Clinical trial results:
An Open-Label, Randomized, Adaptive, Two-Arm, Multicentre Trial to Evaluate Pharmacokinetics and Pharmacodynamics of Two Doses of Oseltamivir (TAMIFLU®) in the Treatment of Influenza in Immunocompromised Children Less Than 13 Years of Age, With Confirmed Influenza Infection

Summary

EudraCT number	2012-002633-11
Trial protocol	ES DE FI IT PL BE GR
Global end of trial date	07 August 2018

Results information

Result version number	v1 (current)
This version publication date	16 February 2019
First version publication date	16 February 2019

Trial information

Trial identification

Sponsor protocol code	NV25719

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01715909
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, globa.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000365-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2018
Global end of trial reached?	Yes
Global end of trial date	07 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to generate data for the purpose of extrapolation of efficacy from adults with immunodeficiency and to compare and/or integrate exposure and response observations in the pediatric immunocompromised population to that seen in other, non-immunocompromised populations.

Protection of trial subjects:

All study subjects, parents or guardians were required to read and sign an Informed Consent Form.

Background therapy:

- Conditioning regimen prior to hematopoietic stem cell transplantation (HSCT) or less than 6 months after HSCT
- Induction, consolidation, or re-intensification chemotherapy for a hematological malignancy (patients on maintenance therapy were excluded)

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 11
Worldwide total number of subjects	30
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	25
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirty subjects were enrolled over 5 northern hemisphere influenza seasons and 5 southern hemisphere influenza seasons at approximately 50 sites in order to enroll at least 20 subjects evaluable for the primary endpoint. The first subject was enrolled on 22 January 2014 and the last visit completed date for the last subject was on 17 July 2018.

Pre-assignment

Screening details:

Subjects with symptoms of less than 96 hours duration were screened by reverse transcriptase polymerase chain reaction (RT-PCR), culture, or rapid influenza diagnostic test (RIDT) for influenza infection prior to randomization. Influenza was confirmed by RT-PCR by the central laboratory.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental: Conventional Dose

Arm description:

Paediatric immunocompromised subjects less than 13 years of age received conventional dose of oseltamivir (30 to 75 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to receive 3 mg/kg

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

Dosage and administration details:

Dose ranging between 30 to 75 milligrams (mg) based on body weight, administered orally as suspension or capsule twice daily for a minimum of 5 days and until a negative result for influenza by RT-PCR for a maximum of 20 days. Either the capsules or the oral suspension could be used as deemed appropriate by the investigator.

Arm title	Experimental: 3x Conventional Dose

Arm description:

Paediatric immunocompromised subjects less than 13 years of age received 3x conventional dose of oseltamivir (90 to 225 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to be assigned to the conventional group only.

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

Dosage and administration details:

Dose ranging between 90 to 225 milligrams (mg) based on body weight, administered orally as suspension or capsule twice daily for a minimum of 5 days and until a negative result for influenza by RT-PCR for a maximum of 20 days. Either the capsules or the oral suspension could be used as deemed appropriate by the investigator.

Number of subjects in period 1	Experimental: Conventional Dose	Experimental: 3x Conventional Dose
Started	15	15
Completed	14	13
Not completed	1	2
Consent withdrawn by subject	-	2
Non-compliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Conventional Dose
Reporting group description:	
Paediatric immunocompromised subjects less than 13 years of age received conventional dose of oseltamivir (30 to 75 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to receive 3 mg/kg	
Reporting group title	Experimental: 3x Conventional Dose
Reporting group description:	
Paediatric immunocompromised subjects less than 13 years of age received 3x conventional dose of oseltamivir (90 to 225 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to be assigned to the conventional group only.	

Reporting group values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose	Total
Number of subjects	15	15	30
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	6.9	4.3	
standard deviation	± 4.2	± 2.3	-
Gender Categorical			
Units: Subjects			
Female	5	4	9
Male	10	11	21

End points

End points reporting groups

Reporting group title	Experimental: Conventional Dose

Reporting group description:

Paediatric immunocompromised subjects less than 13 years of age received conventional dose of oseltamivir (30 to 75 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to receive 3 mg/kg

Reporting group title	Experimental: 3x Conventional Dose

Reporting group description:

Paediatric immunocompromised subjects less than 13 years of age received 3x conventional dose of oseltamivir (90 to 225 milligrams [mg]) according to weight orally twice daily for a minimum of 5 days and a maximum of 20 days. Infants less than 1 year of age were to be assigned to the conventional group only.

Subject analysis set title	Intent-to-Treat (ITT) Patient Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least one dose of oseltamivir regardless of whether they had any follow-up assessments. Subjects were grouped on the basis of randomized treatment. If there was any doubt whether a subject was treated, that subject was assumed to have been treated for the purposes of analysis.

Subject analysis set title	Intent-to-treat influenza-infected (ITTi) Subject Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of ITT subjects who had laboratory confirmed influenza infection from any swab sample collected at baseline or during the study (PCR or culture, not RIDT). The ITTi population is the primary efficacy analysis population unless specified otherwise. This excluded subjects who did not meet the definition of immunocompromised in the protocol. Subjects were grouped based on randomized treatment.

Subject analysis set title	Pharmacokinetic Evaluable (PKEP) Subject Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit timepoint.

Subject analysis set title	Safety Evaluable Patient Population (SEP)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The same as the ITT population. Subjects were classified according to treatment actually received.

Primary: Pharmacokinetics: Steady State Area Under the Concentration-Time Curve From Time 0 to 12 Hours (AUC0-12) of Oseltamivir

End point title	Pharmacokinetics: Steady State Area Under the Concentration-Time Curve From Time 0 to 12 Hours (AUC0-12) of Oseltamivir[1]

End point description:

AUC0-12 was reported at steady state as nanograms per hour per millilitre (ng/mL*hr). Measured in the PKEP population.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours Post-dose on Days 3 or 4

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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL*hr				
arithmetic mean (standard deviation)	265 (± 91.9)	568 (± 162)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics: Steady State AUC0-12 of Oseltamivir Carboxylate

End point title	Pharmacokinetics: Steady State AUC0-12 of Oseltamivir Carboxylate[2]

End point description:

AUC0-12 was reported at steady state as nanograms per hour per millilitre (ng/mL*hr). The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4. 8 hours Post-dose on Days 3 or 4

Notes:

[2] - 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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL*hr				
arithmetic mean (standard deviation)	4350 (± 2320)	8210 (± 2500)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics: Steady-state Maximum Plasma Concentration (Cmax) of Oseltamivir

End point title	Pharmacokinetics: Steady-state Maximum Plasma Concentration (Cmax) of Oseltamivir[3]

End point description:

Cmax was reported as nanograms per millilitre (ng/mL). The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours Post-dose on Days 3 or 4

Notes:

[3] - 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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL				
arithmetic mean (standard deviation)	61.9 (± 19.5)	153 (± 49.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics: Steady-state Cmax of Osltamivir Carboxylate

End point title	Pharmacokinetics: Steady-state Cmax of Osltamivir Carboxylate[4]

End point description:

Cmax was reported as nanograms per millilitre (ng/mL). The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours Post-dose on Days 3 or 4

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL				
arithmetic mean (standard deviation)	434 (± 211)	852 (± 288)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics: Trough Plasma Concentration (Ctrough) of Oseltamivir

End point title	Pharmacokinetics: Trough Plasma Concentration (Ctrough) of

	Oseltamivir[5]

End point description:

Ctrough was reported as nanograms per millilitre (ng/mL). The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration) on Days 3 or 4

Notes:

[5] - 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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL				
arithmetic mean (standard deviation)	5.17 (± 2.43)	9.07 (± 3.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics: Ctrough of Oseltamivir Carboxylate

End point title	Pharmacokinetics: Ctrough of Oseltamivir Carboxylate[6]

End point description:

Ctrough was reported as nanograms per millilitre (ng/mL). The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Primary

