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	v2 (current)
This version publication date	26 February 2017
First version publication date	10 July 2016
Version creation reason	• Correction of full data set Minor changes required.

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 oseltamvir 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 oseltamvir 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	55.2	57.3	55.9
standard deviation	± 18.88	± 17.39	± 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 oseltamvir 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))				
Influenza positive sub-group	5.87 (-99999 to 99999)	5.14 (-99999 to 99999)	5.63 (-99999 to 99999)	
Symptom Onset <=4 days sub-group	5.63 (-99999 to 99999)	4.8 (-99999 to 99999)	4.8 (-99999 to 99999)	
ICU/ Mechanical ventilation sub-group	11.26 (-99999 to 99999)	12.79 (-99999 to 99999)	14.58 (-99999 to 99999)	

Notes:

[1] - IPP population

[2] - IPP population

[3] - IPP population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Influenza Positive Subgroup	
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[4]
P-value	= 0.2496 [5]
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	0.75

Notes:

[4] - Wilcoxon rank-sum 2-sided test stratified by randomization strata

[5] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Influenza Positive Subgroup	
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[6]
P-value	= 0.3912 [7]
Method	Wilcoxon rank-sum
Parameter estimate	Median difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	0.97

Notes:

[6] - Wilcoxon rank-sum 2-sided test stratified by randomization strata

[7] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Symptom Onset <=4 Days Subgroup	
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	= 0.0923 [8]
Method	Wilcoxon rank-sum 2-sided test
Parameter estimate	Median difference (final values)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	0.56

Notes:

[8] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Symptom Onset <=4 Days Subgroup	
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	= 0.8232 [9]
Method	Wilcoxon rank-sum 2 sided test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.97

Notes:

[9] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
ICU/Mechanic Ventilation Subgroup	
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	= 0.8711 [10]
Method	Wilcoxon rank-sum 2-sided test
Parameter estimate	Median difference (final values)
Point estimate	1.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.29
upper limit	8.34

Notes:

[10] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
ICU/Mechanic Ventilation Subgroup	
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	= 0.512 [11]
Method	Wilcoxon rank-sum 2-sided test
Parameter estimate	Median difference (final values)
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	6.92

Notes:

[11] - To control type 1 error, a fallback procedure with pre-specified order of hypothesis tests was used for each pair-wise comparison in the Influenza positive pop and two subgroups (ICU/Mech Vent, symptom onset <4 days).

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

End point title	Percentage of participants with confirmed influenza acheiving a clinical response[12]

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:

[12] - 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[13]	162[14]	163[15]	
Units: Percentage of participants				
number (not applicable)	85	87	77	

Notes:

[13] - IPP Population

[14] - IPP Population

[15] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of participants with respiratory improvement

End point title	Percent of participants with respiratory improvement

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, facetent, 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 acheiving 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[16]	162[17]	163[18]	
Units: Percentage of participants				
number (not applicable)	77	78	74	

Notes:

[16] - IPP Population

[17] - IPP Population

[18] - 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[19]	162[20]	163[21]	
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:

[19] - IPP Population

[20] - IPP Population

[21] - 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[22]	162[23]	163[24]	
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:

[22] - IPP Population

[23] - IPP Population

[24] - 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[25]	162[26]	163[27]	
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:

[25] - IPP Population

[26] - IPP Population

[27] - 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[28]	162[29]	163[30]	
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:

[28] - IPP Population

[29] - IPP Population

[30] - 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 successed 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[31]	137[32]	135[33]	
Units: Days				
median (full range (min-max))	5 (2 to 34)	4 (2 to 31)	4 (1 to 57)	

Notes:

[31] - IPP Population

[32] - IPP Population

[33] - 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[34]	162[35]	163[36]	
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:

[34] - IPP Population

[35] - IPP Population

[36] - 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 symptomps 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[37]	162[38]	163[39]	
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:

[37] - IPP Population

[38] - IPP Population

[39] - 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[40]	162[41]	163[42]	
Units: Participants				
number (not applicable)				
Associated use of any antibiotic	22	16	29	
Any complication of influenza	34	33	41	

Notes:

[40] - IPP Population

[41] - IPP Population

[42] - 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/hospitization 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[43]	162[44]	163[45]	
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:

[43] - IPP Population

[44] - IPP Population

[45] - 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/hospitization 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[46]	162[47]	163[48]	
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:

[46] - IPP Population

[47] - IPP Population

[48] - 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 calculatd 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[49]	162[50]	163[51]	
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:

[49] - IPP Population

[50] - IPP Population

[51] - 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, facetent, nasal canula, etc.) to no need for supplemental oxygen, or a respiratory rate =<24 breaths/minute (without supplemental oxygen). Oxygen saturation response criteria: >=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/hospitization 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[52]	162[53]	163[54]	
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:

[52] - IPP Population

[53] - IPP Population

[54] - 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[55]	162[56]	163[57]	
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:

[55] - IPP Population

[56] - IPP Population

[57] - 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 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 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 was measured by 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[58]	162[59]	163[60]	
Units: log10 TCID50/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:

[58] - IPP Population

[59] - IPP Population

[60] - IPP Population

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline viral load (influenza A or B) by qPCR 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[61]	162[62]	163[63]	
Units: log10 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:

[61] - IPP Population

[62] - IPP Population

[63] - 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[64]	162[65]	163[66]	
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:

[64] - IPP Population

[65] - IPP Population

[66] - 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 (nasopharyngeal swabs) and lower (Endotracheal aspirates, bronchoalveolar lavage samples, where available) respiratory samples were collected daily from Baseline/Day 1 through Day 5 and Day 6 (if the last day of randomized treatment). Endotracheal aspirates were collected in participants who were intubated. 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[67]	162[68]	163[69]	
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:

[67] - IPP Population

[68] - IPP Population

[69] - 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[70]	162[71]	163[72]	
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:

[70] - IPP Population

[71] - IPP Population

[72] - 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[73]	209[74]	205[75]	
Units: Participants				
number (not applicable)	25	22	35	

Notes:

[73] - Safety Population

[74] - Safety Population

[75] - 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[76]	209[77]	205[78]	
Units: Participants				
number (not applicable)	39	45	44	

Notes:

[76] - Safety Population

[77] - Safety Population

[78] - 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[79]	209[80]	205[81]	
Units: Participants				
number (not applicable)	8	10	11	

Notes:

[79] - Safety Population

[80] - Safety Population

[81] - 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[82]	209[83]	205[84]	
Units: Participants				
number (not applicable)	14	16	13	

Notes:

[82] - Safety Population

[83] - Safety Population

[84] - 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[85]	209[86]	205[87]	
Units: Participants				
number (not applicable)	5	3	7	

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 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 tranferase (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[88]	209[89]	205[90]	
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:

[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 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[91]	209[92]	205[93]	
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:

[91] - Safety Population

[92] - Safety Population

[93] - 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[94]	209[95]	205[96]	
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:

[94] - Safety Population

[95] - Safety Population

[96] - 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[97]	209[98]	205[99]	
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:

[97] - Safety Population

[98] - Safety Population

[99] - 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:

Oxygen delivery were assessed three times daily at Baseline (Day 1) and during the treatment period/hospitalization (ideally at least 6 hours apart) and once daily during inpatient/hospitalization and once at Post +5 days, +16 days, and +28 days clinic visits. 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[100]	0[101]	0[102]	
Units: Percentage of oxygen level in blood				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[100] - This end point was not analyzed.

[101] - This end point was not analysed

[102] - 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[103]	208[104]	203[105]	
Units: Participants				
number (not applicable)				
Normal	100	121	99	
Abnormal - Not Clinically Significant	97	86	102	
Abnormal – Clinically Significant	5	4	7	

Notes:

[103] - Safety Population

[104] - Safety Population

[105] - 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[106]	187[107]	0[108]	
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:

[106] - PK Population

[107] - PK Population

[108] - 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 oseltamvir 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