Clinical trial results:
A phase IIIb, open-label, comparative, randomized study on resistance of Influenza A/H1N1 2009 virus to treatment with Oseltamivir at standard dose versus double dose

Summary

EudraCT number	2016-001044-18
Trial protocol	Outside EU/EEA
Global end of trial date	06 October 2010

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	ML22789

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00949533
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 October 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label randomized 2 arm study determined the emergence of viral resistance in participants with seasonal influenza A infection treated with oseltamivir. Eligible participants less than or equal to (</=) 5 years of age were randomized to receive oseltamivir at either standard dose (30-75 milligrams [mg] orally twice daily [bid]) or double dose (60-150 mg orally bid) for 5 days.

Protection of trial subjects:

This protocol and all materials sent to other participating sites or participants were submitted by the investigators to the respective Independent Ethics Committees (IEC) at their research sites. IEC approvals, obtained before the study started, were recorded in opinions, addressed to the Investigators, specifying the date when such documents were analyzed and approved.
All modifications effected on the protocol, after the first approval had been granted by the IEC, were submitted by the investigators to their respective IECs, according to local regulatory requirements.
The Sponsor was aware that the study protocol (and all subsequent changes), as well as the informed consent procedure, had been reviewed and approved by each site's IEC. These Committees worked in accordance to Federal Regulations in force. The approval document was sent by the investigator to the Sponsor at the beginning of the study and no change was made to the protocol without knowledge of both the Sponsor and the IEC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2009
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	Brazil: 37
Worldwide total number of subjects	37
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	0

months)	
Children (2-11 years)	8
Adolescents (12-17 years)	5
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 199 participants, 162 were considered as screening failures, mainly due to the negative result detected by the quick test for Influenza A Antigen. Therefore, 37 participants included in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Dose

Arm description:

Oseltamivir capsule was administered orally at a dose of 75 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 30 mg BID to a maximum dose of 75 mg BID; for 5 days.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Powder for oral suspension, Capsule
Routes of administration	Oral use

Dosage and administration details:

Oseltamivir capsule was administered orally at a dose of 75mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 30 mg BID to a maximum dose of 75 mg BID; for 5 days.

Arm title	Double Dose

Arm description:

Oseltamivir capsule was administered orally at a dose of 150 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 60 mg BID to a maximum dose of 150 mg BID; for 5 days.

Arm type	Active comparator
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oseltamivir capsule was administered orally at a dose of 150 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 60 mg BID to a maximum dose of 150 mg BID; for 5 days.

Number of subjects in period 1	Standard Dose	Double Dose
Started	19	18
Completed	19	17
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 75 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 30 mg BID to a maximum dose of 75 mg BID; for 5 days.	
Reporting group title	Double Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 150 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 60 mg BID to a maximum dose of 150 mg BID; for 5 days.	

Reporting group values	Standard Dose	Double Dose	Total
Number of subjects	19	18	37
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	21.6	22	
standard deviation	± 11	± 12.7	-
Gender, Male/Female Units: participants			
Female	11	9	20
Male	8	9	17

End points

End points reporting groups

Reporting group title	Standard Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 75 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 30 mg BID to a maximum dose of 75 mg BID; for 5 days.	
Reporting group title	Double Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 150 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/mL) based on their body weight with a starting dose of 60 mg BID to a maximum dose of 150 mg BID; for 5 days.	

Primary: Percentage of Participants Excreting Resistant Virus

End point title	Percentage of Participants Excreting Resistant Virus
End point description:	
Resistant virus included new influenza A virus subtype hemagglutinin type 1 and neuraminidase type 1 (New AH1N1). Intention-to-treat (ITT) population included all enrolled participants who received at least one dose of the study drug.	
End point type	Primary
End point timeframe:	
Day 5	

End point values	Standard Dose	Double Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: percentage of participants				
number (not applicable)	26.3	35.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Double Dose v Standard Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.825
Method	Pearson Chi-Square

Secondary: Percentage of Participants With A Reduction in Viral Load

End point title	Percentage of Participants With A Reduction in Viral Load

End point description:

Viral load is defined as the amount of H1N1 virus in blood As per investigator, a participant was considered as having viral load reduction at Day 5 if the Day 5 viral load was lower than the Baseline viral load. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Day 5

End point values	Standard Dose	Double Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	18		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05
Method	Chi-squared

Secondary: Number of Participants With Various Clinical Signs and Symptoms

End point title	Number of Participants With Various Clinical Signs and Symptoms

End point description:

Number of participants with various clinical signs and symptoms, as per investigator's discretion, were reported. Same participants were reported in more than 1 category. "Other" in the category included abdominal pain, breathlessness, thoracic pain and tired. ITT population. Here "number of participants analyzed" included evaluable participants for the outcome measure.

End point type	Secondary

End point timeframe:

Day 5

End point values	Standard Dose	Double Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: participants				
number (not applicable)				
Cough	10	9		

Rhinorrhea	10	5		
Sore throat	2	2		
Shortness of breath	2	1		
Diarrhea	2	0		
Headache	1	2		
Conjunctivitis	1	0		
Vomiting	1	0		
Other	4	0		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Cough: statistical difference between 2 groups was based on chi-squared test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Chi-squared

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Rhinorrhea: statistical difference between 2 groups was based on chi-squared test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.284
Method	Chi-squared

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Sore throat: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Shortness of breath: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Statistical analysis 5
Statistical analysis description: Diarrhea: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.487
Method	Fisher exact

Statistical analysis title	Statistical analysis 6
Statistical analysis description: Conjunctivitis: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Headache: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.593
Method	Fisher exact

Statistical analysis title	Statistical analysis 8

Statistical analysis description:	
Vomiting: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Statistical analysis 9
Statistical analysis description:	
Other: statistical difference between 2 groups was based on fisher-exact test.	
Comparison groups	Standard Dose v Double Dose
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106
Method	Fisher exact

Secondary: Number of Participants With Various Clinical Signs and Symptoms in Whom Resistant Virus Were Detected

End point title	Number of Participants With Various Clinical Signs and Symptoms in Whom Resistant Virus Were Detected
End point description:	
Number of participants with various clinical signs and symptoms, as per investigator's discretion, in whom new AH1N1 virus was detected, were reported. Same participants were reported in more than 1 category. ITT population. Here "number of participants analyzed" included evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
Day 5	

End point values	Standard Dose	Double Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: participants				
number (not applicable)				
Cough	3	4		
Rhinorrhea	3	3		
Shortness of breath	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	0.0

Reporting groups	
Reporting group title	Double Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 150 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/ml) based on their body weight with a starting dose of 60 mg BID to a maximum dose of 150 mg BID; for 5 days.	
Reporting group title	Standard Dose
Reporting group description:	
Oseltamivir capsule was administered orally at a dose of 75 mg BID in adult participants and children received oseltamivir powder for oral suspension dose (at 12 mg/ml) based on their body weight with a starting dose of 30 mg BID to a maximum dose of 75 mg BID; for 5 days.	

Serious adverse events	Double Dose	Standard Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Double Dose	Standard Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	8 / 19 (42.11%)	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	

Feeling hot			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Tracheobronchitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Abdominal cramps			
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 18 (11.11%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1	 0 / 19 (0.00%) 0	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	 0 / 18 (0.00%) 0	 1 / 19 (5.26%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported