Clinical trial results:
An Open Label, Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Intravenous Oseltamivir (Tamiflu®) in the Treatment of Children 1 to 12 Years of Age With Influenza Infection

Summary

EudraCT number	2016-003004-31
Trial protocol	Outside EU/EEA
Global end of trial date	13 December 2012

Results information

Result version number	v1 (current)
This version publication date	23 February 2017
First version publication date	23 February 2017

Trial information

Trial identification

Sponsor protocol code	NP25139

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01033734
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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)	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	01 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study was a prospective, open label, pharmacokinetic (PK)/pharmacodynamic (PD) and safety evaluation of intravenous (IV) oseltamivir therapy in three cohorts of children with influenza infection aged 6-12 years (Cohort I), 3-5 years (Cohort II) and 1-2 years (Cohort III). Children with symptoms of influenza were considered for enrollment into this study.

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	19 December 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	United States: 8
Worldwide total number of subjects	8
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)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	7
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 2836 participants were prescreened, of which 2828 failed evaluation. The most common reasons for screen failure included: negative influenza diagnosis, not meeting the age criterion, ability to tolerate/absorb oral medication, and an 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 - overall

Arm description:

Participants received oseltamivir (Tamiflu) 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 body weight. Participants with body weight less than or equal to (<=) 23 kilograms (kg) received 3 milligrams per kilogram (mg/kg); participants with body weight more than (>) 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 milligrams (mg). 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 oral suspension, Powder for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Participants received oseltamivir twice daily. The oseltamivir doses were based on participant's age.

Number of subjects in period 1	Oseltamivir - overall
Started	8
Completed	7
Not completed	1
Withdrawal by Subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Oseltamivir - overall

Reporting group description:

Participants received oseltamivir (Tamiflu) 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 body weight. Participants with body weight less than or equal to (<=) 23 kilograms (kg) received 3 milligrams per kilogram (mg/kg); participants with body weight more than (>) 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 milligrams (mg). 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 - overall	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 4.8 ± 3.1	 -	
Gender categorical Units: Subjects			
Female	2	2	
Male	6	6	

End points

End points reporting groups

Reporting group title	Oseltamivir - overall

Reporting group description:

Participants received oseltamivir (Tamiflu) 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 body weight. Participants with body weight less than or equal to (<=) 23 kilograms (kg) received 3 milligrams per kilogram (mg/kg); participants with body weight more than (>) 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 milligrams (mg). 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: 6 to 12 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 6 to 12 years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 mg. 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: 3 to 5 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 3 to 5 years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight 40 kg received 100 mg. 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: 1 to 2 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 1 to 2 Years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight 40 kg received 100 mg. 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:

PK population included all treated participants who had at least one blood sample evaluable for drug concentration level. Number of participants 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:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion

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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	0[2]	
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Oseltamivir	829 (± 99999)	1460 (± 46.3)	()	
Oseltamivir Carboxylate	1700 (± 99999)	4550 (± 61.1)	()	

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 participants 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:

Day 2: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[4]	1	1	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	()	1070 (± 99999)	1920 (± 99999)	
Oseltamivir Carboxylate	()	5970 (± 99999)	6760 (± 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 3

End point title	AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 3[5]

End point description:

PK population. Number of participants 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:

Day 3 (with or after fifth dose): 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	0[6]	0[7]	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	943 (± 99999)	()	()	
Oseltamivir Carboxylate	2000 (± 99999)	()	()	

Notes:

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

[7] - 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[8]

End point description:

PK population. Number of participants 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:

Day 4: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

Notes:

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

End point values	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[9]	1	0[10]	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	()	2480 (± 99999)	()	
Oseltamivir Carboxylate	()	3800 (± 99999)	()	

Notes:

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

[10] - 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 5

End point title	AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 5[11]

End point description:

PK population. Number of participants 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:

Day 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	0[12]	0[13]	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	1010 (± 99999)	()	()	
Oseltamivir Carboxylate	2820 (± 99999)	()	()	

Notes:

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

[13] - 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[14]

End point description:

PK population. Number of participants 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:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion

Notes:

[14] - 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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	0[15]	
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Oseltamivir	360 (± 99999)	753 (± 36.9)	()	
Oseltamivir Carboxylate	311 (± 99999)	499 (± 55.1)	()	

Notes:

[15] - 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[16]

End point description:

PK population. Number of participants 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:

Day 2: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

Notes:

[16] - 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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[17]	1	1	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	()	500 (± 99999)	1270 (± 99999)	
Oseltamivir Carboxylate	()	663 (± 99999)	725 (± 99999)	

Notes:

[17] - 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 3

End point title	Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 3[18]

End point description:

PK population. Number of participants 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:

Day 3 (with or after fifth dose): 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

Notes:

[18] - 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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	0[19]	0[20]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	404 (± 99999)	()	()	
Oseltamivir Carboxylate	237 (± 99999)	()	()	

Notes:

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

[20] - 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[21]

End point description:

PK population. Number of participants 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:

Day 4: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

Notes:

[21] - 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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[22]	1	0[23]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	()	915 (± 99999)	()	
Oseltamivir Carboxylate	()	549 (± 99999)	()	

Notes:

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

[23] - 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 5

End point title	Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 5[24]

End point description:

PK population. Number of participants 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:

Day 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

Notes:

[24] - 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: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	0[25]	0[26]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	403 (± 99999)	()	()	
Oseltamivir Carboxylate	408 (± 99999)	()	()	

Notes:

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

[26] - 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 participants 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 time-point and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	1	
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 1, 3, 0)	2 (± 99999)	1.26 (± 41.7)	9999 (± 9999)	
Day 1: Oseltamivir Carboxylate (n = 1, 3, 0)	4 (± 99999)	4.61 (± 53.3)	9999 (± 9999)	
Day 2: Oseltamivir (n = 0, 1, 1)	9999 (± 9999)	2 (± 99999)	1 (± 99999)	
Day 2: Oseltamivir Carboxylate (n = 0, 1, 1)	9999 (± 9999)	4.62 (± 99999)	6 (± 99999)	
Day 3: Oseltamivir (n = 1, 0, 0)	1.05 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 3: Oseltamivir Carboxylate (n = 1, 0, 0)	3.05 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 0, 1, 0)	9999 (± 9999)	2.5 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir Carboxylate (n = 0, 1, 0)	9999 (± 9999)	8.05 (± 99999)	9999 (± 9999)	
Day 5: Oseltamivir (n = 1, 0, 0)	2 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 5: Oseltamivir Carboxylate (n = 1, 0, 0)	4.08 (± 99999)	9999 (± 9999)	9999 (± 9999)	

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 participants 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 time-point and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	1	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 1, 3, 0)	4.4 (± 99999)	2.41 (± 80.6)	9999 (± 9999)	
Day 1: Oseltamivir Carboxylate (n = 1, 3, 0)	237 (± 99999)	308 (± 74.4)	9999 (± 9999)	

Day 2: Oseltamivir (n = 0, 2, 1)	9999 (± 9999)	25.2 (± 1704911.2)	4.76 (± 99999)	
Day 2: Oseltamivir Carboxylate (n = 0, 2, 1)	9999 (± 9999)	319 (± 0.44)	484 (± 99999)	
Day 3: Oseltamivir (n = 1, 0, 0)	2.6 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 3: Oseltamivir Carboxylate (n = 1, 0, 0)	149 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 0, 1, 0)	9999 (± 9999)	25.1 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir Carboxylate (n = 0, 1, 0)	9999 (± 9999)	549 (± 99999)	9999 (± 9999)	
Day 5: Oseltamivir (n = 1, 0, 0)	15.1 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 5: Oseltamivir Carboxylate (n = 1, 0, 0)	339 (± 99999)	9999 (± 9999)	9999 (± 9999)	

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 participants 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 time-point and 99999 represent data not estimable due to single participant analyzed.

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	3	1	
Units: hours				
geometric mean (geometric coefficient of variation)				
Day 1: Oseltamivir (n = 1, 3, 0)	7.42 (± 99999)	10.5 (± 23.4)	9999 (± 9999)	
Day 1: Oseltamivir Carboxylate (n = 1, 3, 0)	7.42 (± 99999)	11.98 (± 0.2)	9999 (± 9999)	
Day 2: Oseltamivir (n = 0, 2, 1)	9999 (± 9999)	3.5 (± 448.5)	12 (± 99999)	
Day 2: Oseltamivir Carboxylate (n = 0, 2, 1)	9999 (± 9999)	3.5 (± 448.47)	12 (± 99999)	
Day 3: Oseltamivir (n = 1, 0, 0)	10.13 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 3: Oseltamivir Carboxylate (n = 1, 0, 0)	10.13 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 4: Oseltamivir (n = 0, 1, 0)	9999 (± 9999)	8.05 (± 99999)	9999 (± 9999)	
Day 4: Oseltamivir Carboxylate (n = 0, 1, 0)	9999 (± 9999)	8.05 (± 99999)	9999 (± 9999)	

Day 5: Oseltamivir (n = 1, 0, 0)	7.92 (± 99999)	9999 (± 9999)	9999 (± 9999)	
Day 5: Oseltamivir Carboxylate (n = 1, 0, 0)	7.92 (± 99999)	9999 (± 9999)	9999 (± 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Rate Constant (ke) of Oseltamivir and Oseltamivir Carboxylate

End point title	Elimination Rate Constant (ke) of Oseltamivir and Oseltamivir Carboxylate

End point description:

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir - overall			
Subject group type	Reporting group			
Number of subjects analysed	0[27]			
Units: 1/hour				
geometric mean (geometric coefficient of variation)	()			

Notes:

[27] - Data not available as no participant was evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Clearance of Drug (CL) of Oseltamivir and Oseltamivir Carboxylate

End point title	Total Clearance of Drug (CL) of Oseltamivir and Oseltamivir Carboxylate

End point description:

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir - overall			
Subject group type	Reporting group			
Number of subjects analysed	0[28]			
Units: liters per hour (L/hour)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[28] - Data not available as no participant was evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (V) of Oseltamivir and Oseltamivir Carboxylate

End point title	Volume of Distribution (V) of Oseltamivir and Oseltamivir Carboxylate

End point description:

End point type	Secondary

End point timeframe:

Day 1: 15 minutes pre-infusion start, 1, 2, 3, 4, 6, 8, 12 hours post start of infusion; Day 2, 3 (with or after fifth dose), 4 or 5: 15 minutes pre-infusion start, 2, 4, 8 hours after start of infusion

End point values	Oseltamivir - overall			
Subject group type	Reporting group			
Number of subjects analysed	0[29]			
Units: liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[29] - Data not collected because of changes in planned analysis, due to early study termination.

Statistical analyses

No statistical analyses for this end point

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

End point title	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, >=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 participants 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 time-point.

End point type	Secondary

End point timeframe:

Baseline, Days 1, 6 and 30

End point values	Oseltamivir - overall	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years	Oseltamivir: 1 to 2 Years
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	3	1
Units: participants				
Day 1 (n=6, 2, 3, 1)	1	0	1	0
Day 6 (n=1, 0, 1, 0)	1	9999	1	9999
Day 30 (n=1, 1, 0, 0)	0	0	9999	9999

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Oseltamivir - overall

Reporting group description:

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 body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight >23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 mg. 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: 6 to 12 Years

Reporting group description:

Participants aged 6 to 12 years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight >40 kg received 100 mg. 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: 3 to 5 Years

Reporting group description:

Participants aged 3 to 5 years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight 40 kg received 100 mg. 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: 1 to 2 Years

Reporting group description:

Participants aged 1 to 2 Years received oseltamivir twice daily IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's body weight. Participants with body weight <=23 kg received 3 mg/kg; participants with body weight 23 kg to 40 kg received 2.5 mg/kg; and participants with body weight 40 kg received 100 mg. 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 - overall	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	1 / 2 (50.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	0 / 5 (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
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Oseltamivir: 1 to 2 Years		
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			
General disorders and administration site conditions			
Pyrexia			
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			
Bronchospasm			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			

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: 5 %

Non-serious adverse events	Oseltamivir - overall	Oseltamivir: 6 to 12 Years	Oseltamivir: 3 to 5 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	0 / 2 (0.00%)	4 / 5 (80.00%)
Investigations			
Body Temperature Increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Cardiac disorders			
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Catheter Site Erosion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Device Expulsion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Drug Withdrawal Syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infusion Site Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Ingrowing Nail			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pain of Skin			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1

Non-serious adverse events	Oseltamivir: 1 to 2 Years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Investigations			
Body Temperature Increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter Site Erosion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Device Expulsion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Drug Withdrawal Syndrome			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Infusion Site Erythema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Skin and subcutaneous tissue disorders Ingrowing Nail subjects affected / exposed occurrences (all) Pain of Skin subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2010	• Provided additional information regarding oseltamivir central nervous system (CNS) distribution • Modified the requirements of IV therapy for a specified number of days and provided clarification on dosing for participants on continuous renal replacement therapy • Removed optional blood pressure monitoring in children <5 years of age and clarified the study population and excluded medication • Provided an updated schedule with amended timepoints • Reduced the maximum concentration of IV oseltamivir to 1 milligrams per milliliter (mg/mL) • Specified that adverse events (AEs) were to be graded based on the Division of Acquired Immune Deficiency Syndrome (AIDS) table for grading the severity of adult and pediatric AEs
13 May 2010	• Updated the synopsis to reflect changes in the protocol text • Corrected the exposure data • Modified dosing in participants with moderate renal impairment • Revised Exclusion Criterion 1 to accommodate participants with moderate renal impairment • Specified in the PD assessments section that, for participants who were discharged prior to Study Day 6, it was preferred that the participant returned to the clinic to have the swabs collected on the mornings of Study Day 3 or 4 since PK sampling could occur on Study Day 3 or 4 depending on the time of day (am or pm) initial dose was administered • Corrected the pH value listed for the reconstituted solution of Tamiflu • Increased the flexibility of PK sampling by specifying in the PK assessments section that sample collection (1) could occur on a day other than Study Day 1 due to operational logistics, and (2) could occur on Study Day 3 or 4 depending on the time of day (am or pm) that the initial dose was administered • Added dosing recommendation for participants with renal impairment
19 September 2011	• Added results from nonclinical studies in juvenile animals • Added clinical experience with the IV formulation text based on results from the previously ongoing adult multiple-dose Study NP25140 • Updated the exposure margins based on data from the multiple-dose IV Study NP25140 • Clarified the day of treatment completion depending on when dosing was started and whether one or two doses were received on Study Day 1 • Changed the upper limit of the range for moderate renal impairment from 50 milliliters per minute (mL/min) to 60 mL/min to reflect the most recent Food and Drug Administration (FDA) Guidance • 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 to allow flexibility in PK sampling and clarification regarding blood collection

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

13 December 2012	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: