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	v1
This version publication date	16 November 2017
First version publication date	16 November 2017

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	Investigator, Monitor, Carer, Data analyst, Subject, 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	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.

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.

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.

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 treated with at least one dose of study medication.

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 hypothesis testing was performed in this study as this study does not include a placebo control.

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:

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: Data analyses were not available and will be released at a later time. No hypothesis testing was performed in this study as this study does not include a placebo control.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

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)[5]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 40

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: Data analyses were not available and will be released at a later time. No hypothesis testing was performed in this study as this study does not include a placebo control.

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of All Clinical Influenza Symptoms

End point title	Time to Alleviation of All Clinical Influenza Symptoms

End point description:

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	0[8]	0[9]		
Units: days				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Viral Shedding Assessed by Culture and Reverse Transcription Polymerase Chain Reaction (RT-PCR)

End point title	Percentage of Subjects With Viral Shedding Assessed by Culture and Reverse Transcription Polymerase Chain Reaction (RT-PCR)

End point description:

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	0[10]	0[11]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Viral Load Assessed by Culture and RT-PCR

End point title	Percentage of Subjects With Viral Load Assessed by Culture and RT-PCR

End point description:

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	0[12]	0[13]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Developed Secondary Illness (otitis media, bronchitis, pneumonia, or sinusitis)

End point title	Percentage of Subjects Who Developed Secondary Illness (otitis media, bronchitis, pneumonia, or sinusitis)

End point description:

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	0[14]	0[15]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

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

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

End point description:

AUC0-12 will be reported at steady state as nanograms per hour per millilitre (ng*h/mL).

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[16]	0[17]		
Units: ng * h/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Maximum Plasma Concentration (Cmax)

End point title	Pharmacokinetics: Maximum Plasma Concentration (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[18]	0[19]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Trough Plasma Concentration (Ctrough)

End point title	Pharmacokinetics: Trough Plasma Concentration (Ctrough)

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[20]	0[21]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Half-life (t 1/2), if appropriate

End point title	Pharmacokinetics: Elimination Half-life (t 1/2), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[22]	0[23]		
Units: hours				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Time to Maximum Concentration (tmax), if appropriate

End point title	Pharmacokinetics: Time to Maximum Concentration (tmax), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[24]	0[25]		
Units: hours				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination Constant (ke), if appropriate

End point title	Pharmacokinetics: Elimination Constant (ke), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[26]	0[27]		
Units: unitless constant				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Clearance (CL/F), if appropriate

End point title	Pharmacokinetics: Apparent Clearance (CL/F), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[28]	0[29]		
Units: L/hour				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Volume of Distribution (Vc/F), if appropriate

End point title	Pharmacokinetics: Apparent Volume of Distribution (Vc/F), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[30]	0[31]		
Units: L/hour				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Apparent Total Clearance of Metabolite (CLm), if appropriate

End point title	Pharmacokinetics: Apparent Total Clearance of Metabolite (CLm), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[32]	0[33]		
Units: L/hour				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Last Measureable Concentration (Clast), if appropriate

End point title	Pharmacokinetics: Last Measureable Concentration (Clast), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[34]	0[35]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Time to Last Measureable Concentration (tlast), if appropriate

End point title	Pharmacokinetics: Time to Last Measureable Concentration (tlast), if appropriate

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (30 minutes), 1.5, 4, 8 hours (h) 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	0[36]	0[37]		
Units: hours				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Each Individual Symptom Score

End point title	Percentage of Subjects With Each Individual Symptom Score

End point description:

End point type	Secondary

End point timeframe:

Day 1 up to Day 40

End point values	Experimental: Conventional dose	Experimental: Double dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[38]	0[39]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

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:

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	0[40]	0[41]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Hospitalized

End point title	Percentage of Subjects Hospitalized

End point description:

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	0[42]	0[43]		
Units: percentage of subjects				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalization

End point title	Duration of Hospitalization

End point description:

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	0[44]	0[45]		
Units: days				
arithmetic mean (standard deviation)	()	()		

Notes:

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

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

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: 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.

Serious adverse events	Experimental: Conventional dose	Experimental: Double dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 105 (7.62%)	10 / 110 (9.09%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia recurrent			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases of meninges			
subjects affected / exposed	1 / 105 (0.95%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 105 (0.95%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 105 (1.90%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 105 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 105 (0.95%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 105 (0.95%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental: Conventional dose	Experimental: Double dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 105 (50.48%)	65 / 110 (59.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 105 (4.76%)	12 / 110 (10.91%)	
occurrences (all)	6	14	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 105 (9.52%)	11 / 110 (10.00%)	
occurrences (all)	11	15	
Nausea			
subjects affected / exposed	10 / 105 (9.52%)	14 / 110 (12.73%)	
occurrences (all)	11	18	
Vomiting			
subjects affected / exposed	10 / 105 (9.52%)	12 / 110 (10.91%)	
occurrences (all)	10	14	

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