End point timeframe:

Pre-dose (within 30 minutes prior to administration) on Days 3 or 4

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL				
arithmetic mean (standard deviation)	276 (± 173)	486 (± 136)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Cessation of Viral Shedding, as Assessed by Culture Testing

End point title	Time to Cessation of Viral Shedding, as Assessed by Culture Testing[7]

End point description:

Viral titer was determined from nasal swabs. It was reported in log10 scale and expressed in 50% tissue culture infectious dose (TCID50) obtained after viral culture followed by hemagglutination assay for H1N1 and Flu B strains or viral nucleoprotein (NP) ELISA for H3N2 strains. Time to cessation of viral shedding was summarized by the median of the Kaplan-Meier curve for each of the two dose regimens and associated 95% CIs.The ITTi population was used in the analysis.

End point type	Primary

End point timeframe:

From randomization to negative culture test result (up to Day 50)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: hours				
median (confidence interval 95%)	109.2 (60.9 to 153.0)	75.9 (54.7 to 344.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Cessation of Viral Shedding, as Assessed by Polymerase Chain Reaction (PCR)

End point title	Time to Cessation of Viral Shedding, as Assessed by Polymerase Chain Reaction (PCR)[8]

End point description:

Viral load was determined from nasal swabs. It was reported in log10 scale and expressed in virus particles per millilitre (vp/mL) calculated from the quantitative reverse transcription polymerase chain reaction (RT-PCR) assay. Time to cessation of viral shedding was summarized by the median of the Kaplan-Meier curve for each of the two dose regimens and associated 95% CIs. The ITTi population was used in the analysis.

End point type	Primary

End point timeframe:

From randomization to negative PCR test result (up to Day 50)

Notes:

[8] - 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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: hours				
median (confidence interval 95%)	157.2 (125.3 to 658.0)	242.3 (60.4 to 392.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution (TTR) of Influenza Symptoms (including fever)

End point title	Time to Resolution (TTR) of Influenza Symptoms (including fever)

End point description:

TTR of all influenza symptoms was defined as the time in hours from randomization to the start of the 24 hour period in which all 18 symptoms items (Canadian Acute Respiratory Infections Scale [CARIFS] 18-symptom scale) had scores of </= 1 (minor problem) and remained </= 1 for at least 21.5 hours. Reported are TTRs in the ITTi population. 9999=not estimable

End point type	Secondary

End point timeframe:

From randomization to resolution of all influenza symptoms (up to Day 50)

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: hours				
median (confidence interval 95%)	179.4 (24.7 to 9999)	34.5 (0.0 to 84.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population included all subjects

who received at least one dose of study drug and had a safety assessment performed post randomisation.

End point type	Secondary

End point timeframe:

Baseline up to Day 50

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: number of subjects				
number (not applicable)				
Adverse Events	96	77		
Serious Adverse Events	11	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Influenza Associated Complications

End point title	Number of Subjects With Influenza Associated Complications

End point description:

Influenza associated complications include secondary bacterial infections (e.g. bronchitis, sinusitis, pneumonia and otitis media), length of hospital stay and intensive care unit (ICU) admissions, frequency of O2 use and time on ventilator. Reported is the number of subjects with at least one event in the ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Day 50

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Number of Subjects				
number (not applicable)				
Number of subjects with secondary infections	0	2		
Number of subjects hospitalized	10	7		
Number of subjects requiring O2 use	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Viral Resistance

End point title	Number of Subjects With Viral Resistance

End point description:

Viral resistance was determined from nasal swabs. Genotypic and phenotypic viral resistance were investigated. Susceptibility of the virus to inhibition by oseltamivir was determined with the NA-Star assay using the cell culture supernatants of samples from which infectious viruses could be detected by titration after culture (baseline and last titration positive sample). The IC50 (concentration of drug required to inhibit the viral neuraminidase activity by 50%) of each sample was determined together with the reference IC50 value using the appropriate reference virus (A/Puerto Rico/8/34 for influenza A viruses, B/Lee/40 for influenza B viruses) run in parallel. The IC50 values were expressed in units of nanomoles per liter (nM/l). Reported is the number of subjects who developed viral resistance in the ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Day 50

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: Number				
number (not applicable)				
Overall Resistance	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of Oseltamivir

End point title	Half-life (t1/2) of Oseltamivir

End point description:

Elimination half-life (t1/2) was reported as hours. The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: hour				
arithmetic mean (standard deviation)	1.97 (± 0.245)	1.83 (± 0.117)		

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2 of Oseltamivir Carboxylate

End point title	t1/2 of Oseltamivir Carboxylate

End point description:

Elimination half-life (t1/2) was reported as hours. The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: hour				
arithmetic mean (standard deviation)	0.189 (± 0.153)	0.0881 (± 0.0417)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Oseltamivir

End point title	Time to Maximum Concentration (Tmax) of Oseltamivir

End point description:

Time to maximum concentration (tmax) was reported as hours. The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: hour				
arithmetic mean (standard deviation)	1.41 (± 0.56)	1.25 (± 0.354)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Oseltamivir Carboxylate

End point title	Tmax of Oseltamivir Carboxylate

End point description:

Time to maximum concentration (tmax) was reported as hours. The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Experimental: Conventional Dose	Experimental: 3x Conventional Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: hour				
arithmetic mean (standard deviation)	4.18 (± 1.05)	3.83 (± 0.634)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Rate Constant (Ke) of Oseltamivir

End point title	Elimination Rate Constant (Ke) of Oseltamivir

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: 1/hour				
arithmetic mean (standard deviation)	6.43 (± 1.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ke of Oseltamivir Carboxylate

End point title	Ke of Oseltamivir Carboxylate

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: 1/hour				
arithmetic mean (standard deviation)	8.2 (± 5.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (V/F) of Oseltamivir

End point title	Apparent Volume of Distribution (V/F) of Oseltamivir

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: litre (L)				
arithmetic mean (standard deviation)	35.8 (± 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: V/F of Oseltamivir Carboxylate

End point title	V/F of Oseltamivir Carboxylate

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: litre				
arithmetic mean (standard deviation)	2.67 (± 1.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Oseltamivir

End point title	Apparent Clearance (CL/F) of Oseltamivir

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: litre per hour (L/hr)				
arithmetic mean (standard deviation)	228 (± 97.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F of Oseltamivir Carboxylate

End point title	CL/F of Oseltamivir Carboxylate

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: L/hr				
arithmetic mean (standard deviation)	14.9 (± 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) of Oseltamivir

End point title	Time to Last Measurable Concentration (Tlast) of Oseltamivir

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	0[9]			
Units: hour				
arithmetic mean (standard deviation)	()			

Notes:

[9] - Data was not analysed for this end point

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast of Oseltamivir Carboxylate

End point title	Tlast of Oseltamivir Carboxylate

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	0[10]			
Units: hour				
arithmetic mean (standard deviation)	()			

Notes:

[10] - Data was not analysed for this end point

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Concentration (Clast) of Oseltamivir

End point title	Last Measurable Concentration (Clast) of Oseltamivir

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	0[11]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[11] - Data was not analysed for this end point

Statistical analyses

No statistical analyses for this end point

Secondary: Clast of Oseltamivir Carboxylate

End point title	Clast of Oseltamivir Carboxylate

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit time point.

End point type	Secondary

End point timeframe:

Pre-dose (within 30 minutes prior to administration), 1.5, 4, 8 hours post-dose on Days 3 or 4

End point values	Pharmacokinetic Evaluable (PKEP) Subject Population			
Subject group type	Subject analysis set			
Number of subjects analysed	0[12]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:
[12] - Data was not analysed for this end point

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 50	
Adverse event reporting additional description:	
The safety population included all subjects who received at least one treatment with study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Experimental: Triple Standard Dose
Reporting group description:	
Immunocompromised participants will receive triple standard dose (90 to 225 mg) of oseltamivir orally daily for up to maximum of 20 days. Standard dose of oseltamivir according to weight (except infants): 30 mg twice daily for </= 15 kilograms (kg) body weight participants; 45 mg twice daily for 15 to 23 kg body weight participants; 60 mg twice daily for 23 to 40 kg body weight participants; and 75 mg twice daily for greater than (>) 40 kg body weight participants. Standard dose for infants is 3 mg/kg.	
Reporting group title	Experimental: Standard Dose
Reporting group description:	
Immunocompromised paticipants will receive standard dose (30 to 75 milligrams [mg]) of oseltamivir orally daily for up to maximum of 20 days. Standard dose of oseltamivir according to weight (except infants): 30 mg twice daily for </= 15 kilograms (kg) body weight participants; 45 mg twice daily for 15 to 23 kg body weight participants; 60 mg twice daily for 23 to 40 kg body weight participants; and 75 mg twice daily for greater than (>) 40 kg body weight participants. Standard dose for infants is 3 mg/kg.	

Serious adverse events	Experimental: Triple Standard Dose	Experimental: Standard Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)	7 / 15 (46.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Body Temperature Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Febrile Neutropenia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft Versus Host Disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Erythema of Eyelid			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid Oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoventilation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Bacteraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Malfunction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental: Triple Standard Dose	Experimental: Standard Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	12 / 15 (80.00%)	
Vascular disorders			
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Platelet Transfusion			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Chills			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Mucosal Inflammation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Immune system disorders			
Graft Versus Host Disease in Skin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Respiratory Distress			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Body Temperature Increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
C-Reactive Protein Increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Escherichia Test Positive			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Transfusion Reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Tremor			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	4 / 15 (26.67%)	
occurrences (all)	3	6	
Febrile Neutropenia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	3	5	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Retinal Haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	8	2	
Abdominal Pain Upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Anal Inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	3 / 15 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	5 / 15 (33.33%)	
occurrences (all)	2	5	
Dyschezia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Intestinal Pseudo-obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lip Swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 15 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Parotid Gland Enlargement			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	6 / 15 (40.00%)	5 / 15 (33.33%)	
occurrences (all)	8	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 15 (13.33%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Rash Erythematous			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin Discolouration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Renal Impairment			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Back Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Neck Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pain in Extremity			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Citrobacter Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Eye Infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastroenteritis Clostridial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Herpes Virus Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Septic Shock			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Viral Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vulvovaginitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hyperuricaemia			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Hypoproteinaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2013	In Protocol Version 2, the following significant changes were made: 1) The middle dose cohort (2x conventional oseltamivir dose) was discontinued with a concomitant increase in the size of the remaining two dose cohorts from 7 patients to 10 patients. This enriched the PK and PD data collected from the conventional and 3x conventional dose cohort and balanced the density of data collected for the doses tested compared to having more doses tested but with a lower data density per dose. 2) The age of the study population was restricted to patients aged 2 weeks to less than 13 years of age (as opposed to 0 − 18 years of age previously), which intended to enrich the dataset by allowing the data collected to be spread over a narrower age range. 3) Inclusion criteria referring to females in the reproductive age group were removed. 4) Study enrollment was modified to require at least 12 patients with onset of influenza symptoms less than < 48 hours prior to randomization. 5) Objectives were rephrased in order to clarify the purpose of the study. 6) Schedule of Assessments were amended to add a serum biochemistry sample requirement at baseline and on the PK sampling day (if serum creatinine results for these timepoints were not otherwise available) to allow estimation of creatinine clearance required for the population PK modeling.
23 June 2014	In Protocol Version 3, the following significant changes were made: 1) Study population was modified to remove the restriction that infants had to be 2 weeks of age. 2) An additional follow-up visit (Follow-Up Visit 2 occurring at least 30 days after the end of study treatment) was added. 3) Creatinine clearance estimates were corrected to include normalization for height, in line with the 2009 Schwartz formula. 4) Dose modification for infants (<1 year of age) with renal impairment was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported