



Clinical trial results:

A Multicenter, Study of the Safety of Oseltamivir Administered Intravenously for the Treatment of Influenza in Patients Aged ≥ 13 Years Summary

EudraCT number	2010-020083-38
Trial protocol	HU DE LT DK FR IT ES PL
Global end of trial date	14 September 2012

Results information

Result version number	v1 (current)
This version publication date	24 March 2016
First version publication date	24 March 2016

Trial information

Trial identification

Sponsor protocol code	NV25118
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01050257
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 September 2012
Global end of trial reached?	Yes
Global end of trial date	14 September 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of oseltamivir administered by intravenous infusion in the treatment of influenza (seasonal or pandemic [H1N1] 2009 influenza).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and good clinical practices (GCP) guidelines, or with the laws of the country if these afforded greater protection. Written informed consent for participation in the study was obtained prior to performing any study-specific assessments or procedures. Participants had the right to withdraw from the study at any time for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	118
EEA total number of subjects	54

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	4
Adults (18-64 years)	90
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 122 participants screened, 118 were enrolled into the study. Participants were enrolled at 38 active centers in 6 countries.

Pre-assignment

Screening details:

This study included a 5-day treatment period and an optional extension treatment period. Participants were considered to have completed treatment if they completed the 5-day course of treatment (IV and/or oral).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Oseltamivir 100 mg IV bid

Arm description:

Participants received 100 mg of oseltamivir administered by controlled IV infusion over 2 hours, twice daily (bid), for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir (intravenous)
Investigational medicinal product code	Ro 64-0796/F09-01
Other name	Oseltamivir phosphate
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous oseltamivir was administered by slow infusion over 2 hours, every 12 hours.

Investigational medicinal product name	Oseltamivir capsules (75 mg)
Investigational medicinal product code	
Other name	Oseltamivir phosphate
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral oseltamivir was administered as 75 mg capsules for the randomized treatment groups. Participants randomized to the 100 mg IV treatment group who switched to oral therapy received one 75 mg capsule twice daily.

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

Dosage and administration details:

One placebo capsule was administered twice daily to participants randomized to the 100 mg IV treatment group who switched to oral therapy.

Arm title	Oseltamivir 200 mg IV bid
------------------	---------------------------

Arm description:

Participants received 200 mg of oseltamivir administered by controlled IV infusion over 2 hours, every 12 hours, for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir (intravenous)
Investigational medicinal product code	Ro 64-0796/F09-01
Other name	Oseltamivir phosphate
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous oseltamivir was administered by slow infusion over 2 hours, every 12 hours.

Investigational medicinal product name	Oseltamivir capsules (75 mg)
Investigational medicinal product code	
Other name	Oseltamivir phosphate
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral oseltamivir was administered as 75 mg capsules for the randomized treatment groups. Participants randomized to the 200 mg IV treatment group who switched to oral therapy received two 75 mg capsules twice daily.

Arm title	Oseltamivir open-label
------------------	------------------------

Arm description:

Participants with moderate/severe renal impairment or renal failure were offered a 5-day course of treatment with IV oseltamivir at a dosage of 40 mg bid or 40 mg once daily (qd), depending on their creatinine clearance range and whether or not they were on continuous renal replacement therapy (CRRT). For participants with moderate or severe renal impairment who did not receive the full treatment course intravenously, oral oseltamivir was supplied as 30 mg capsules in an open-label fashion. Participants on hemodialysis (HD) received 25 mg IV after every HD session. Participants on continuous ambulatory peritoneal dialysis (CAPD) received a single IV dose of 40 mg. For participants on HD or CAPD who switched to oral dosing during the treatment extension period, oral oseltamivir was supplied as 30 mg capsules.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir (intravenous)
Investigational medicinal product code	Ro 64-0796/F09-01
Other name	Oseltamivir phosphate
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In participants with moderate renal impairment, 40 mg dose was given as a slow IV infusion over 2 hours every 12 hours. In participants with severe renal impairment, 40 mg dose was given as a slow IV infusion over 2 hours every 24 hours.

Investigational medicinal product name	Oseltamivir capsules (30 mg)
Investigational medicinal product code	
Other name	oseltamivir phosphate
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For participants with moderate or severe renal impairment who did not receive the full treatment course intravenously, oral oseltamivir was supplied as 30 mg capsules in an open-label fashion. Participants with moderate renal impairment received one 30 mg capsule twice daily, while participants with severe renal impairment received one 30 mg capsule once daily.

Number of subjects in period 1	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open- label
Started	50	53	15
Completed	39	40	8
Not completed	11	13	7
Violation criteria	-	1	-
Failure to return	-	2	-
No reason specified	-	-	2
withdrawal by subject	-	3	-
Death	-	-	1
Adverse event	4	4	2
Refused treatment/did not cooperate	1	1	-
Admin/other (did not switch to oral)	6	2	2

Baseline characteristics

Reporting groups

Reporting group title	Oseltamivir 100 mg IV bid
Reporting group description:	
Participants received 100 mg of oseltamivir administered by controlled IV infusion over 2 hours, twice daily (bid), for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.	
Reporting group title	Oseltamivir 200 mg IV bid
Reporting group description:	
Participants received 200 mg of oseltamivir administered by controlled IV infusion over 2 hours, every 12 hours, for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.	
Reporting group title	Oseltamivir open-label
Reporting group description:	
Participants with moderate/severe renal impairment or renal failure were offered a 5-day course of treatment with IV oseltamivir at a dosage of 40 mg bid or 40 mg once daily (qd), depending on their creatinine clearance range and whether or not they were on continuous renal replacement therapy (CRRT). For participants with moderate or severe renal impairment who did not receive the full treatment course intravenously, oral oseltamivir was supplied as 30 mg capsules in an open-label fashion. Participants on hemodialysis (HD) received 25 mg IV after every HD session. Participants on continuous ambulatory peritoneal dialysis (CAPD) received a single IV dose of 40 mg. For participants on HD or CAPD who switched to oral dosing during the treatment extension period, oral oseltamivir was supplied as 30 mg capsules.	

Reporting group values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label
Number of subjects	50	53	15
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	2	2	0
Adults (18-64 years)	41	43	6
From 65-84 years	7	8	9
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.8	44.3	66.9
standard deviation	± 16.68	± 18.09	± 18.28
Gender categorical			
Units: Subjects			
Female	25	27	8
Male	25	26	7

Reporting group values	Total		
------------------------	-------	--	--

Number of subjects	118		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	4		
Adults (18-64 years)	90		
From 65-84 years	24		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	60		
Male	58		

End points

End points reporting groups

Reporting group title	Oseltamivir 100 mg IV bid
-----------------------	---------------------------

Reporting group description:

Participants received 100 mg of oseltamivir administered by controlled IV infusion over 2 hours, twice daily (bid), for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Reporting group title	Oseltamivir 200 mg IV bid
-----------------------	---------------------------

Reporting group description:

Participants received 200 mg of oseltamivir administered by controlled IV infusion over 2 hours, every 12 hours, for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Reporting group title	Oseltamivir open-label
-----------------------	------------------------

Reporting group description:

Participants with moderate/severe renal impairment or renal failure were offered a 5-day course of treatment with IV oseltamivir at a dosage of 40 mg bid or 40 mg once daily (qd), depending on their creatinine clearance range and whether or not they were on continuous renal replacement therapy (CRRT). For participants with moderate or severe renal impairment who did not receive the full treatment course intravenously, oral oseltamivir was supplied as 30 mg capsules in an open-label fashion. Participants on hemodialysis (HD) received 25 mg IV after every HD session. Participants on continuous ambulatory peritoneal dialysis (CAPD) received a single IV dose of 40 mg. For participants on HD or CAPD who switched to oral dosing during the treatment extension period, oral oseltamivir was supplied as 30 mg capsules.

Subject analysis set title	Safety Population
----------------------------	-------------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

The safety population included all participants who received at least one dose of study medication (IV or oral) and had a safety assessment performed after initiation of treatment.

Subject analysis set title	Intent-to-Treat Population
----------------------------	----------------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

All participants who received at least one dose of study medication (IV or oral) were included in the intent-to-treat (ITT) population.

Subject analysis set title	Intent-to-Treat Influenza Infected (ITTI) Population
----------------------------	--

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The subset of participants in the ITT population who had laboratory confirmation of influenza infection (positive viral culture or RT-PCR), excluding participants infected with oseltamivir resistant influenza at baseline (as determined by phenotypic and, where necessary, genotypic testing), were included in the intent-to-treat infected (ITTI) population. The ITTI population was the primary population for the analysis of the efficacy variables.

Subject analysis set title	Oseltamivir open-label 40 mg IV bid
----------------------------	-------------------------------------

Subject analysis set type	Sub-group analysis
---------------------------	--------------------

Subject analysis set description:

Participants with moderate/severe renal impairment not on CRRT with creatinine clearance (CrCL) >30 to 60 millilitre/minute (mL/min), received intravenous oseltamivir at a dose of 40 mg bid. Participants who were on CRRT and who had CRRTCL \pm CrCL >30 mL/min also received intravenous oseltamivir at a dose of 40 mg bid.

Subject analysis set title	Oseltamivir open-label 40 mg IV qd
----------------------------	------------------------------------

Subject analysis set type	Sub-group analysis
---------------------------	--------------------

Subject analysis set description:

Participants with moderate/severe renal impairment not on CRRT with CrCl 10 to 30 mL/min, received intravenous oseltamivir at a dose of 40 mg daily. Participants who were on CRRT and who had CRRTCL \pm CrCL 10 to 30 mL/min also received intravenous oseltamivir at a dose of 40 mg daily.

Primary: Number of participants with any adverse events or serious adverse events

End point title	Number of participants with any adverse events or serious adverse events ^[1]
-----------------	---

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution that results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. On treatment = AEs that started between the day of first dose and within 2 days after the last dose. Off treatment = AEs that started more than 2 days after the last dose of study drug.

End point type	Primary
----------------	---------

End point timeframe:

Up to Day 30

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: Statistical analysis was not carried out for the primary end point.

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	51	14	
Units: Number of participants				
Participants with AEs On treatment (IV dosing)	24	27	11	
Participants with AEs On treatment (oral dosing)	10	9	4	
Participants with AEs Off treatment	13	13	5	
Participants with SAEs On treatment (IV dosing)	3	4	2	
Participants with SAEs On treatment (oral dosing)	2	0	2	
Participants with SAEs Off treatment	5	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with viral shedding by culture

End point title	Number of participants with viral shedding by culture
-----------------	---

End point description:

Viral culturing from throat and nasal swabs was used to confirm the occurrence of viral shedding. The presence of viral shedding was determined by means of positive viral culture = log₁₀ TCID₅₀ > 0.5 TCID₅₀ = 50% tissue culture infective dose. Only participants with data available at particular timepoint were analysed. n = the number of participants analysed at the given time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1, 4, 6, 11, 15, and 30

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	32	10	
Units: Number of participants				
Day 1, (n=29, 30, 10)	22	24	9	
Day 4 (n=28, 28, 10)	4	8	3	
Day 6 (n=22, 28, 8)	1	0	0	
Day 11, (n=22, 26, 8)	0	1	0	
Day 15, (n=17, 24, 7)	0	1	1	
Day 30, (n=22, 28, 6)	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with viral shedding by reverse transcriptase polymerase chain reaction

End point title	Number of participants with viral shedding by reverse transcriptase polymerase chain reaction
-----------------	---

End point description:

Nasal and throat swabs from participants were used to evaluate the occurrence of viral shedding by reverse transcriptase polymerase chain reaction (RT-PCR) (log 10 copies/mL). Only participants with data available at particular time point were analysed. n = the number of participants analysed at the given time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1, 4, 6, 11, 15, and 30

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	32	10	
Units: Number of participants				
Day 1 (n=29, 30, 10)	25	28	9	
Day 4 (n=28, 28, 10)	18	20	6	
Day 6 (n=22, 28, 8)	9	10	5	
Day 11 (n=22, 26, 8)	2	3	1	
Day 15 (n=17, 24, 7)	0	1	0	
Day 30 (n=22, 28, 6)	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in influenza titer by culture at Day 4

End point title	Mean change from baseline in influenza titer by culture at Day 4
-----------------	--

End point description:

Throat and nasal swabs from participants were used to evaluate viral load (amount of virus present) determined by culture. Positive culture was indicated by a log₁₀ median TCID₅₀ > 0.5. A negative change from baseline indicated improvement (less virus present). n = the number of participants analysed at the given time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 0) and Day 4

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	24	9	
Units: Log ₁₀ (TCID ₅₀)				
arithmetic mean (standard deviation)				
Day 4 (n = 4, 8, 3)	-1.38 (± 1.92)	-2.19 (± 1.186)	-3 (± 0.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in body temperature until last value

End point title	Mean change from baseline in body temperature until last value
-----------------	--

End point description:

Body temperature was recorded twice daily from baseline up to Day 30. Body temperature is presented as the change from baseline until the last value recorded.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, up to Day 30

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	51	14	
Units: Centigrade (C)				
arithmetic mean (standard deviation)	-0.81 (± 1.06)	-0.64 (± 0.99)	-0.45 (± 1.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who had fever during the study

End point title	Number of participants who had fever during the study
-----------------	---

End point description:

Fever is defined as a body temperature ≥ 37.8 degrees Celcius. The number of participants with fever (on a 12-hourly basis) was reported. Only participants with fever at particular time point were analysed. n = the number of participants analysed at the given time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline and Hours 12, 24, 36, 48, 60, 72, 84, 96 and 108

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	32	10	
Units: Number of participants				
Baseline, n = 7, 6, 2	7	6	2	
Hour 12, n = 7, 5, 1	2	3	1	
Hour 24, n = 7, 6, 1	2	0	0	
Hour 36, n = 7, 5, 2	1	1	2	
Hour 48, n = 7, 6, 1	1	2	0	
Hour 60, n = 5, 6, 0	0	2	0	
Hour 72, n = 6, 5, 1	0	1	0	
Hour 84, n = 5, 6, 0	0	0	0	
Hour 96, n = 5, 6, 1	0	1	0	
Hour 108, n = 5, 5, 0	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to resolution of fever for participants who had a fever at baseline

End point title	Time to resolution of fever for participants who had a fever at baseline
-----------------	--

End point description:

Participants who had fever at baseline (based on baseline temperature) were included in the time to resolution of fever (afebrile state) analysis. Fever was defined as a temperature of ≥ 37.8 degrees Celsius. Resolution of fever was a temperature ≤ 37.2 for at least 21.5 hours.

End point type	Secondary
End point timeframe:	
Baseline, Up to Day 30	

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	2 ^[2]	
Units: hours				
median (confidence interval 95%)	11.8 (7.8 to 43.5)	18.6 (8.4 to 66.8)	47.7 (47.7 to 1000)	

Notes:

[2] - Median could not be calculated due to small number of participants analysed (1 participant censored)

Statistical analyses

Statistical analysis title	Oseltamivir 200 mg vs. Oseltamivir 100 mg
Statistical analysis description:	
The time to resolution of fever was compared for the two treatment groups (200 mg oseltamivir and 100 mg oseltamivir). Median time was estimated from the Kaplan-Meier curve. Wilcoxon test was used for testing the homogeneity of the two survival curves.	
Comparison groups	Oseltamivir 100 mg IV bid v Oseltamivir 200 mg IV bid
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.671
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65
upper limit	29.7

Secondary: Number of participants with influenza symptoms

End point title	Number of participants with influenza symptoms
End point description:	
Influenza symptoms included nasal congestion, sore throat, cough, aches and pains, fatigue, chills/sweats (feverish), headache, vomiting, and diarrhea. The number of participants with influenza symptoms by study day is reported. Only participants with influenza symptoms at particular time point were analysed. n = the number of participants analysed at the given time point.	
End point type	Secondary
End point timeframe:	
Days 1, 11, 15, 30	

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	50	14	
Units: Number of participants				
Day 1, n= 49, 50, 14	49	50	13	
Day 11, n= 41, 41, 11	31	32	11	
Day 15, n=35, 38, 10	25	22	9	
Day 30, n=38, 40, 9	16	13	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with viral resistance

End point title	Number of participants with viral resistance
End point description: Nasal and Throat swabs were collected on Days 1, 4, 6, 11, 15 and 30 and were sent to a central laboratory for testing. Viral resistance was determined by phenotypic and genotypic testing.	
End point type	Secondary
End point timeframe: Up to Day 30	

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	32	10	
Units: Number of participants	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated creatinine clearance

End point title	Calculated creatinine clearance ^[3]
End point description: Creatinine Clearance (CrCl) was estimated according to Cockcroft-Gault for participants ≥ 18 years and according to Schwartz equation for participants < 18 years. Calculated creatinine clearance measures the rate creatinine (substance formed from metabolism of creatine) is cleared from blood by the kidneys.	
End point type	Secondary

End point timeframe:

Screening

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The subject analysis sets - Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd contain participants from the Oseltamivir open-label arm reported in the baseline period. Data for the Oseltamivir open-label arm, for this end point, is represented via the Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd subject analysis sets.

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label 40 mg IV bid	Oseltamivir open-label 40 mg IV qd
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	49	6	4
Units: mL/min				
arithmetic mean (standard deviation)				
CrCl	113 (± 44)	122 (± 59)	39.2 (± 5.99)	23.3 (± 7.37)

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve at steady state of oseltamivir and oseltamivir carboxylate

End point title	Area under the curve at steady state of oseltamivir and oseltamivir carboxylate ^[4]
-----------------	--

End point description:

The area under the plot of plasma concentration of drug against time after drug administration is defined as the area under the curve (AUC). The area under the curve at steady state (AUC_{ss}) is the area under the curve during the steady-state period. Participants treated with oseltamivir and who had measurable concentrations of oseltamivir and oseltamivir carboxylate were included in the pharmacokinetic (PK) analysis unless major protocol deviations or unavailability of information occurred which could interfere with PK evaluation.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 5

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The subject analysis sets - Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd contain participants from the Oseltamivir open-label arm reported in the baseline period. Data for the Oseltamivir open-label arm, for this end point, is represented via the Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd subject analysis sets.

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label 40 mg IV bid	Oseltamivir open-label 40 mg IV qd
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	49	6	4
Units: nanogram/millilitre*hour				
arithmetic mean (standard deviation)				
AUC _{ss} , oseltamivir	546 (± 120)	1120 (± 370)	261 (± 22.8)	301 (± 38.6)
AUC _{ss} , oseltamivir carboxylate	5170 (± 2480)	10200 (± 4190)	7230 (± 3540)	13900 (± 7030)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration at steady state and trough concentration at the end of the dosing interval of oseltamivir and oseltamivir carboxylate

End point title	Maximum concentration at steady state and trough concentration at the end of the dosing interval of oseltamivir and oseltamivir carboxylate ^[5]
-----------------	--

End point description:

The Plasma Concentration (C_{max}) is defined as the maximum observed drug/analyte concentration. The trough concentration is defined as the plasma level of a drug measured just before the next dose.

Trough concentration at the end of the dosing interval (C_{tr}) values were computed over the 12-hour or 24-hour period depending on the inter-dose interval of each participant. Participants treated with oseltamivir and who had measurable concentrations of oseltamivir and oseltamivir carboxylate were included in the PK analysis unless major protocol deviations or unavailability of information occurred which could interfere with PK evaluation.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 5

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The subject analysis sets - Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd contain participants from the Oseltamivir open-label arm reported in the baseline period. Data for the Oseltamivir open-label arm, for this end point, is represented via the Oseltamivir open-label 40 mg IV bid and Oseltamivir open-label 40 mg IV qd subject analysis sets.

End point values	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label 40 mg IV bid	Oseltamivir open-label 40 mg IV qd
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	49	6	4
Units: nanogram/millilitre				
arithmetic mean (standard deviation)				
C _{max} oseltamivir	230 (± 44.5)	468 (± 116)	108 (± 8.08)	121 (± 11.9)
C _{max} oseltamivir carboxylate	555 (± 251)	1100 (± 422)	721 (± 327)	845 (± 403)
C _{tr} oseltamivir	0.554 (± 0.454)	1.5 (± 2.51)	0.34 (± 0.0991)	0.00344 (± 0.0025)
C _{tr} oseltamivir carboxylate	292 (± 164)	573 (± 270)	451 (± 248)	302 (± 186)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 2 days after last dose of treatment

Adverse event reporting additional description:

An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All AEs (related and unrelated) occurring during the treatment period were reported.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.1
--------------------	------

Reporting groups

Reporting group title	Oseltamivir 100 mg IV bid
-----------------------	---------------------------

Reporting group description:

Participants received 100 mg of oseltamivir administered by controlled IV infusion over 2 hours, every 12 hours, for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Reporting group title	Oseltamivir 200 mg IV bid
-----------------------	---------------------------

Reporting group description:

Participants received 200 mg of oseltamivir administered by controlled IV infusion over 2 hours, every 12 hours, for 5 days. A minimum of 6 doses (3 days) of IV oseltamivir was required. Thereafter, at the discretion of the investigator, participants had the option of completing the 5-day course with either IV or oral oseltamivir.

Reporting group title	Oseltamivir open-label
-----------------------	------------------------

Reporting group description:

Participants with moderate/severe renal impairment or renal failure were offered a 5-day course of treatment with IV oseltamivir at a dosage of 40 mg bid or 40 mg once daily qd, depending on their creatinine clearance range and whether or not they were on CRRT. For participants with moderate or severe renal impairment who did not receive the full treatment course intravenously, oral oseltamivir was supplied as 30 mg capsules in an open-label fashion. Participants on HD received 25 mg IV after every HD session. Participants on CAPD received a single IV dose of 40 mg. For participants on HD or CAPD who switched to oral dosing during the treatment extension period, oral oseltamivir was supplied as 30 mg capsules.

Serious adverse events	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open-label
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 48 (10.42%)	4 / 51 (7.84%)	4 / 14 (28.57%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 48 (0.00%)	0 / 51 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 51 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 51 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 51 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Respiratory failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 48 (0.00%)	0 / 51 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection pseudomonal			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Oseltamivir 100 mg IV bid	Oseltamivir 200 mg IV bid	Oseltamivir open- label
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 48 (35.42%)	18 / 51 (35.29%)	10 / 14 (71.43%)
Investigations			
Blood magnesium decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 51 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Hypotension subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	2 / 14 (14.29%) 2
Cardiac disorders Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	2 / 14 (14.29%) 2
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	4 / 51 (7.84%) 4	2 / 14 (14.29%) 2
Dizziness subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
General disorders and administration site conditions Infusion site pain subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	4 / 51 (7.84%) 5	0 / 14 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 51 (0.00%) 0	2 / 14 (14.29%) 2
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 8	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Vomiting subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	4 / 51 (7.84%) 4	0 / 14 (0.00%) 0
Constipation			

subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	3 / 51 (5.88%) 3	1 / 14 (7.14%) 1
Diarrhoea subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4	1 / 51 (1.96%) 1	0 / 14 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Hepatobiliary disorders Liver disorder subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Respiratory, thoracic and mediastinal disorders Acute respiratory distress syndrome subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Asthma subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Pneumomediastinum subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Agitation subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Delirium subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Depression			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 51 (1.96%) 1	2 / 14 (14.29%) 2
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 51 (1.96%) 1	1 / 14 (7.14%) 1
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 51 (0.00%) 0	1 / 14 (7.14%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2010	Enrollment to participants outside of the US was opened. Participants with renal impairment and renal failure were enrolled and treated. New guidelines for the preparation of IV investigational product for the randomized population (change in infusion volume from 50 mL to 100 mL) were provided.
14 October 2011	Participants undergoing HD and CAPD could be switched from IV to oral dosing. Oral dosing recommendations for participants with renal impairment were updated as a result of the availability of lower dose oseltamivir capsules and the desire to better align oral dosing recommendations with those anticipated for IV oseltamivir. This amendment allowed enrollment of participants up to 144 hours after the onset of first influenza symptoms to allow for the enrollment of participants who may have started on oral oseltamivir and whose condition then necessitated IV oseltamivir. The creatinine clearance cutoff value in moderate renal impairment was corrected from 50 to 60 mL/min to be consistent with available regulatory guidance and prior clinical studies of oseltamivir in participants with renal impairment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported