Clinical trial results:
A Phase 3, Randomized, Open Label, Active-controlled Study to Evaluate the Safety, Pharmacokinetics and Effectiveness of IV Peramivir Compared to Oral Oseltamivir in Pediatric Subjects With Acute Uncomplicated Influenza

Summary

EudraCT number	2021-001018-13
Trial protocol	Outside EU/EEA
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	27 May 2021
First version publication date	27 May 2021

Trial information

Trial identification

Sponsor protocol code	BCX1812-305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369159
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals Inc.
Sponsor organisation address	4505 Emperor Blvd., Suite 200, Durham, United States, NC 27703
Public contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919859 1302, clinicaltrials@biocryst.com
Scientific contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919859 1302, clinicaltrials@biocryst.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001856-PIP02-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2019
Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of intravenous (IV) peramivir compared with oral oseltamivir in pediatric subjects with acute uncomplicated influenza (here within referred to as influenza)

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, and in accordance with the Declaration of Helsinki. The informed consent form (ICF), protocol and amendments for this trial were submitted to and approved by an appropriate Independent Ethics Committee (IEC). Routine monitoring was performed to verify that rights and well-being of subjects were protected. Emergency equipment and medications were available within the clinical unit as per current standard procedures. Any medication considered necessary for the subject's safety and well-being was given at the discretion of the Investigator. Signed informed consent was obtained from each parent or guardian prior to performing any study-related procedures. Similarly, age-appropriate subject assent by subjects ≥ 7 years of age was obtained from each child or adolescent prior to performing any study-related procedures. The informed consent/assent process took place under conditions where the subject and parent/guardian had adequate time to consider the risks and benefits associated with the subject's participation in the study. The Investigator explained to subjects and their parent/guardian the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail.

Background therapy: -

Evidence for comparator:

The active control, oseltamivir, is widely used for the treatment of influenza and it is currently approved in the US for adults and children ≥ 2 weeks of age and in the EU for patients 1 year of age and older for seasonal/epidemic influenza, and in infants less than 1 year of age during a pandemic influenza outbreak.

Actual start date of recruitment	11 March 2015
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	United States: 131
Country: Number of subjects enrolled	South Africa: 6
Worldwide total number of subjects	137
EEA total number of subjects	0

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)	21
Children (2-11 years)	86
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were enrolled into the study after confirmation they satisfied the eligibility criteria including having clinical signs & symptoms consistent with acute influenza infection (oral temperature ≥ 37.8°C or rectal temperature ≥ 38.5ºC, with at least one respiratory symptom; i.e. cough or rhinitis), or a positive influenza rapid antigen test.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Peramivir

Arm description:

Age-appropriate dose Peramivir, administered as a single short iv infusion.

Arm type	Experimental
Investigational medicinal product name	Peramivir
Investigational medicinal product code	BCX1812
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Age-appropriate dose Peramivir, administered as a single short iv infusion on study Day 1 (baseline):
Subjects ≥13 years - 600 mg.
Subjects ≥ 6 months to ≤12 years - 12 mg/kg (max. 600 mg).
Subjects < 6 months - 8 mg/kg.

Arm title	Oseltamivir

Arm description:

Age appropriate oral dose of Oseltamivir BID for 5 days.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Age appropriate oral dose of Oseltamivir BID for 5 days as capsules or an oral suspension for subjects who could not swallow a capsule:
Subjects ≥ 13 years - 75mg BID
Subjects < 13 years - weight-based dose: ≤ 15 kg 30 mg BID, 15.1 to 23 kg 45 mg BID, 23.1 to 40 kg 60 mg BID, > 40 kg 75 mg BID

Number of subjects in period 1	Peramivir	Oseltamivir
Started	114	23
Completed	106	21
Not completed	8	2
Consent withdrawn by subject	7	-
Adverse event, non-fatal	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Peramivir
Reporting group description:	
Age-appropriate dose Peramivir, administered as a single short iv infusion.	
Reporting group title	Oseltamivir
Reporting group description:	
Age appropriate oral dose of Oseltamivir BID for 5 days.	

Reporting group values	Peramivir	Oseltamivir	Total
Number of subjects	114	23	137
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	8.0	9.9	
standard deviation	± 5.07	± 4.99	-
Gender categorical			
Units: Subjects			
Female	59	14	73
Male	55	9	64
Baseline Influenza Viral Titer			
Units: Subjects			
Positive	70	14	84
Negative	37	9	46
Missing	7	0	7

Subject analysis sets

Subject analysis set title	Peramivir (≥ 28 Days - < 2 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Age-appropriated dose Peramivir, administered as a single short iv infusion: Subjects ≥ 6 months to ≤ 2 years - 12mg/kg (max.600 mg). Subjects < 6months - 8mg/kg.	

Subject analysis set title	Oseltamivir (≥ 28 Days - < 2 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5 days.

Subject analysis set title	Peramivir (≥ 2 - < 7 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

12 mg/kg(max. 600mg) dose Peramivir, administered as a single short iv infusion

Subject analysis set title	Oseltamivir (≥ 2 - < 7 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5days.

Subject analysis set title	Peramivir (≥ 7 - < 13 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Age-appropriate dose Peramivir, administered as a single short iv infusion:
Subjects ≥12 years -600 mg.
Subjects <12 years -12 mg/kg (max. 600mg).

Subject analysis set title	Oseltamivir (≥ 7 - < 13 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5 days.

Subject analysis set title	Peramivir (≥ 13 - < 18 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

600 mg dose Peramivir, administered as a single short iv infusion

Subject analysis set title	Oseltamivir (≥ 13 - < 18 Years)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

75mg dose of Oseltamivir as a capsule or oral suspension BID for 5 days

Reporting group values	Peramivir (≥ 28 Days - < 2 Years)	Oseltamivir (≥ 28 Days - < 2 Years)	Peramivir (≥ 2 - < 7 Years)
Number of subjects	20	1	32
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	1.3	1.0	4.9
standard deviation	± 0.47	±	± 1.47
Gender categorical			
Units: Subjects			
Female	13	1	16
Male	7	0	16

Baseline Influenza Viral Titer Units: Subjects			
Positive	8	1	23
Negative	10	0	6
Missing	2	0	3

Reporting group values	Oseltamivir (≥ 2 - < 7 Years)	Peramivir (≥ 7 - < 13 Years)	Oseltamivir (≥ 7 - < 13 Years)
Number of subjects	6	39	9
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	4.7	9.6	9.7
standard deviation	± 1.60	± 1.75	± 1.92
Gender categorical Units: Subjects			
Female	4	20	6
Male	2	19	3
Baseline Influenza Viral Titer Units: Subjects			
Positive	2	27	6
Negative	4	12	3
Missing	0	0	0

Reporting group values	Peramivir (≥ 13 - < 18 Years)	Oseltamivir (≥ 13 - < 18 Years)	
Number of subjects	23	7	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years			
arithmetic mean	15.7	15.9	
standard deviation	± 1.45	± 1.50	
Gender categorical Units: Subjects			
Female	10	3	
Male	13	4	
Baseline Influenza Viral Titer Units: Subjects			
Positive	12	5	
Negative	9	2	
Missing	2	0	

End points

End points reporting groups

Reporting group title	Peramivir
Reporting group description:	
Age-appropriate dose Peramivir, administered as a single short iv infusion.	
Reporting group title	Oseltamivir
Reporting group description:	
Age appropriate oral dose of Oseltamivir BID for 5 days.	
Subject analysis set title	Peramivir (≥ 28 Days - < 2 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Age-appropriated dose Peramivir, administered as a single short iv infusion: Subjects ≥ 6 months to ≤ 2 years - 12mg/kg (max.600 mg). Subjects < 6months - 8mg/kg.	
Subject analysis set title	Oseltamivir (≥ 28 Days - < 2 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5 days.	
Subject analysis set title	Peramivir (≥ 2 - < 7 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
12 mg/kg(max. 600mg) dose Peramivir, administered as a single short iv infusion	
Subject analysis set title	Oseltamivir (≥ 2 - < 7 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5days.	
Subject analysis set title	Peramivir (≥ 7 - < 13 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Age-appropriate dose Peramivir, administered as a single short iv infusion: Subjects ≥12 years -600 mg. Subjects <12 years -12 mg/kg (max. 600mg).	
Subject analysis set title	Oseltamivir (≥ 7 - < 13 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Weight-based dose of Oseltamivir as a capsule or oral suspension BID for 5 days.	
Subject analysis set title	Peramivir (≥ 13 - < 18 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
600 mg dose Peramivir, administered as a single short iv infusion	
Subject analysis set title	Oseltamivir (≥ 13 - < 18 Years)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
75mg dose of Oseltamivir as a capsule or oral suspension BID for 5 days	

Primary: Safety and Tolerability, as Measured by the Number of Participants Experiencing Adverse Events.

End point title	Safety and Tolerability, as Measured by the Number of Participants Experiencing Adverse Events.[1]

End point description:

The Safety population included all randomized subjects who received ≥ 1 partial dose of peramivir or oseltamivir. Safety evaluation included assessment of Adverse Events (AEs).

End point type	Primary

End point timeframe:

14 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing via statistical analysis was performed.

End point values	Peramivir	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	23		
Units: subjects				
Adverse Event	22	5		
Severe or life-threatening Adverse Event	2	0		
Adverse Event related to study drug	8	4		
Serious Adverse Events	0	0		
Adverse Event leading to discontinuation	0	1		
Adverse Event leading to Death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Exposure of IV Peramivir as Measured by the Drug Concentration Over 6 Hours Post-dose

End point title	Plasma Exposure of IV Peramivir as Measured by the Drug Concentration Over 6 Hours Post-dose

End point description:

Up to 4 blood samples were drawn, where possible: immediately following infusion and 30 to 60 mins, 1 to 3 hrs and 4 to 6 hrs post-infusions. AUC calculations were performed in Phoenix WinNonlin using the linear/log trapezoidal rule. AUC_0-last = area under the plasma concentration vs. time curve from the start of the infusion until the time of the last measurable concentration. AUC_0-3 = area under the plasma concentration vs. time curve from the start of the infusion until 3 hrs post-infusion. The Intent-to-Treat (ITT) population included all randomized subjects. Of these 114 subjects, 106 had sufficient PK samples collected for inclusion in the peramivir PK analysis

End point type	Secondary

End point timeframe:

Up to 6 hours post peramivir infusion

End point values	Peramivir (≥ 28 Days - < 2 Years)	Peramivir (≥ 2 - < 7 Years)	Peramivir (≥ 7 - < 13 Years)	Peramivir (≥ 13 - < 18 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18[2]	29[3]	39	20
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AUC_0-last	56200 (± 21430)	71200 (± 31380)	87000 (± 40750)	72400 (± 19970)
AUC_0-3	53300 (± 19100)	68100 (± 27060)	81400 (± 35090)	68300 (± 19190)

Notes:

[2] - 15 participants analysed for AUC_0-3

[3] - 28 participants analysed for AUC_0-3

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Fever

End point title	Time to Resolution of Fever

End point description:

Time for fever resolution based on subject diary record of temperature recorded twice daily. A subject had resolution of fever if he/she had oral temperature of < 99.4°F or an axillary temperature of < 98.4°F and no antipyretic medications were taken for ≥12 hours. The time to resolution of fever was estimated for each age group and overall using the Kaplan-Meier method with temperature and symptom relief medication information obtained from the Subject Diary data. Data from the Intent to treat infected (ITTI) population was used in this analysis. Subjects who did not have resolution of fever were censored at the time of their last non-missing post-baseline temperature assessment; this included 1 subject in the '≥ 28 days - < 2 years' cohort treated with Peramivir. Seventeen subjects were excluded from summaries due to missing data or events resolving prior to initiation of study drug.

End point type	Secondary

End point timeframe:

14 days

End point values	Peramivir (≥ 28 Days - < 2 Years)	Oseltamivir (≥ 28 Days - < 2 Years)	Peramivir (≥ 2 - < 7 Years)	Oseltamivir (≥ 2 - < 7 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	1	21	2
Units: hours				
arithmetic mean (standard deviation)	39.7 (± 6.55)	61.8 (± 0)	58.8 (± 8.42)	16.0 (± 2.38)

End point values	Peramivir (≥ 7 - < 13 Years)	Oseltamivir (≥ 7 - < 13 Years)	Peramivir (≥ 13 - < 18 Years)	Oseltamivir (≥ 13 - < 18 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	5	9	5
Units: hours				
arithmetic mean (standard deviation)	36.3 (± 5.00)	29.7 (± 7.82)	51.3 (± 11.59)	43.9 (± 13.67)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Influenza Symptoms

End point title	Time to Resolution of Influenza Symptoms

End point description:

Subjects or parents or caregivers were asked to provide an assessment of age-appropriate influenza symptoms on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily beginning before screening on Day 1 until symptoms resolved or until the last follow-up visit. Time to alleviation of symptoms was the number of hours from initiation of study drug until the start of the time period in which all age-appropriate symptoms of influenza were either absent or present at a level no greater than mild for at least 21.5 (24 - 10%) hours. Data from the Intent to treat infected (ITTI) population was used in this analysis. Subjects who did not experience alleviation of symptoms were censored at the last observed symptom assessment. Seven subjects were excluded due to missing data or events resolving prior to initiation of study drug.

End point type	Secondary

End point timeframe:

14 days

End point values	Peramivir (≥ 28 Days - < 2 Years)	Oseltamivir (≥ 28 Days - < 2 Years)	Peramivir (≥ 2 - < 7 Years)	Oseltamivir (≥ 2 - < 7 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	1	24	2
Units: hours				
arithmetic mean (standard deviation)	76.1 (± 19.77)	98.9 (± 0)	94.1 (± 11.53)	20.7 (± 2.32)

End point values	Peramivir (≥ 7 - < 13 Years)	Oseltamivir (≥ 7 - < 13 Years)	Peramivir (≥ 13 - < 18 Years)	Oseltamivir (≥ 13 - < 18 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	7	13	5
Units: hours				
arithmetic mean (standard deviation)	66.6 (± 7.83)	134.4 (± 15.74)	101.3 (± 18.46)	75.5 (± 12.76)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reduction in Viral Shedding

End point title	Time to Reduction in Viral Shedding

End point description:

Assessment of viral shedding in bilateral, mid-nasal swab specimens taken at baseline and then on Day 3, 7 and 14. The analysis population corresponded to the Intent to treat infected (ITTI) population + ITT population with positive baseline influenza viral titers [> 0.5 log10 TCID50/mL]; a total of 84 subjects.

End point type	Secondary

End point timeframe:

14 days

End point values	Peramivir (≥ 28 Days - < 2 Years)	Oseltamivir (≥ 28 Days - < 2 Years)	Peramivir (≥ 2 - < 7 Years)	Oseltamivir (≥ 2 - < 7 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	1	23[4]	2[5]
Units: Participants with positive viral titre				
Baseline	8	1	23	2
Day 3	6	1	12	1
Day 7	1	0	2	0
Day 14	0	0	0	0

Notes:

[4] - 22 participants analysed at day 3

[5] - 1 participant analysed at day 3, 7 & 14

End point values	Peramivir (≥ 7 - < 13 Years)	Oseltamivir (≥ 7 - < 13 Years)	Peramivir (≥ 13 - < 18 Years)	Oseltamivir (≥ 13 - < 18 Years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27[6]	6	12	5
Units: Participants with positive viral titre				
Baseline	27	6	12	5
Day 3	13	6	6	2
Day 7	1	0	0	0
Day 14	0	0	0	0

Notes:

[6] - 26 subjects analysed day 7 & 14

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Influenza Virus Titer in Nasopharyngeal Samples in Response to Treatment

End point title	Changes in Influenza Virus Titer in Nasopharyngeal Samples in Response to Treatment

End point description:

Change in influenza viral titers was defined as the time-weighted change from Baseline in log_10 tissue culture infective dose_50 (TCID50/mL) and was summarized for each treatment group. Analysis was performed for the Intent To Treat Infected (ITTI) population which included all subjects who were enrolled, received study drug, and had confirmed influenza A and/or B by PCR. Thirteen subjects were

excluded due to a negative or missing baseline titer.

End point type	Secondary

End point timeframe:

Change from baseline assessed on days 3, 7 and 14.

End point values	Peramivir	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	14		
Units: influenza viral titer - log10 TCID50/mL				
median (full range (min-max))				
Baseline	4.38 (0.75 to 6.50)	4.50 (1.50 to 5.75)		
Day 3 - Change from baseline	-2.75 (-6.00 to 2.50)	-3.25 (-5.00 to 1.25)		
Day 7 - Change from baseline	-3.75 (-6.00 to 1.00)	-4.00 (-5.25 to -1.00)		
Day 14 - Change from baseline	-3.75 (-6.00 to -0.25)	-4.00 (-5.25 to -1.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Influenza-Related Complications Assessment.

End point title	Influenza-Related Complications Assessment.

End point description:

The investigator performed a full physical exam at baseline. At each follow-up visit, study personnel evaluated the subject for the presence of clinical signs and symptoms of the following influenza-related complications: sinusitis, otitis media, bronchitis, and pneumonia requiring antibiotic use, diagnosed after initiation of treatment. Analysis was performed for the Intent To Treat Infected (ITTI) population which included all subjects who were enrolled, received study drug, and had confirmed influenza A and/or B by PCR.

End point type	Secondary

End point timeframe:

14 days

End point values	Peramivir	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	16		
Units: Participants				
Otitis	3	0		
Sinusitis	2	0		
Bronchitis	0	0		
Pneumonia	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded on Day 1, Day 3, Day 7 and Day 14/Early Withdraw visit.

Adverse event reporting additional description:

Adverse events were graded through use of the Division of Acquired Immune Deficiency Syndrome (DAIDS) Tables for Grading Adult and Pediatric Adverse Experiences. Influenza-related complications were not considered AEs unless they met the criteria for an SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Peramivir

Reporting group description:

Age-appropriate dose Peramivir, administered as a single short iv infusion.

Reporting group title	Oseltamivir

Reporting group description:

Age appropriate oral dose of Oseltamivir BID for 5 days.

Serious adverse events	Peramivir	Oseltamivir	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 107 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Peramivir	Oseltamivir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 107 (20.56%)	5 / 23 (21.74%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Carbon dioxide decreased			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Elevated aspartate aminotransferase			
subjects affected / exposed	2 / 107 (1.87%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Elevated blood lactate dehydrogenase			
subjects affected / exposed	2 / 107 (1.87%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 107 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injection site coldness			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injection site paraesthesia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injection site rash			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 107 (1.87%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Tympanic membrane disorder			
subjects affected / exposed	1 / 107 (0.93%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Tympanic membrane hyperaemia subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	0 / 23 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	0 / 23 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	2 / 23 (8.70%) 2	
Vomiting subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	2 / 23 (8.70%) 2	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Tonsillar disorder subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	

Psychiatric disorders Hallucination subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 23 (4.35%) 1	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Paronychia subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 23 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2014	A description of the DSMC was added. Since the study was open label, a sponsor-led DSMC was to oversee safety. A full review and summary of safety utilizing all collected safety assessments was to occur after each influenza season. Full procedures were to be described in the SAP.
21 June 2015	Planned number of subjects updated from 72 to 130, of which ~100 subjects to be randomized to peramivir. IV peramivir to oral oseltamivir randomization ratios updated to 4:1 for each age cohort. Youngest subject age allowed into the study was changed from 2 years to 28 day; age cohort groupings updated accordingly. Age of subjects requiring assent changed from ≥14 to ≥7 years. Dose of IV peramivir updated to 600mg IV or 12 mg/kg depending on age. Oseltamivir dosing for subjects aged 28 days to <1 year was specified as weight-based, using an oral suspension of 3mg/kg BID ×5 days. RAT or PCR testing for influenza A/B removed from the screening procedure; Positive RAT or PCR influenza A test was removed from the inclusion criteria. Instead, inclusion criterion 2 specified that clinical signs & symptoms consistent with acute influenza infection OR a positive influenza RAT was required. Exclusion criterion 2 added; receipt of a live attenuated influenza infection within 14 days of presentation. Exclusion criterion 6 updated to include examples of exclusionary chronic diseases or illnesses. Dose adjustment for subjects with renal impairment was removed. Permitted concomitant medications updated regarding medications used for symptomatic treatment of influenza-related symptoms. Serum sample for future influenza antibody analysis added to the study procedures. Vital sign procedures specified that blood pressure was to be measured in children < 2 years of age only if clinically indicated. Procedures for assessing influenza symptoms were updated based on the allowable subject ages. Full procedures for DSMC safety oversight to be described in a DSMC charter, rather than the SAP. Informed consent procedures updated to specify that if the local IRB/IEC or state requirements limited the age of assent, then assent was to be obtained based on those requirements, but in all cases, assent was to be obtained for adolescents ≥ 14 years of age.

20 October 2016	Lower age limit for inclusion criterion 1 changed from 28 days to birth. Overall number of subjects to be enrolled increased from 130 to 140. The age cohorts and treatments updated to include cohort 'Birth to < 28 days' to include up to 10 subjects receiving IV peramivir. The 2 to < 7 year-old cohort was split into 2 new cohorts: 2 to < 4 years (up to 10 subjects) and 4 to < 7 years (up to 30 subjects). Exclusion criteria updated to provide further clarification of subject eligibility. Justification added for dosing in neonates (0 to < 28 days): To maintain safe blood sampling levels for neonates, PK sampling limited to no more than two 1.0 mL samples for subjects who weigh <5 kg & the need for serum antibody testing limited to subjects who weigh <10 kg. Day 14 schedule of assessments description updated to clarify the need to perform repeat safety laboratory testing. To maintain appropriate fluid volume for children under the age of 12 months, the dilution of peramivir calculated using a subject's age and weight. Clarification provided regarding the duration of collection of information on daily activity and eating patterns. Clarification provided regarding the timing of temperature taken at Baseline visit. Time cut-off for collection of AE reports changed from Day 7 to Day 14 following subject consent. To minimize blood loss for hospitalized subjects, text added regarding testing at local versus central laboratories. The descriptive statistical methodology and definitions updated to match the Statistical Analysis Plan for the study.
10 January 2017	The peramivir IV dosing specification by age group was changed from 600 mg IV or 12 mg/kg IV depending on age to 600 mg IV for subjects ≥ 13 years, 12 mg/kg IV for subjects ≥ 6 months to ≤ 12 years, 8 mg/kg IV for subjects < 6 months. Prior to this amendment 4, the dose for all subjects ≤ 12 years of age was 12 mg/kg. The peramivir dilution protocol for children < 12 months of age was updated.
05 November 2018	Inclusion criterion 3 and Exclusion criterion 6 changed from 'onset of symptoms no more than 48 hours before presentation for screening for subjects < 2 years old' to 'onset of symptoms no more than 72 hours before presentation for screening for subjects < 2 years old'. Exclusion criterion 8 changed to allow subjects with identified risk factors. Exclusion criterion 9 changed from the specification of immunocompromised status to severe immunocompromised status. Sponsor Medical Officer's contact information updated. Contact information for the submission of SAE report forms updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No subjects randomised to 'birth to 28 days' age cohort; no eligible subjects identified for whom parent/guardian willing to provide consent.

Notes: