------|--------------------------|------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 180 ^[100] | 187 ^[101] | 0 ^[102] | |
| Units: microgram/Liter (mcg/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| CL <15, Day 1, 30 min, n=1,3,0 | 14454.6 (± 99999) | 26410.8 (± 21335.43) | () | |
| CL <15, Day 4, pre-dose n=1,2,0 | 293.2 (± 99999) | 9635.6 (± 8270.67) | () | |
| CL <15, Day 4, 30 min n=1,1,0 | 1329.4 (± 99999) | 19828.9 (± 99999) | () | |
| CL <15, Day 4, 11-12 hr n=1,1,0 | 605.1 (± 99999) | 15459.1 (± 99999) | () | |
| CL 15-<30, Day 13, 30 min, n=13,9,0 | 20403.3 (± 11623.28) | 41102.8 (± 13884.08) | () | |
| CL 15-<30, Day 4, pre-dose n=10,6,0 | 5906.4 (± 7167.87) | 4995.6 (± 1966.72) | () | |
| CL 15-<30, Day 4, 30 min n=10,6,0 | 13636.4 (± 14029.44) | 13378 (± 2581.36) | () | |
| CL 15-<30, Day 4, 11-12 hr n=8,5,0 | 7600.3 (± 8061.65) | 4953.4 (± 2232.16) | () | |
| CL 30-<50, Day 1, 30 min, n=28,18,0 | 18756.8 (± 12806.43) | 42467.3 (± 14574.82) | () | |
| CL 30-<50, Day 4, pre-dose n=12,15,0 | 2094.8 (± 1300.99) | 7637.4 (± 7212.1) | () | |
| CL 30-<50, Day 4, 30 min n=12,13,0 | 12334.4 (± 12121.18) | 159292.1 (± 473267.3) | () | |
| CL 30-<50, Day 4, 11-12 hr n=11,13,0 | 2932.5 (± 2425.81) | 19549.2 (± 40577.76) | () | |
| CL 50-<80, Day 1, 30 min, n=36,49,0 | 19146.7 (± 8853.11) | 49666.1 (± 111785.9) | () | |
| CL 50-<80, Day 4, pre-dose n=31,25,0 | 2793.3 (± 4694.43) | 13107.7 (± 33768.61) | () | |
| CL 50-<80, Day 4, 30 min n=32,25,0 | 31541.3 (± 93381) | 22220.4 (± 10064.83) | () | |
| CL 50-<80, Day 4, 11-12 hr n=30,23,0 | 1345.9 (± 1122.18) | 22623.9 (± 57663.24) | () | |
| CL ≥80, Day 1, 30 min, n=93,96,0 | 18561.7 (± 10332.14) | 35139.2 (± 17693.85) | () | |
| CL ≥80, Day 4, pre-dose n=99,107,0 | 2342.6 (± 6672.12) | 19379.8 (± 105056.3) | () | |
| CL ≥80, Day 4, 30 min n=100,106,,0 | 21580.7 (± 22062.69) | 75255.1 (± 167670.6) | () | |

| | | | | |
|------------------------------------|--------------------|----------------------|----|--|
| CL >=80, Day 4, 11-12 hr n=94,99,0 | 2036.2 (± 4412.75) | 19428.7 (± 142284.7) | () | |
| Missing, Day 1, 30 min n=0,2,0 | 99999 (± 99999) | 41109.7 (± 3831.74) | () | |

Notes:

[100] - PK Population

[101] - PK Population

[102] - This end point was not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until follow-up (up to 42 days).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | IV zanamivir 300 mg |
|-----------------------|---------------------|

Reporting group description:

Participants ≥ 16 years of age received intravenous (IV) zanamivir 300 milligrams (mg) twice daily, adjusted for renal function for 5–10 days.

| | |
|-----------------------|---------------------|
| Reporting group title | IV zanamivir 600 mg |
|-----------------------|---------------------|

Reporting group description:

Participants ≥ 16 years of age received IV zanamivir 600 mg twice daily, adjusted for renal function for 5–10 days.

| | |
|-----------------------|------------------------|
| Reporting group title | Oral oseltamivir 75 mg |
|-----------------------|------------------------|

Reporting group description:

Participants ≥ 16 years of age received oral oseltamivir 75 mg twice daily, adjusted for renal function for 5–10 days.

| Serious adverse events | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg |
|---|---------------------|---------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 38 / 201 (18.91%) | 33 / 209 (15.79%) | 38 / 205 (18.54%) |
| number of deaths (all causes) | 15 | 15 | 11 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Distributive shock | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Surgical and medical procedures | | | |
| Mechanical ventilation | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 | 2 / 201 (1.00%) | 2 / 209 (0.96%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Immune system disorders | | | |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 5 / 201 (2.49%) | 4 / 209 (1.91%) | 5 / 205 (2.44%) |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 3 | 1 / 3 | 0 / 2 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 4 / 201 (1.99%) | 3 / 209 (1.44%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 2 / 209 (0.96%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 2 / 209 (0.96%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Delirium febrile | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| ECG signs of ventricular hypertrophy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheostomy malfunction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 1 / 209 (0.48%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Cardiogenic shock | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Neuromyopathy | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Seizure | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal haemorrhage subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 201 (1.99%) | 0 / 209 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| IgA nephropathy | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 201 (3.48%) | 1 / 209 (0.48%) | 4 / 205 (1.95%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 4 / 201 (1.99%) | 1 / 209 (0.48%) | 2 / 205 (0.98%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Sepsis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 209 (0.48%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Influenza | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 209 (0.00%) | 1 / 205 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Pneumonia necrotising | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 209 (0.48%) | 0 / 205 (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 |
| Vestibular neuronitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 infection | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 209 (0.00%) | 0 / 205 (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 |

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

| Non-serious adverse events | IV zanamivir 300 mg | IV zanamivir 600 mg | Oral oseltamivir 75 mg |
|---|---------------------|---------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 201 (8.46%) | 26 / 209 (12.44%) | 24 / 205 (11.71%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 15 / 209 (7.18%) | 14 / 205 (6.83%) |
| occurrences (all) | 11 | 20 | 14 |
| Constipation | | | |
| subjects affected / exposed | 7 / 201 (3.48%) | 13 / 209 (6.22%) | 10 / 205 (4.88%) |
| occurrences (all) | 8 | 16 | 10 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 31 January 2011 | (i) the liver criteria stopping exemption was deleted, (ii) update and clarification to inclusion criteria 1, 2, 4 and 5, and exclusion criteria 5, 7, 13 and 14, and (iii) update to the background information and some minor clarifications within the protocol. The majority of changes detailed in points (i) and (ii) were made in response to requests from regulatory authorities and Ethics Committees. |
| 01 June 2012 | (i) included a contingency study design change to allow for continuation of the study in the event of widespread oseltamivir resistance by temporarily or permanently discontinuing the oseltamivir arm, (ii) removal of exclusion criterion 13 (QTc entry criteria) and removal of Day 4 ECG measurements, and (iii) includes updates and clarifications within the protocol. The major change detailed in point (i) was made in response to comments from regulatory and health agencies to allow the study to be completed in the event of significant oseltamivir resistance developing during the course of the study. |
| 24 January 2014 | (i) changes to the data analysis and statistical considerations section of the protocol, including details of a second interim analysis, (ii) included a few clarifications and updates within the protocol. The major change detailed in point (i) was made following the outcome of the first interim analysis where the IDMC recommended that the study continue with all three treatment arms, resulting in an increase to the sample size from 462 to 600 participants. A second interim analysis was included to inform on whether it was appropriate to continue to recruit 600 participants. The statistical analysis framework was updated to allow for consideration of additional evidence beyond the original primary and secondary endpoints. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported