Clinical trial results:
An Open-Label, Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Intravenous Oseltamivir (Tamiflu®) in the Treatment of Infants Less Than One Year of Age With Influenza Infection

Summary

EudraCT number	2016-003003-54
Trial protocol	Outside EU/EEA
Global end of trial date	28 January 2013

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017

Trial information

Trial identification

Sponsor protocol code	NP25138

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01053663
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, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F.Hoffmann-La Roche, +41 616878333, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This prospective, open-label, pharmacokinetic (PK)/pharmacodynamic (PD) and safety study was designed to define the PK of oseltamivir and oseltamivir carboxylate and evaluate the safety profile following intravenous (IV) administration of oseltamivir phosphate in infants less than 1 year of age with influenza. The study was also planned to evaluate viral load, viral shedding, and to evaluate all isolates for phenotypic and, where necessary, genotypic resistance.

Protection of trial subjects:

The study was conducted in accordance with the principles of the ''Declaration of Helsinki" and Good Clinical Practice according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 January 2011
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	United States: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	8
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2428 participants were prescreened; of which, 2419 failed the prescreening evaluation. The most common reasons for failing the prescreening evaluation included the following: negative influenza diagnosis, not meeting the age criterion, ability to tolerate/absorb oral medication, and inability to comply with the study procedures.

Period 1

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

Arms

Arm title	Oseltamivir - All Participants

Arm description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	RO0640796
Other name	Tamiflu®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received oseltamivir twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's age.

Number of subjects in period 1	Oseltamivir - All Participants
Started	9
Completed	3
Not completed	6
Transferred to Another Hospital	1
Death	2
Poor IV Access	1
Negative Influenza Diagnosis	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Oseltamivir - All Participants

Reporting group description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Reporting group values	Oseltamivir - All Participants	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
Age continuous			
Here, 99999 represent data not estimable due to single participant analyzed.			
Units: days			
arithmetic mean	143.2		
standard deviation	± 82.9	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	7	7	

Subject analysis sets

Subject analysis set title	Oseltamivir: Age 91 to <365 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Subject analysis set title	Oseltamivir: Age 31 to 90 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Subject analysis set title	Oseltamivir: Age 0 to 30 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Reporting group values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days
Number of subjects	7	1	1
Age categorical Units: Subjects			
Age continuous			
Here, 99999 represent data not estimable due to single participant analyzed.			
Units: days			
arithmetic mean	175	41	23
standard deviation	± 62	± 99999	± 99999
Gender categorical Units: Subjects			
Female	2	0	0
Male	5	1	1

End points

End points reporting groups

Reporting group title	Oseltamivir - All Participants

Reporting group description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Subject analysis set title	Oseltamivir: Age 91 to <365 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Subject analysis set title	Oseltamivir: Age 31 to 90 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Subject analysis set title	Oseltamivir: Age 0 to 30 Days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Primary: Area Under the Concentration Versus Time Curve From Time Zero to Last Measurable Plasma Concentration (AUClast) of Oseltamivir and Oseltamivir Carboxylate on Day 1

End point title	Area Under the Concentration Versus Time Curve From Time Zero to Last Measurable Plasma Concentration (AUClast) of Oseltamivir and Oseltamivir Carboxylate on Day 1[1]

End point description:

Pharmacokinetic (PK) population included all treated participants who had at least one blood sample evaluable for drug concentration level. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1

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 analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0[2]	1	
Units: hour*nanograms/milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Oseltamivir	777 (± 162.8)	()	494 (± 99999)	
Oseltamivir Carboxylate	5200 (± 87.8)	()	7510 (± 99999)	

Notes:

[2] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 2

End point title	AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 2[3]

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 2

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 analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	0[4]	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	988 (± 57.8)	481 (± 99999)	()	
Oseltamivir Carboxylate	7270 (± 42.2)	5330 (± 99999)	()	

Notes:

[4] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 4

End point title	AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 4[5]

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here,

99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	0[6]	1	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	1520 (± 33.9)	()	389 (± 99999)	
Oseltamivir Carboxylate	3880 (± 98)	()	2070 (± 99999)	

Notes:

[6] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) of Oseltamivir and Oseltamivir Carboxylate on Day 1

End point title	Maximum Observed Plasma Concentration (Cmax) of Oseltamivir and Oseltamivir Carboxylate on Day 1[7]

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	0[8]	1	
Units: nanograms/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Oseltamivir	307 (± 315.7)	()	203 (± 99999)	
Oseltamivir Carboxylate	736 (± 55.5)	()	871 (± 99999)	

Notes:

[8] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 2

End point title	Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 2[9]

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 2

Notes:

[9] - 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 analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	0[10]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	419 (± 78.4)	194 (± 99999)	()	
Oseltamivir Carboxylate	1080 (± 43.6)	1050 (± 99999)	()	

Notes:

[10] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 4

End point title	Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 4[11]

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

End point type	Primary

End point timeframe:

Pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

Notes:

[11] - 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 analysis was planned for this open-label study.

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	0[12]	1	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	742 (± 31.1)	()	189 (± 99999)	
Oseltamivir Carboxylate	1370 (± 89.6)	()	727 (± 99999)	

Notes:

[12] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the Maximum Observed Plasma Concentration (Tmax) of Oseltamivir and Oseltamivir Carboxylate

End point title	Time to the Maximum Observed Plasma Concentration (Tmax) of Oseltamivir and Oseltamivir Carboxylate

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	1	
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 3, 0, 1)	2.51 (± 55.4)	9999 (± 9999)	2 (± 99999)	
Day 1: Oseltamivir Carboxylate (n = 3, 0, 1)	4.57 (± 32.5)	9999 (± 9999)	5.58 (± 99999)	
Day 2: Oseltamivir (n = 3, 1, 0)	2.02 (± 1.4)	2.13 (± 99999)	9999 (± 9999)	
Day 2: Oseltamivir Carboxylate (n = 3, 1, 0)	3.4 (± 47.8)	4.3 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 2, 0, 1)	2.02 (± 1.2)	9999 (± 9999)	1.93 (± 99999)	
Day 4: Oseltamivir Carboxylate (n = 2, 0, 1)	3.85 (± 6.7)	9999 (± 9999)	3.98 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Plasma Concentration (Clast) of Oseltamivir and Oseltamivir Carboxylate

End point title	Last Measurable Plasma Concentration (Clast) of Oseltamivir and Oseltamivir Carboxylate

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	1	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 3, 0, 1)	5.58 (± 183)	9999 (± 9999)	2.76 (± 99999)	
Day 1: Oseltamivir Carboxylate (n = 3, 0, 1)	505 (± 82.9)	9999 (± 9999)	503 (± 99999)	
Day 2: Oseltamivir (n = 3, 1, 0)	8.22 (± 183.5)	6.84 (± 99999)	9999 (± 9999)	
Day 2: Oseltamivir Carboxylate (n = 3, 1, 0)	849 (± 67.9)	948 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 2, 0, 1)	66.2 (± 28.8)	9999 (± 9999)	10.7 (± 99999)	
Day 4: Oseltamivir Carboxylate (n = 2, 0, 1)	1370 (± 89.6)	9999 (± 9999)	727 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time of the Last Measurable Plasma Concentration (Tlast) of Oseltamivir and Oseltamivir Carboxylate

End point title	Time of the Last Measurable Plasma Concentration (Tlast) of Oseltamivir and Oseltamivir Carboxylate

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

End point values	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	1	
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 3, 0, 1)	9.62 (± 24.7)	9999 (± 9999)	10.58 (± 99999)	
Day 1: Oseltamivir Carboxylate (n = 3, 0, 1)	9.62 (± 24.7)	9999 (± 9999)	10.58 (± 99999)	
Day 2: Oseltamivir (n = 3, 1, 0)	8.55 (± 51.1)	6.47 (± 99999)	9999 (± 9999)	
Day 2: Oseltamivir Carboxylate (n = 3, 1, 0)	8.55 (± 51.1)	6.47 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 2, 0, 1)	3.85 (± 6.7)	9999 (± 9999)	3.98 (± 99999)	
Day 4: Oseltamivir Carboxylate (n = 2, 0, 1)	3.85 (± 6.7)	9999 (± 9999)	3.98 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Greater Than or Equal to (>/=) 5−Fold Change in Neuraminidase Inhibition (NAI) Assay 50 Percent (%) Inhibitory Concentration (IC50) Values

End point title	Number of Participants With Greater Than or Equal to (>/=) 5−Fold Change in Neuraminidase Inhibition (NAI) Assay 50 Percent (%) Inhibitory Concentration (IC50) Values

End point description:

IC50 was defined as the concentration that causes 50% inhibition of viral activity. IC50 values were calculated using NAI assay. The 5-fold change was calculated as either >/=5 times change in the NAI IC50 visit value from the Reference value at a visit or >/=5 times change in the NAI IC50 Visit value from the Baseline value. Safety population included all participants who received at least one dose of IV study medication and had a safety assessment performed after initiation of treatment. Here, number of subjects analyzed = participants evaluable for this outcome measure, and n = participants evaluable for specified time-point, for each arm, respectively. Here, 9999 represent data not available as no participant was evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 1, 3, 4, 6, 15

End point values	Oseltamivir - All Participants	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	4	0[13]	1
Units: participants				
Day 1 (n=5, 4, 0, 1)	1	1		0
Day 3 (n=1, 0, 0, 1)	0	9999		0
Day 4 (n=3, 3, 0, 0)	1	1		9999
Day 6 (n=1, 0, 0, 1)	0	9999		0
Day 15 (n=1, 1, 0, 0)	0	0		9999

Notes:

[13] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Oseltamivir Resistance Mutation

End point title	Number of Participants With Oseltamivir Resistance Mutation

End point description:

Resistance was assessed by neuraminidase (NA) and hemagglutinin (HA) genes sequencing analysis, using Reverse Transcription Polymerase Chain Reaction (RT-PCR). Safety population.

End point type	Secondary

End point timeframe:

Up to Day 30

End point values	Oseltamivir - All Participants	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days	Oseltamivir: Age 0 to 30 Days
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	7	1	1
Units: participants	1	1	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 30

Adverse event reporting additional description:

Safety population

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Oseltamivir - All Participants

Reporting group description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to <365 days received 3 mg/kg; participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Reporting group title	Oseltamivir: Age 91 to <365 Days

Reporting group description:

Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Reporting group title	Oseltamivir: Age 31 to 90 Days

Reporting group description:

Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Reporting group title	Oseltamivir: Age 0 to 30 Days

Reporting group description:

Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Serious adverse events	Oseltamivir - All Participants	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)	5 / 7 (71.43%)	0 / 1 (0.00%)
number of deaths (all causes)	3	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebral Ischaemia			

subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
General disorders and administration site conditions			
Multi−Organ Failure			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory Disorder			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory Failure			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Oseltamivir: Age 0 to 30 Days		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi−Organ Failure			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory Disorder			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Distress			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Oseltamivir - All Participants	Oseltamivir: Age 91 to <365 Days	Oseltamivir: Age 31 to 90 Days
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)	4 / 7 (57.14%)	0 / 1 (0.00%)
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Sinus Bradycardia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			

Brain Oedema			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Application Site Vesicles			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Oseltamivir: Age 0 to 30 Days		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus Bradycardia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application Site Vesicles			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Hypertension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2010	• Modified the requirements for the IV therapy duration and clarified the study population influenza diagnosis and duration of IV therapy • Provided an updated Assessments and Procedures schedule • Specified adverse events grading system
14 May 2010	• Decreased the required number of IV doses to at least one and clarified that participants could have switched to oral dosing with oseltamivir after IV therapy was no longer medically necessary • Modified dosing in participants with moderate or severe renal impairment or who required continuous renal replacement therapy • Revised exclusion criteria and increased the flexibility of PK sampling
19 September 2011	• Clarified the day of treatment completion depending on when dosing was started and whether one or two doses were received on Day 1 • Revised the screening and eligibility text to allow flexibility to include data obtained from standard-of-care procedures prior to obtaining informed consent for study participation • Revised PK sample collection time-points

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 January 2013	The study was terminated prematurely after three influenza seasons.	-

Notes:

Limitations and caveats

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

Low number of participants enrolled in the study at the time that the study was terminated limits conclusions that can be derived from the study data.

Notes: