Clinical trial results:
A Double-blind, Randomized, Stratified Multi-center Trial Evaluating Conventional and Double Dose Oseltamivir in the Treatment of Immunocompromised Patients With Influenza

Summary

EudraCT number	2006-002468-24
Trial protocol	GB ES FR BE HU LT CZ EE IT GR BG LV DE
Global end of trial date	02 May 2017

Results information

Result version number	v2 (current)
This version publication date	16 February 2018
First version publication date	16 November 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NV20234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00545532
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, global.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-PIP08-08
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	02 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2017
Global end of trial reached?	Yes
Global end of trial date	02 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This 2-arm study will investigate the safety and tolerability of oseltamivir for the treatment of influenza in immunocompromised subjects and characterize the effects of oseltamivir in immunocompromised subjects on the development of resistant influenza virus.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Ukraine: 2
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	South Africa: 40
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Guatemala: 2
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 3

Worldwide total number of subjects	215
EEA total number of subjects	91

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)	9
Adolescents (12-17 years)	7
Adults (18-64 years)	180
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Immunocompromised subjects with primary or secondary immunodeficiency and symptoms suggestive of influenza-like illness were recruited for this study.

Pre-assignment

Screening details:

Rapid diagnostic test, polymerase chain reaction (PCR), or viral culture had to be positive for influenza in the 96 hours prior to first dose. Subject disposition and baseline characteristics are provided for the safety population.

Period 1

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

Arms

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

Arm description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 30 to 75 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 75 mg twice daily for adults/adolescents greater than or equal to (>/=13 years old) or placebo-matched to oseltamivir twice daily over 10 days.

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

Dosage and administration details:

Dose ranging between 30 to 75 milligrams (mg) orally administered as syrup or capsules (depending on participants age and weight) twice daily for 10 days.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Syrup
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to oseltamivir administered orally twice daily for 10 days.

Arm title	Experimental: Double dose

Arm description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 60 to 150 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 150 mg twice daily for adults/adolescents (>/=13 years old) or placebo matched to oseltamivir twice daily over 10 days.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Syrup
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to oseltamivir administered orally twice daily for 10 days.

Investigational medicinal product name	oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule, Syrup
Routes of administration	Oral use

Dosage and administration details:

Dose ranging between 60 to 150 mg orally administered as syrup or capsules (depending on participants age and weight) twice daily for 10 days.

Number of subjects in period 1	Experimental: Conventional dose	Experimental: Double dose
Started	105	110
Completed	99	100
Not completed	6	10
Death	-	1
Withdrawal by Subject	1	3
Lost to follow-up	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Conventional dose
Reporting group description:	
Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 30 to 75 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 75 mg twice daily for adults/adolescents greater than or equal to (>/=13 years old) or placebo-matched to oseltamivir twice daily over 10 days.	
Reporting group title	Experimental: Double dose
Reporting group description:	
Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 60 to 150 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 150 mg twice daily for adults/adolescents (>/=13 years old) or placebo matched to oseltamivir twice daily over 10 days.	

Reporting group values	Experimental: Conventional dose	Experimental: Double dose	Total
Number of subjects	105	110	215
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.0	43.9	
standard deviation	± 15.5	± 16.5	-
Gender Categorical			
Units: Subjects			
Female	57	62	119
Male	48	48	96

End points

End points reporting groups

Reporting group title	Experimental: Conventional dose

Reporting group description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 30 to 75 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 75 mg twice daily for adults/adolescents greater than or equal to (>/=13 years old) or placebo-matched to oseltamivir twice daily over 10 days.

Reporting group title	Experimental: Double dose

Reporting group description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 60 to 150 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 150 mg twice daily for adults/adolescents (>/=13 years old) or placebo matched to oseltamivir twice daily over 10 days.

Subject analysis set title	Adults With Pharmacokinetic Evaluation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises subjects >/= 18 years from both arms in the study who underwent pharmacokinetic evaluation.

Subject analysis set title	Adolescents and Children With Pharmacokinetic Evaluation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set comprises adolescents and children < 18 years from both arms in the study who underwent pharmacokinetic evaluation.

Primary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events[1]

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	Primary

End point timeframe:

Baseline up to Day 40

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 statistical hypothesis could be defined for this endpoint as the study has no control group.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	110		
Units: percentage of subjects				
number (not applicable)				
On Treatment	40.0	47.3		
Off Treatment	25.7	29.1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Who Developed Viral Resistance to Oseltamivir

End point title	Percentage of Subjects Who Developed Viral Resistance to Oseltamivir[2]

End point description:

Resistance was defined as the presence of oseltamivir resistance mutations in viruses isolated from nasopharyngeal swab samples, identified by sequencing of the neuraminidase (NA) and hemagglutinin (HA) genes (genotypic resistance) and/or determination of the oseltamivir concentration at which the response is reduced by half (IC50) in an NA inhibition assay (phenotypic resistance). Modified Intent-to-Treat infected (mITTi) population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. Reported are post-baseline phenotypic and genotypic resistance in adults >/= 18 years and children and adolescents <18 years in the mITTi population. n indicates the number of subjects analysed in the respective study arms.

End point type	Primary

End point timeframe:

Baseline up to Day 40

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: No statistical hypothesis could be defined for this endpoint as the study has no control group.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: percentage of subjects				
number (not applicable)				
Post-BL Phenotypic Resist, >/= 18 years (n=73, 78)	8.2	1.3		
Post-BL Genotypic Resist, >/= 18 years (n=73, 78)	9.6	2.6		
Post-BL Phenotypic Resist, < 18 years (n=8, 8)	25.0	0		
Post-BL Genotypic Resist, < 18 years (n=8,8)	25.0	12.5		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Tissue Rejection or Graft Versus Host Disease

(GvHD)

End point title	Percentage of Subjects With Tissue Rejection or Graft Versus Host Disease (GvHD)[3]

End point description:

The percentage of transplant patients in the safety population who experienced tissue rejection and/or GvHD is reported. 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	Primary

End point timeframe:

Baseline up to Day 40

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: No statistical hypothesis could be defined for this endpoint as the study has no control group.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[4]	110[5]		
Units: percentage of subjects				
number (not applicable)	0	0		

Notes:

[4] - Analyses will be released once data become available.

[5] - Analyses will be released once data become available.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution (TTR) of All Clinical Influenza Symptoms

End point title	Time to Resolution (TTR) of All Clinical Influenza Symptoms

End point description:

TTR of all clinical influenza symptoms was defined as the time from treatment initiation to the start of the 24-hour period in which all 7 influenza symptoms had scores </= 1 (mild) and remained </=1 for at least 21.5 hours. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. Reported are TTRs in adults and adolescents >/= 13 years and children <13 years in the mITTi population. n indicates the number of subjects analysed in the respective study arms. 9999=not estimable

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	86		
Units: hours				
median (confidence interval 95%)				

Adults >/= 18 years (n=71, 75)	103.3 (69.0 to 112.7)	103.6 (57.1 to 140.0)		
Adults and adolescents >/= 13 years (n=75, 78)	103.4 (75.4 to 122.7)	107.2 (63.9 to 140.0)		
Children < 13 years (n=4, 5)	32.1 (20.2 to 9999)	115.9 (45.5 to 495.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Symptom Score Area Under the Effect-Time Curve (AUE)

End point title	Total Symptom Score Area Under the Effect-Time Curve (AUE)

End point description:

The overall extent and severity of illness was quantified by the AUE of the total symptom scores over the duration of illness, i.e., from the start of treatment to the time symptoms first alleviated. Total symptom scores were calculated from the sum of seven individual symptom scores. The AUE of these average scores was then calculated for each subject using the trapezoidal rule (the trapezoidal rule calculates the area under any curve by adding up all trapezoids under such a curve). The area of each trapezoid is calculated as the average between consecutive measures. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. Reported are results for adults >/= 18 years in the mITTi population.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	67		
Units: score * hour				
median (full range (min-max))	774.7 (60.8 to 11435.5)	811.5 (63.0 to 8648.1)		

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:

Fever was defined as temperature >/= 37.8 degrees Celsius at any time point during the study. TTR of fever was determined in Adults >/= 18 years, Adults and adolescents >/= 13 years and Children < 13 years of the mITTi population. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with

oseltamivir-resistant influenza at baseline. n indicates the number of subjects analysed in the respective study arms. 9999 = subject censored for analysis

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: hours				
median (confidence interval 95%)				
>/= 18 years (n=35, 32)	11.0 (0.0 to 16.2)	0.5 (0.0 to 8.8)		
>/= 13 years (n=37, 33)	11.0 (0.0 to 16.2)	0.5 (0.0 to 8.8)		
< 13 years (n=1, 2)	9999 (9999 to 9999)	26.0 (0.0 to 51.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Viral Load Assessed by Culture

End point title	Change from Baseline in Viral Load Assessed by Culture

End point description:

Nasopharyngeal swab samples were cultured in Madin-Darby Canine Kidney cells. Culture supernatants were harvested after 2 weeks, or after a full-blown cytopathic effect was observed. Presence of infectious viruses in the cell culture supernatants (viral titer), expressed as log10 50% Tissue Culture Infectious Dose/millilitre (TCID50/mL), was determined by hemagglutination assay using turkey erythrocytes for H1 and B viruses or by detection of the virus nucleoprotein (NP) using ELISA for H3 viruses. A value of < 0.5 log10 TCID50/mL was interpreted as negative. Data are reported for adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2/3, Day 6, Day 8, Day 11 end of treatment (EOT), follow-up (FU) Day 15 and FU Day 40.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: TCID50/mL				
median (full range (min-max))				
>/= 18 years, Baseline (BL) (n=70, 76)	3.38 (0.5 to 6.0)	3.75 (0.5 to 6.3)		
>/= 18 years, Change from BL on Day 2/3 (n=67, 73)	-1.50 (-5.3 to 0.8)	-1.50 (-5.0 to 1.50)		
>/= 18 years, Change from BL on Day 6 (n=65, 71)	-2.50 (-5.5 to 0.0)	-3.00 (-5.8 to 1.0)		
>/= 18 years, Change from BL on Day 8 (n=62, 62)	-2.75 (-5.5 to 0.0)	-3.25 (-5.8 to 0.0)		
>/= 18 years, Change from BL on Day 11 (n=64, 71)	-2.88 (-5.5 to 0.0)	-3.25 (-5.8 to 0.3)		
>/= 18 years, Change from BL on Day 15 (n=62, 65)	-3.00 (-5.5 to 0.3)	-3.25 (-5.8 to 0.0)		
>/= 18 years, Change from BL on Day 40 (n=64, 65)	-3.00 (-5.5 to 0.0)	-3.25 (-5.8 to 0.0)		
< 18 years, BL (n=8, 8)	3.13 (0.8 to 6.0)	4.00 (1.8 to 5.3)		
< 18 years, Change from BL on Day 2/3 (n=7, 8)	-1.00 (-2.3 to 0.8)	-2.00 (-3.3 to 0.0)		
< 18 years, Change from BL on Day 6 (n=7, 7)	-2.00 (-3.3 to -0.3)	-3.50 (-4.8 to -2.3)		
< 18 years, Change from BL on Day 8 (n=5, 7)	-2.50 (-3.3 to -0.3)	-3.50 (-4.8 to -1.3)		
< 18 years, Change from BL on Day 11 (n=7, 7)	-2.50 (-5.3 to 0.0)	-3.50 (-4.8 to -2.3)		
< 18 years, Change from BL on Day 15 (n=7, 7)	-2.50 (-5.3 to 1.0)	-3.50 (-4.8 to -2.3)		
< 18 years, Change from BL on Day 40 (n=7, 8)	-2.50 (-5.3 to 0.3)	-3.50 (-4.8 to -1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Viral Shedding Assessed by Culture over Time

End point title	Percentage of Subjects with Viral Shedding Assessed by Culture over Time

End point description:

Viral shedding was determined through measurement of the viral titer after viral culture in Madin-Darby Canine Kidney cells by
hemagglutination assay (for Flu A/H1N1 and Flu B) and NP-ELISA (for Flu A/H3N2) and expressed in log10 TCID50/mL. Reported is the percentage of subjects with viral shedding over time in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2/3, Day 6, Day 8, Day 11 end of treatment (EOT), follow-up (FU) Day 15 and FU Day 40.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: percentage of subjects				
number (not applicable)				
>/= 18 years, Baseline (n=70, 76)	91.4	84.2		
>/= 18 years, Day 2/3 (n=67, 73)	67.2	58.9		
>/= 18 years, Day 6 (n=65, 71)	15.4	18.3		
>/= 18 years, Day 8 (n=63, 62)	3.2	4.8		
>/= 18 years, Day 11 (n=65, 71)	1.5	4.2		
>/= 18 years, Day 15 (n=63, 65)	7.9	1.5		
>/= 18 years, Day 40 (n=65, 65)	0.0	0.0		
< 18 years, Baseline (n=8, 8)	100.0	100.0		
< 18 years, Day 2/3 (n=7, 8)	71.4	75.0		
< 18 years, Day 6 (n=7, 7)	42.9	0.0		
< 18 years, Day 8 (n=5, 7)	0.0	0.0		
< 18 years, Day 11 (n=7, 7)	14.3	0.0		
< 18 years, Day 15 (n=7, 7)	28.6	0.0		
< 18 years, Day 40 (n=7, 8)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Viral Shedding by Cell Culture

End point title	Time to Cessation of Viral Shedding by Cell Culture

End point description:

Viral shedding was determined through measurement of the viral titer after viral culture in Madin-Darby Canine Kidney cells by
hemagglutination assay (for Flu A/H1N1 and Flu B) and NP-ELISA (for Flu A/H3N2) and expressed in log10 TCID50/mL. Reported is the time to cessation of viral shedding over time in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. . n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: hours				
median (confidence interval 95%)				
>/= 18 years (n=64, 64)	105.0 (98.3 to 109.2)	105.4 (83.0 to 107.7)		
< 18 years (n=8, 8)	150.3 (34.2 to 891.3)	94.9 (8.6 to 109.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Viral Load Assessed by Reverse Transcription Polymerase Chain Reaction (RT-PCR)

End point title	Change from Baseline in Viral Load Assessed by Reverse Transcription Polymerase Chain Reaction (RT-PCR)

End point description:

Nasopharyngeal swab samples were tested for influenza A and B RNA using semi-quantitative RT-PCR specific for influenza A and B matrix gene, respectively, after viral RNA isolation. Cycle threshold (Ct) value was determined for each sample. Conversion of Ct values into viral load, expressed as log10 virus particles/mL (vp/mL), was obtained using external standard curves ran in parallel in all RT-PCR experiments. A value of < 2.6 log10 vp/mL for Flu A strains and < 3.0 log10 vp/mL for Flu B strains was interpreted as a negative result. Data are reported for adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2/3, Day 6, Day 8, Day 11 end of treatment (EOT), follow-up (FU) Day 15 and FU Day 40.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86[6]		
Units: log10 vp/mL				
median (full range (min-max))				
>/= 18 years, Baseline (BL) (n=72, 76)	6.47 (2.7 to 8.8)	6.52 (2.8 to 8.5)		
>/= 18 years, Change from BL on Day 2/3 (n=65, 67)	-1.20 (-6.4 to 1.6)	-1.35 (-4.6 to 1.1)		
>/= 18 years, Change from BL on Day 6 (n=41, 39)	-2.36 (-8.0 to 0.1)	-2.34 (-7.7 to 0.1)		
>/= 18 years, Change from BL on Day 8 (n=28, 20)	-2.66 (-5.4 to -0.3)	-2.62 (-7.8 to -0.3)		
>/= 18 years, Change from BL on Day 11 (n=19, 17)	-3.51 (-7.3 to -2.2)	-2.96 (-4.5 to 1.3)		

>/= 18 years, Change from BL on Day 15 (n=10, 6)	-3.63 (-8.0 to -0.9)	-2.60 (-3.4 to 0.0)		
>/= 18 years, Change from BL on Day 40 (n=3, 1)	-4.80 (-5.4 to 0.8)	-7.71 (-7.71 to -7.71)		
< 18 years, BL (n=8, 8)	5.88 (2.8 to 7.7)	5.96 (5.5 to 7.3)		
< 18 years, Change from BL on Day 2/3 (n=6, 8)	-0.66 (-2.7 to 1.4)	-0.71 (-5.6 to 0.4)		
< 18 years, Change from BL on Day 6 (n=6, 4)	-1.97 (-2.7 to 0.3)	-1.73 (-2.7 to -1.2)		
< 18 years, Change from BL on Day 8 (n=1, 3)	1.56 (1.56 to 1.56)	-2.26 (-2.9 to -1.5)		
< 18 years, Change from BL on Day 11 (n=2, 1)	-0.89 (-3.2 to 1.4)	-2.41 (-2.41 to -2.41)		
< 18 years, Change from BL on Day 15 (n=3, 0)	1.26 (-2.9 to 1.9)	9999 (9999 to 9999)		

Notes:

[6] - 9999 = 0 subjects analysed, no data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Viral Shedding Assessed by RT-PCR over Time

End point title	Percentage of Subjects with Viral Shedding Assessed by RT-PCR over Time

End point description:

Viral shedding was determined by direct viral load measurement from nasopharyngeal swabs by RT-PCR assay and expressed in log10 vp/mL. Reported is the percentage of subjects with viral shedding over time in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 2/3, Day 6, Day 8, Day 11 end of treatment (EOT), follow-up (FU) Day 15 and FU Day 40.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: percentage of subjects				
number (not applicable)				
>/= 18 years, Baseline (n=72, 78)	100.0	97.4		
>/= 18 years, Day 2/3 (n=69, 75)	92.8	88.0		
>/= 18 years, Day 6 (n=67, 73)	56.7	49.3		
>/= 18 years, Day 8 (n=65, 64)	41.5	23.4		
>/= 18 years, Day 11 (n=67, 73)	25.4	21.9		
>/= 18 years, Day 15 (n=66, 67)	10.6	9.0		
>/= 18 years, Day 40 (n=68, 67)	1.5	1.5		

< 18 years, Baseline (n=8, 8)	100.0	100.0		
< 18 years, Day 2/3 (n=7, 8)	85.7	75.0		
< 18 years, Day 6 (n=7, 7)	85.7	57.1		
< 18 years, Day 8 (n=5, 7)	20.0	42.9		
< 18 years, Day 11 (n=7, 7)	28.6	14.3		
< 18 years, Day 15 (n=7, 7)	42.9	0.0		
< 18 years, Day 40 (n=7, 8)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Viral Shedding by RT-PCR

End point title	Time to Cessation of Viral Shedding by RT-PCR

End point description:

Viral shedding was determined by direct viral load measurement from nasopharyngeal swabs by RT-PCR assay and expressed in log10 vp/mL. Reported is the time to cessation of viral shedding over time in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: hours				
median (confidence interval 95%)				
>/= 18 years (n=72, 76)	178.0 (152.2 to 227.0)	154.1 (128.5 to 171.0)		
< 18 years (n=8, 8)	181.0 (106.2 to 943.7)	180.5 (8.6 to 247.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Persistent Viral Shedding

End point title	Percentage of Subjects with Persistent Viral Shedding

End point description:

Persistent shedding was defined as a viral load reduction <1 log10 vp/mL at end of treatment compared with baseline. Reported is the percentage of subjects with persistent viral shedding at end of treatment in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects

randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline.

End point type	Secondary

End point timeframe:

Baseline to Day 11 (EOT)

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: percentage of subjects				
number (not applicable)	1.2	4.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Developed Secondary Illness

End point title	Percentage of Subjects Who Developed Secondary Illness

End point description:

Secondary illness included bronchitis, pneumonia, acute sinusitis, sinusitis, lower respiratory infection or otitis media. Reported is the percentage of subjects with at least one event in adults >/= 18 years and adolescents and children < 18 years. mITTi population: all subjects randomised to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	86		
Units: percentage of subjects				
number (not applicable)				
>/=18 years (n=73, 78)	8.2	5.1		
< 18 years (n=8, 8)	12.5	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Initiated Antibiotic Treatment

End point title	Percentage of Subjects Who Initiated Antibiotic Treatment

End point description:

Secondary illness included bronchitis, pneumonia, acute sinusitis, sinusitis, lower respiratory infection or otitis media. Reported is the percentage of subjects with secondary illness, who initiated antibiotic treatment, in adults >/= 18 years and adolescents and children < 18 years. The safety population included all subjects who received at least one dose of study drug and had a safety assessment performed post randomisation. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	110		
Units: percentage of subjects				
number (not applicable)				
>/= 18 years (n=98, 101)	8.2	5.0		
< 18 years (n=7, 9)	14.3	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Hospitalised

End point title	Percentage of Subjects Hospitalised

End point description:

Reported is the percentage of subjects, who required hospitalisation at any time between treatment initiation and the end of the study period, in adults >/= 18 years and adolescents and children < 18 years. The ITTi population included all subjects randomised and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: percentage of subjects				
number (not applicable)				
>/= 18 years (n=74, 78)	6.8	7.7		
< 18 years (n=9, 8)	11.1	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalisation

End point title	Duration of Hospitalisation

End point description:

Reported is the duration of hospitalizsation at any time between treatment initiation and the end of the study period, in adults >/= 18 years and adolescents and children < 18 years. The ITTi population included all subjects randomised and with central laboratory confirmation of influenza infection, excluding subjects infected with oseltamivir-resistant influenza at baseline. n = number of subjects analysed. 9999 = not estimable as no subject was hospitalised.

End point type	Secondary

End point timeframe:

Baseline up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: days				
median (full range (min-max))				
>/= 18 years (n=74, 78)	7.0 (5.0 to 14.0)	6.50 (4.0 to 32.0)		
< 18 years (n=9, 8)	5.0 (5.0 to 5.0)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Maximum Plasma Concentration (Cmax) of Oseltamivir in Adults

End point title	Pharmacokinetics: Maximum Plasma Concentration (Cmax) of Oseltamivir in Adults

End point description:

The pharmacokinetic evaluable patient (PKEP) population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)	65.5 (± 26.8)	149 (± 80.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Trough Plasma Concentration (Ctrough) of Oseltamivir in Adults

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

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: ng/mL				
arithmetic mean (standard deviation)	2.33 (± 0.641)	6.98 (± 5.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics : Area Under the Concentration-Time Curve from 0 to 12 hours (AUC0-12) at Steady State of Oseltamivir in Adults

End point title	Pharmacokinetics : Area Under the Concentration-Time Curve from 0 to 12 hours (AUC0-12) at Steady State of Oseltamivir in Adults

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 valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: ng/mL*hr				
arithmetic mean (standard deviation)	197 (± 49.7)	501 (± 320)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Time to Maximum Concentration (tmax) of Oseltamivir in Adults

End point title	Pharmacokinetics: Time to Maximum Concentration (tmax) of Oseltamivir in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: hour				
arithmetic mean (standard deviation)	1.08 (± 0.484)	1.08 (± 0.504)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Constant (ke) of Oseltamivir in Adults

End point title	Pharmacokinetics: Elimination Constant (ke) of Oseltamivir in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: 1/hr				
arithmetic mean (standard deviation)	4.93 (± 1.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir in Adults

End point title	Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: litre/hour (L/hr)				
arithmetic mean (standard deviation)	381 (± 113)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir in Adults

End point title	Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: litre (L)				
arithmetic mean (standard deviation)	76.2 (± 15.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Cmax of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Cmax of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: ng/mL				
arithmetic mean (standard deviation)	655 (± 276)	1420 (± 574)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Ctrough of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Ctrough of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: ng/mL				
arithmetic mean (standard deviation)	363 (± 167)	831 (± 358)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics : AUC0-12 at Steady State of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics : AUC0-12 at Steady State of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: ng/mL*hr				
arithmetic mean (standard deviation)	6240 (± 2710)	13800 (± 5670)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Tmax of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Tmax of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	13		
Units: hour				
arithmetic mean (standard deviation)	3.83 (± 1.08)	3.96 (± 0.841)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Constant (ke) of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Elimination Constant (ke) of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose

drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: 1/hr				
arithmetic mean (standard deviation)	1.63 (± 0.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: L/hr				
arithmetic mean (standard deviation)	13.7 (± 6.79)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir Carboxylate in Adults

End point title	Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir Carboxylate in Adults

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adults >/= 18 years.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adults With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: litre (L)				
arithmetic mean (standard deviation)	8.39 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Cmax of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Cmax of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[7]			
Units: ng/mL				
number (not applicable)				
Conventional Dose: 60 mg	61.9			
Conventional Dose: 75 mg	45.9			
Double Dose: 90 mg	107			
Double Dose: 150 mg	86.6			

Notes:

[7] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Ctrough of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Ctrough of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[8]			
Units: ng/mL				
number (not applicable)				
Conventional Dose: 60 mg	2.84			
Conventional Dose: 75 mg	3.37			
Double Dose: 90 mg	6.65			
Double Dose: 150 mg	3.88			

Notes:

[8] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: AUC0-12 at Steady State of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: AUC0-12 at Steady State of Oseltamivir in Adolescents and Children

End point description:

AUC0-12 will be reported at steady state as nanograms per hour per millilitre (ng*h/mL). The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[9]			
Units: ng*h/mL				
number (not applicable)				
Conventional Dose: 60 mg	229			
Conventional Dose: 75 mg	171			
Double Dose: 90 mg	425			
Double Dose: 150 mg	339			

Notes:

[9] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Tmax of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Tmax of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[10]			
Units: hour				
number (not applicable)				
Conventional Dose: 60 mg	1			
Conventional Dose: 75 mg	1			
Double Dose: 90 mg	1			
Double Dose: 150 mg	1.25			

Notes:

[10] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Cmax of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Cmax of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[11]			
Units: ng/mL				
number (not applicable)				
Conventional Dose: 60 mg	363			
Conventional Dose: 75 mg	848			
Double Dose: 90 mg	770			
Double Dose: 150 mg	906			

Notes:

[11] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Ctrough of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Ctrough of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[12]			
Units: ng/mL				
number (not applicable)				
Conventional Dose: 60 mg	215			
Conventional Dose: 75 mg	459			
Double Dose: 90 mg	445			
Double Dose: 150 mg	464			

Notes:

[12] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: AUC0-12 at Steady State of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: AUC0-12 at Steady State of Oseltamivir Carboxylate in Adolescents and Children

End point description:

AUC0-12 will be reported at steady state as nanograms per hour per millilitre (ng*h/mL). The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[13]			
Units: ng*h/mL				
number (not applicable)				
Conventional Dose: 60 mg	3550			
Conventional Dose: 75 mg	8010			

Double Dose: 90 mg	7460			
Double Dose: 150 mg	8420			

Notes:

[13] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Tmax of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Tmax of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[14]			
Units: hour				
number (not applicable)				
Conventional Dose: 60 mg	3.75			
Conventional Dose: 75 mg	4			
Double Dose: 90 mg	4			
Double Dose: 150 mg	4			

Notes:

[14] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Constant (ke) of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Elimination Constant (ke) of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[15]			
Units: 1/hr				
number (not applicable)				
Conventional Dose: 60 mg	4.22			
Conventional Dose: 75 mg	4.56			
Double Dose: 90 mg	3.40			
Double Dose: 150 mg	5.74			

Notes:

[15] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Apparent Clearance (CL/F) of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[16]			
Units: L/hr				
number (not applicable)				
Conventional Dose: 60 mg	263			
Conventional Dose: 75 mg	439			
Double Dose: 90 mg	212			

Double Dose: 150 mg	442			

Notes:

[16] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir in Adolescents and Children

End point title	Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[17]			
Units: Litre				
number (not applicable)				
Conventional Dose: 60 mg	62.3			
Conventional Dose: 75 mg	96.4			
Double Dose: 90 mg	62.3			
Double Dose: 150 mg	76.9			

Notes:

[17] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Constant (ke) of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Elimination Constant (ke) of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[18]			
Units: 1/hr				
number (not applicable)				
Conventional Dose: 60 mg	2.01			
Conventional Dose: 75 mg	1.12			
Double Dose: 90 mg	1.44			
Double Dose: 150 mg	2.12			

Notes:

[18] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Clearance (CL/F), of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Apparent Clearance (CL/F), of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[19]			
Units: L/hr				
number (not applicable)				
Conventional Dose: 60 mg	16.9			
Conventional Dose: 75 mg	9.36			
Double Dose: 90 mg	12.1			

Double Dose: 150 mg	17.8			

Notes:

[19] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir Carboxylate in Adolescents and Children

End point title	Pharmacokinetics: Apparent Volume of Distribution (Vc/F) of Oseltamivir Carboxylate in Adolescents and Children

End point description:

The PKEP population comprised all subjects in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit time point. Reported here are data for adolescents and children < 18 years. Individual data are provided as subjects received different drug doses. Drug dose is indicated in the row title for each subject.

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours postdose on Day 6 or any day after the 11th dose

End point values	Adolescents and Children With Pharmacokinetic Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	4[20]			
Units: Litre				
number (not applicable)				
Conventional Dose: 60 mg	8.39			
Conventional Dose: 75 mg	8.39			
Double Dose: 90 mg	8.39			
Double Dose: 150 mg	8.39			

Notes:

[20] - Data for each subject reported individually.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 40

Adverse event reporting additional description:

The safety population included all subjects who received at least one treatment with study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Experimental: Double dose

Reporting group description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 60 to 150 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 150 mg twice daily for adults/adolescents (>/=13 years old) or placebo matched to oseltamivir twice daily over 10 days.

Reporting group title	Experimental: Conventional dose

Reporting group description:

Immunocompromised participants will receive oseltamivir syrup at a dose ranging from 30 to 75 mg based on body weight, twice daily for children (1 to 12 years old) and oseltamivir capsules 75 mg twice daily for adults/adolescents greater than or equal to (>/=13 years old) or placebo-matched to oseltamivir twice daily over 10 days.

Serious adverse events	Experimental: Double dose	Experimental: Conventional dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 110 (9.09%)	8 / 105 (7.62%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia recurrent			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases of meninges			
subjects affected / exposed	0 / 110 (0.00%)	1 / 105 (0.95%)	
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 / 110 (0.91%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 110 (0.91%)	2 / 105 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 110 (1.82%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 110 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 110 (0.00%)	1 / 105 (0.95%)	
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 / 110 (0.91%)	0 / 105 (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: Double dose	Experimental: Conventional dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 110 (59.09%)	53 / 105 (50.48%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 110 (10.91%)	5 / 105 (4.76%)	
occurrences (all)	14	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 110 (10.00%)	10 / 105 (9.52%)	
occurrences (all)	15	11	
Nausea			
subjects affected / exposed	14 / 110 (12.73%)	10 / 105 (9.52%)	
occurrences (all)	18	11	
Vomiting			
subjects affected / exposed	12 / 110 (10.91%)	10 / 105 (9.52%)	
occurrences (all)	14	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2008	In Amendment B, the following significant changes were made: 1) A more timely assessment of baseline nasal and throat swab samples for oseltamivir-resistant virus was added due to the significant increase in oseltamivir-resistant viruses circulating within many countries identified by routine influenza virus surveillance during the 2007/2008 influenza season. Results of real-time PCR-based resistance testing were to be reported promptly to clinical sites to assist in determining the most appropriate treatment options for individual subjects. 2) New criterion was added for premature withdrawal of subjects from study treatment if additional antivirals were added to the patient's treatment regimen. The protocol was modified to allow replacement of subjects identified as having oseltamivir-resistant influenza virus at baseline by enrolling subjects on a rolling basis. 3) Clarification was made to allow treatment with other antivirals, if in the best interest of the patients and provided study oseltamivir was discontinued. 4) Efficacy data from subjects receiving other antivirals after discontinuing oseltamivir treatment were excluded from efficacy analyses after the date of commencement of other antiviral treatment and these subjects considered as treatment failures. The definition of the ITTi population was revised to exclude subjects with oseltamivir-resistant influenza A H1N1 H274Y virus at baseline.
28 March 2011	In Amendment C, the following significant changes were made: 1) Because of the need to enroll subjects within 48 hours of the onset of influenza, a number of subjects were ineligible for screening. Inclusion criteria were therefore modified to broaden the time between onset of influenza-like symptoms and first dose of study drug from 48 hours to 96 hours. 2) PCR and culture were added as diagnostic tests at baseline to overcome the high screening failure rate due to low sensitivity of rapid diagnostic tests. 3) The primary objective of the study was revised to become a descriptive characterization of safety, tolerability and resistance. 4) The sample size and number of participating centers were revised to reflect the amended study primary objective. 5) The criteria for withdrawal of subjects with renal failure was stated as subjects with creatinine clearance < 60 mL/min/1.73m^2.
28 September 2012	In Amendment D, the following significant changes were made: 1) The protocol was amended to include the Southern Hemisphere and allow global enrollment into the trial. Inclusion and exclusion criteria were amended to facilitate enrollment of as much of the immunocompromised population as possible. 2) The protocol was revised to allow self-swabbing at home when there was a home visit planned, thereby allowing shipment of the sample in an expedited manner. 3) The pharmacokinetic component of the study (removed in Amendment B) was reintroduced using a sparse PK sampling schedule not requiring blood a sample collection on multiple days and which was available to subjects who provided additional consent to that of the main study.
30 October 2013	In Amendment E, the following significant changes were made: 1) The protocol was amended to provide clarity and additional guidance on the inclusion criteria regarding CD4 cell counts for subjects with human immunodeficiency virus (HIV). 2) The criteria for withdrawal of subjects with renal failure was revised to state subjects with creatinine clearance < 45 mL/min/1.73m2. A lower limit of 45 mL/min for creatinine clearance was used to allow for subjects with mild to moderate renal impairment. 3) The statistical methods section was updated to include an overview of the planned pharmacokinetic analysis. 4) Removal of exclusion criterion for subjects who "have evidence of a serious secondary respiratory or disseminated infection that may confound or overlay the diagnosis and/or symptomatology of influenza" to prevent ambiguity around the category of subjects who should not be enrolled.

18 June 2014	In Amendment F, the following significant change was made: Throughout the protocol, 'oseltamivir' was re-introduced to all pharmacokinetic analysis sections, as applicable as both oseltamivir (parent) and oseltamivir carboxylate (metabolite) plasma concentrations were to be determined from blood samples. The term was inadvertently removed in protocol Version E.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported