



Clinical trial results:

An open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) in the treatment of infants 0 to less than 12 months of age with confirmed influenza infection.

Summary

EudraCT number	2009-014365-12
Trial protocol	ES FR DE GB BE NL IT
Global end of trial date	04 June 2014

Results information

Result version number	v1
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	WP22849
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988325
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)	Yes
EMA paediatric investigation plan number(s)	EMA-000365-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2012
Global end of trial reached?	Yes
Global end of trial date	04 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To define the pharmacokinetics of oseltamivir and oseltamivir carboxylate in children with confirmed influenza up to one year of age.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and ICH E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. Participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	65
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	5
Infants and toddlers (28 days-23	60

months)	
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:

The study was conducted across 11 centers in Spain, Italy, France, Germany, Belgium, and Poland from 10 January 2011 to 04 April 2012.

Pre-assignment

Screening details:

A total of 65 participants were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Oseltamivir 3 mg

Arm description:

Participants aged 91 to <365 days received oral suspension of oseltamivir 3 milligram/kilogram (mg/kg) twice a day for 5 days.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	Ro 64-0796
Other name	Tamiflu
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The investigational medicinal product (IMP) was provided as 75 mg oseltamivir capsules; however, this was compounded to final concentration of the 10 milligram per milliliter (mg/mL) of oseltamivir in water. It was referred as a bottle of compounded suspension and was used while administering the prescribed dose.

Arm title	Oseltamivir 2.5 mg
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Arm description:

Participants aged 31 to 90 days received oral suspension of oseltamivir 2.5 mg/kg twice a day for 5 days.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	Ro 64-0796
Other name	Tamiflu
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The investigational medicinal product (IMP) was provided as 75 mg oseltamivir capsules; however, this was compounded to final concentration of the 10 milligram per milliliter (mg/mL) of oseltamivir in water. It was referred as a bottle of compounded suspension and was used while administering the prescribed dose.

Arm title	Oseltamivir 2 mg
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Arm description:

Participants aged 0 to 30 days received oral suspension of oseltamivir 2 mg/kg twice a day for 5 days.

Arm type	Experimental
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Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	Ro 64-0796
Other name	Tamiflu
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The investigational medicinal product (IMP) was provided as 75 mg oseltamivir capsules; however, this was compounded to final concentration of the 10 milligram per milliliter (mg/mL) of oseltamivir in water. It was referred as a bottle of compounded suspension and was used while administering the prescribed dose.

Number of subjects in period 1	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg
Started	40	20	5
Completed	40	20	5

Baseline characteristics

Reporting groups

Reporting group title	Oseltamivir 3 mg
Reporting group description: Participants aged 91 to <365 days received oral suspension of oseltamivir 3 milligram/kilogram (mg/kg) twice a day for 5 days.	
Reporting group title	Oseltamivir 2.5 mg
Reporting group description: Participants aged 31 to 90 days received oral suspension of oseltamivir 2.5 mg/kg twice a day for 5 days.	
Reporting group title	Oseltamivir 2 mg
Reporting group description: Participants aged 0 to 30 days received oral suspension of oseltamivir 2 mg/kg twice a day for 5 days.	

Reporting group values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg
Number of subjects	40	20	5
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	5
Infants and toddlers (28 days-23 months)	40	20	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	19	8	2
Male	21	12	3

Reporting group values	Total		
Number of subjects	65		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	5		
Infants and toddlers (28 days-23 months)	60		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Gender categorical			
Units: Subjects			
Female	29		
Male	36		

End points

End points reporting groups

Reporting group title	Oseltamivir 3 mg
Reporting group description: Participants aged 91 to <365 days received oral suspension of oseltamivir 3 milligram/kilogram (mg/kg) twice a day for 5 days.	
Reporting group title	Oseltamivir 2.5 mg
Reporting group description: Participants aged 31 to 90 days received oral suspension of oseltamivir 2.5 mg/kg twice a day for 5 days.	
Reporting group title	Oseltamivir 2 mg
Reporting group description: Participants aged 0 to 30 days received oral suspension of oseltamivir 2 mg/kg twice a day for 5 days.	
Subject analysis set title	Pharmacokinetic population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Pharmacokinetic (PK) population included all treated participants with at least one blood sample evaluable for drug concentration level and who adhered to the protocol.	
Subject analysis set title	Intent to treat infection (ITTI) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITTI population consisted of all infants who had a positive PCR or viral culture at baseline or any time after first dose administration and was same as pharmacodynamics (PD) population.	
Subject analysis set title	Safety population
Subject analysis set type	Full analysis
Subject analysis set description: Safety population included all treated participants with at least one post-baseline safety assessment (vital signs like temperature, respiratory rate, blood pressure, pulse rate).	
Subject analysis set title	Reporting group: Genotype A (H1N1)pdm09
Subject analysis set type	Sub-group analysis
Subject analysis set description: Genotype A (H1N1)pdm09 was present in 21 participants of age group 91 to <365 days, 9 participants of age group 31 to 90 days, and 2 participants of age group less than or equal to ($\leq$) 30 days.	
Subject analysis set title	Reporting group: Genotype A H3
Subject analysis set type	Sub-group analysis
Subject analysis set description: Genotype Type A H3 was present in 4 participants and 6 participants of age groups 91 to <365 days and 31 to 90 days, respectively.	
Subject analysis set title	Reporting group: Genotype B
Subject analysis set type	Sub-group analysis
Subject analysis set description: Genotype B was present in 12, 2, and 2 participants of age groups <365 days, 31 to 90 days, and $\leq$ 30 days, respectively.	

Primary: Mean steady state area under plasma concentration time curve time zero to 12 hours of oseltamivir and oseltamivir carboxylate

End point title	Mean steady state area under plasma concentration time curve time zero to 12 hours of oseltamivir and oseltamivir carboxylate ^[1]
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. At steady state, area under curve from time zero to 12 hours (AUC₀₋₁₂) was estimated for oseltamivir and oseltamivir carboxylate by linear trapezoidal rule. This analysis was performed on PK population. As the EudraCT portal does not accept 'not estimated', we have presented an arbitrary value (99999999) for the same.

End point type	Primary
End point timeframe:	
15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken 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 performed for this end point.

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[2]	17 ^[3]	4 ^[4]	
Units: hour*nanogram/milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n=37, 17, 4	277 (± 36.2)	194 (± 47.8)	142 (± 48.8)	
Oseltamivir carboxylate, n=18,11, 2	4990 (± 27.4)	4920 (± 35.3)	99999999 (± 99999999)	

Notes:

[2] - Data is presented for the participants available at the time of assessment.

[3] - Data is presented for the participants available at the time of assessment.

[4] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Mean steady-state maximum observed plasma concentration of oseltamivir and oseltamivir carboxylate

End point title	Mean steady-state maximum observed plasma concentration of oseltamivir and oseltamivir carboxylate ^[5]
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. Maximum observed plasma concentration was estimated for both oseltamivir and oseltamivir carboxylate by non-compartmental analysis. This analysis was performed on PK population.

End point type	Primary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

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 performed for this end point.

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[6]	17 ^[7]	4 ^[8]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n=37, 17, 4	80.8 (± 47)	62.5 (± 69.1)	25.2 (± 211.6)	

Oseltamivir carboxylate, , n=18, 11, 2	464 (± 37.7)	530 (± 33.1)	501 (± 22.2)	
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Notes:

[6] - Data is presented for the participants available at the time of assessment.

[7] - Data is presented for the participants available at the time of assessment.

[8] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Mean steady-state minimum observed plasma concentration of oseltamivir and oseltamivir carboxylate

End point title	Mean steady-state minimum observed plasma concentration of oseltamivir and oseltamivir carboxylate ^[9]
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End point description:

Oseltamivir carboxylate is active metabolite of oseltamivir. Minimum observed plasma concentration was estimated for both oseltamivir and oseltamivir carboxylate by non-compartmental analysis. This analysis was performed on PK population.

End point type	Primary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

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 performed for this end point.

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[10]	17 ^[11]	4 ^[12]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n=37, 17, 4	2.88 (± 65.4)	2.09 (± 52.6)	2.56 (± 90)	
Oseltamivir carboxylate, n=18, 11, 2	238 (± 43.8)	248 (± 51.5)	169 (± 96.4)	

Notes:

[10] - Data is presented for the participants available at the time of assessment.

[11] - Data is presented for the participants available at the time of assessment.

[12] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to the maximum observed plasma concentration of oseltamivir and oseltamivir carboxylate

End point title	Median time to the maximum observed plasma concentration of oseltamivir and oseltamivir carboxylate
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. Time for required to attend maximum plasma concentration was estimated using non-compartmental methods. This analysis was performed on PK population.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[13]	17 ^[14]	4 ^[15]	
Units: hour				
median (full range (min-max))				
Oseltamivir, n=37, 17, 4	1.08 (0.88 to 3.08)	1.08 (0 to 2.92)	1.08 (1 to 3)	
Oseltamivir carboxylate, n=18, 11, 2	5.04 (2.08 to 7)	2.88 (0 to 6.67)	5.83 (2.58 to 6.67)	

Notes:

[13] - Data is presented for the participants available at the time of assessment.

[14] - Data is presented for the participants available at the time of assessment.

[15] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean apparent elimination half life of oseltamivir and oseltamivir carboxylate

End point title	Mean apparent elimination half life of oseltamivir and oseltamivir carboxylate
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End point description:

Elimination half life is defined as the time required for elimination of a drug to half its plasma concentration and was computed using non-compartmental method. This analysis was performed on PK population. As the EudraCT portal does not accept 'not estimated', we have presented an arbitrary value (99999999) for the same.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/-15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[16]	17 ^[17]	4 ^[18]	
Units: hours				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n= 37, 17, 4	2.02 (± 38.5)	2.01 (± 49.3)	1.66 (± 41.5)	
Oseltamivir carboxylate, n=18, 11, 2	9.45 (± 53.3)	11.3 (± 92.7)	99999999 (± 99999999)	

Notes:

[16] - Data is presented for the participants available at the time of assessment.

[17] - Data is presented for the participants available at the time of assessment.

[18] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean apparent first-order elimination rate constant of oseltamivir and oseltamivir carboxylate

End point title	Mean apparent first-order elimination rate constant of oseltamivir and oseltamivir carboxylate
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End point description:

Oseltamivir carboxylate is active metabolite of oseltamivir. The apparent first-order elimination rate constant was determined by linear regression analysis of terminal data points. A minimum of 3 data points were used for lambda Z estimation. By reporting tool convention, if $n < 3$, no summary statistics were calculated. This analysis was performed on PK population. As the EudraCT portal does not accept 'not estimated', we have presented an arbitrary value (99999999) for the same.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[19]	17 ^[20]	4 ^[21]	
Units: 1/hour				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n= 37, 17, 4	0.349 (± 39.9)	0.338 (± 52.9)	0.418 (± 41.5)	
Oseltamivir carboxylate, n=18, 11, 2	0.0735 (± 55.2)	0.0475 (± 110.6)	99999999 (± 99999999)	

Notes:

[19] - Data is presented for the participants available at the time of assessment.

[20] - Data is presented for the participants available at the time of assessment.

[21] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean total plasma clearance as a function of bioavailability and apparent plasma clearance of the metabolite as a function of bioavailability of oseltamivir and oseltamivir carboxylate

End point title	Mean total plasma clearance as a function of bioavailability and apparent plasma clearance of the metabolite as a function of bioavailability of oseltamivir and oseltamivir carboxylate
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. Total plasma clearance as a function of bioavailability was calculated as dose/AUCinf, where AUCinf represents the area under the plasma concentration-time curve of the analyte over the time interval from zero extrapolated to infinity. This analysis was performed on PK population. As the EudraCT portal does not accept 'not estimated', we have presented an arbitrary value (99999999) for the same.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[22]	17 ^[23]	4 ^[24]	
Units: mL/hour				
arithmetic mean (standard deviation)				
Oseltamivir, n= 37, 17, 4	80500 (± 42.8)	63000 (± 63.7)	50600 (± 39.9)	
Oseltamivir carboxylate, n=18,11, 2	3940 (± 38.8)	2180 (± 54.8)	99999999 (± 99999999)	

Notes:

[22] - Data is presented for the participants available at the time of assessment.

[23] - Data is presented for the participants available at the time of assessment.

[24] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean volume of distribution as a function of bioavailability of oseltamivir and oseltamivir carboxylate

End point title	Mean volume of distribution as a function of bioavailability of oseltamivir and oseltamivir carboxylate
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. The volume of distribution as a function of bioavailability is defined as the theoretical volume in which the total amount of analyte would need to be uniformly distributed to produce the desired blood concentration of a drug. This analysis was performed on PK population. As the EudraCT portal does not accept 'not estimated', we have presented an arbitrary value (99999999) for the same.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[25]	17 ^[26]	4 ^[27]	
Units: mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir, n= 37, 17, 4	234000 (± 66.2)	183000 (± 87.9)	121000 (± 69.8)	
Oseltamivir carboxylate, n=18,11, 2	53700 (± 78.1)	35400 (± 96.5)	99999999 (± 99999999)	

Notes:

[25] - Data is presented for the participants available at the time of assessment.

[26] - Data is presented for the participants available at the time of assessment.

[27] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean time of the last measurable plasma concentration for oseltamivir and oseltamivir carboxylate

End point title	Mean time of the last measurable plasma concentration for oseltamivir and oseltamivir carboxylate
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End point description:

Oseltamivir carboxylate is an active metabolite of oseltamivir. This analysis was performed on PK population.

End point type	Secondary
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End point timeframe:

15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: hours				
geometric mean (geometric coefficient of variation)				
Oseltamivir	9.23 (± 30.1)	8.53 (± 32.9)	6.93 (± 24.2)	
Oseltamivir carboxylate	10.11 (± 21.2)	10.64 (± 5.4)	10.45 (± 5.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in neurological assessment scores over time

End point title	Number of participants with change from Baseline in
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End point description:

Neurological assessment was performed to assess the mental state of the participants through two scales: Infant face scale and Glasgow coma scale. Each scale consists of 3 sub-scales: eye opening (ranging 1 to 4), verbal response (ranging 1 to 5), and motor responses (ranging 1 to 6). The final score is the sum of these ranges and is scored between 3 and 15. Three being the worst, and 15 the best. Change from Baseline (Day 1) is change of final score post-baseline minus the final score at Baseline. The final score of the participants at Baseline was reported as 15. This analysis was performed on safety population.

End point type	Secondary
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End point timeframe:

From Baseline (Day 1) to Day 30

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: Number of participants				
With change in infant face scale measurement	0	2	0	
With change in Glasgow coma scale assessment score	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to cessation of viral shedding in participants with positive culture at Baseline

End point title	Median time to cessation of viral shedding in participants with positive culture at Baseline
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End point description:

Median time to cessation of viral shedding was calculated for all participants with positive by culture / by PCR at Baseline using all data points between the start of the treatment and the 1st time point of negative culture without subsequent positive culture results. These time-to-event analyses were only performed for the viral titre. The day when participants stopped shedding the virus and all the participants from respective groups showed negative viral culture on the corresponding days. This time point was equivalent to change from Baseline of 50% tissue culture infective dose [(log₁₀TCID₅₀)]. This analysis was performed using ITTI population.

End point type	Secondary
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End point timeframe:

From Baseline (Day 1) to Day 30

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: hour				
median (confidence interval 95%)				
Median time to Cessation of Viral Shedding	228.5 (118 to 231)	113 (63 to 230)	113 (110 to 116)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with virus shedding by virus type over time

End point title	Number of participants with virus shedding by virus type over time
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End point description:

The viral titer was measured by culture and reported in log10 (50% tissue culture infective dose [TCID50]). The viral load was analyzed by PCR and reported as log10 particles/mL. It analyzed the number of days required by observed number of participants to completely shed virus from their body reflecting change from Baseline in log10 (TCID50). This analysis was performed using ITTI population.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Day3/4, Day 6, Day 11, Day 18, Day 30

End point values	Reporting group: Genotype A (H1N1)pdm09	Reporting group: Genotype A H3	Reporting group: Genotype B	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[28]	10 ^[29]	16 ^[30]	
Units: Number of participants				
Baseline	32	10	14	
Day 3 or 4	20	5	14	
Day 6	12	4	7	
Day 11	32	9	16	
Day 18	0	1	0	
Day 30	0	0	0	

Notes:

[28] - Data is presented for the participants available at the time of assessment.

[29] - Data is presented for the participants available at the time of assessment.

[30] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to resolution of fever in participants with fever at the Baseline

End point title	Median time to resolution of fever in participants with fever at the Baseline
End point description: This was performed for all participants who had fever at Baseline. Fever is defined as body temperature > 37.0 degree Celsius. Rectal temperature is converted by subtracting 1 degree Celsius. Time to resolution of fever was defined as the time from the initiation of treatment to first time the afebrile state was reached and maintained for at least 21.5 hours, where afebrile state was defined as axillary temperature <= 37 degree Celsius. This analysis was performed on ITTI population.	
End point type	Secondary
End point timeframe: From Baseline (Day 1) to Day 30	

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[31]	17 ^[32]	4 ^[33]	
Units: hours				
median (full range (min-max))				
Time to Resolution of Fever	12 (9 to 17)	20.5 (12 to 36)	24 (14 to 43)	

Notes:

[31] - Data is presented for the participants available at the time of assessment.

[32] - Data is presented for the participants available at the time of assessment.

[33] - Data is presented for the participants available at the time of assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with decline of body temperature to the afebrile state over time

End point title	Percentage of participants with decline of body temperature to the afebrile state over time
End point description: This was performed for all participants who had fever at baseline Fever is defined as body temperature >37.0°C. Rectal temperature is converted by subtracting 1 °C. The rate of decline of body temperature was calculated as the slope of body temperature between the baseline temperature and the 1st temperature below 37°C. Participants with decline in body temperature were considered to have no fever; however, participants who did not show any decline in body temperature were considered to have persisting fever. This analysis was performed on ITTI population.	
End point type	Secondary
End point timeframe: Baseline (Day 1), Day3/4, Day 6, Day 11, Day 18, Day 30	

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33 ^[34]	11 ^[35]	4 ^[36]	
Units: Percentage of participants				
Baseline, n=33, 11, 4, decline	36	55	25	
Baseline, n=33, 11, 4, no decline	64	45	75	

Day 4, n=33, 11, 4, decline	94	91	100	
Day 4, n=33, 11, 4, no decline	6	9	0	
Day 11, n=33, 11, 4, decline	97	100	100	
Day 11, n=33, 11, 4, no decline	3	0	0	
Day 18, n=16, 5, 1, decline	94	100	100	
Day 18, n=16, 5, 1, no decline	6	0	0	
Day 30, n=31, 9, 4, decline	97	89	100	
Day 30, n=31, 9, 4, no decline	3	11	0	

Notes:

[34] - Participants available at a particular time of assessment were included in the analysis.

[35] - Participants available at a particular time of assessment were included in the analysis.

[36] - Participants available at a particular time of assessment were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events, serious adverse events and secondary illness

End point title	Number of participants with adverse events, serious adverse events and secondary illness
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. A serious adverse event (SAE) is any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or results in a congenital anomaly/birth defect. Secondary illnesses were influenza disease-related events, namely bronchitis, pneumonia, otitis media, and sinusitis that resolved without sequelae. This analysis was performed using safety population.

End point type	Secondary
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End point timeframe:

Up to Day 23

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: Number of participants				
Participants with AEs	17	13	2	
Participants with SAEs	6	1	0	
Participants with secondary illness	2	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants showing within-participant variability in vital signs

End point title	Number of participants showing within-participant variability in vital signs
End point description: Systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and heart rate were examined for any consistent within-participant post-baseline changes and none were identified. Due to the small numbers of participants in a cohort and the extent of influenza induced variability, clinically significant changes in vital sign patterns cannot be detected. This analysis was performed on ITTI population.	
End point type	Secondary
End point timeframe: Up to Day 30	

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: Number of participants				
Participants with Variability in Vital Signs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean last measurable plasma concentration of oseltamivir and oseltamivir carboxylate

End point title	Mean last measurable plasma concentration of oseltamivir and oseltamivir carboxylate
End point description: The last measurable plasma concentration of oseltamivir and oseltamivir carboxylate was the last quantifiable concentration of oseltamivir or oseltamivir carboxylate, respectively. This analysis was performed on PK population.	
End point type	Secondary
End point timeframe: 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 3 if two doses were taken on Day 1 or 15 minutes pre-dose; 1 hour +/- 15 minutes, 2-3, 5-7, 10-12 hours post-dose on Day 4 if one dose was taken on Day 1	

End point values	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	20	5	
Units: h*mg/mL				
geometric mean (geometric coefficient of variation)				
Oseltamivir	262 (± 39.2)	176 (± 58.3)	84.3 (± 154.4)	
Oseltamivir carboxylate	3800 (± 50.1)	4410 (± 34)	3940 (± 28.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 23 days

Adverse event reporting additional description:

Serious adverse events (SAEs) and other adverse events (AEs) were reported for the safety population. Safety population included all treated participants with at least one post-baseline safety assessment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Oseltamivir 3 mg
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Reporting group description:

Participants aged 91 to <365 days received oral suspension of oseltamivir 3 mg/kg twice a day for 5 days.

Reporting group title	Oseltamivir 2.5 mg
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Reporting group description:

Participants aged 31 to 90 days received oral suspension of oseltamivir 2.5 mg/Kg twice a day for 5 days.

Reporting group title	Oseltamivir 2 mg
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Reporting group description:

Participants of age 0 to 30 days received oral suspension of oseltamivir 2 mg/Kg twice a day for 5 days.

Serious adverse events	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)	1 / 20 (5.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis orbital			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 5 (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 syncytial virus bronchiolitis			

subjects affected / exposed	1 / 40 (2.50%)	1 / 20 (5.00%)	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

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

Non-serious adverse events	Oseltamivir 3 mg	Oseltamivir 2.5 mg	Oseltamivir 2 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 40 (32.50%)	12 / 20 (60.00%)	2 / 5 (40.00%)
General disorders and administration site conditions			
Crepitations			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 40 (0.00%)	2 / 20 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)	0 / 20 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 40 (5.00%)	0 / 20 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	1 / 20 (5.00%)	0 / 5 (0.00%)
occurrences (all)	4	1	0
Regurgitation			
subjects affected / exposed	1 / 40 (2.50%)	1 / 20 (5.00%)	1 / 5 (20.00%)
occurrences (all)	1	6	2
Vomiting			
subjects affected / exposed	6 / 40 (15.00%)	5 / 20 (25.00%)	0 / 5 (0.00%)
occurrences (all)	10	11	0
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0
Tachypnoea subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0
Skin and subcutaneous tissue disorders			
Dermatitis diaper subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	0 / 20 (0.00%) 0	1 / 5 (20.00%) 1
Rash maculo–papular subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0
Infections and infestations			
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	1 / 5 (20.00%) 1
Otitis media subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0
Rotavirus infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 20 (5.00%) 1	0 / 5 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2009	a) Added a third cohort, changing the number of cohorts from two to three, such that the original second cohort (0 to < 3 months) was now Cohort II (1 to < 3 months) and Cohort III (0 to 30 days), allowing infants younger than 1 month to participate. b) Allowed dosing to continue for a further 5 days (an additional 10 doses) if the specimen collected on Day 6 was positive for influenza or the participant had viral infection symptoms.
01 October 2009	Changed the dosing of oseltamivir such that younger infants received a lower dose of oseltamivir i.e. (2.5 mg/Kg for participants of 1 to < 3 months and 2 mg/Kg for participants of 0 to 30 days), instead of all infants receiving 3 mg/Kg.
23 October 2009	Changed, at FDA request, study drug preparation such that oseltamivir dry powder was reconstituted to a suspension with a concentration of 11 mg/mL instead of 12 mg/mL.
30 November 2009	a) For consistency, changed the grading of the intensity of AEs from a 3-point scale to a 4-point scale (mild, moderate, severe, and life threatening). b) Cohorts were defined in terms of infant's age in days instead of age in months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: