Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of MHAA4549A, a Monoclonal Antibody, Administered as Monotherapy for the Treatment of Acute Uncomplicated Seasonal Influenza A Infection in Otherwise Healthy Adults

Summary

EudraCT number	2016-000425-40
Trial protocol	ES
Global end of trial date	13 November 2017

Results information

Result version number	v1 (current)
This version publication date	16 November 2018
First version publication date	16 November 2018

Trial information

Trial identification

Sponsor protocol code	GV29893

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02623322
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and tolerability of a single intravenous (IV) dose of MHAA4549A as compared to placebo when administered in otherwise healthy subjects with acute uncomplicated seasonal influenza A.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	South Africa: 52
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	124
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

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

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	123
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 34 investigational sites in 6 countries including the United States (15 centers), South Africa (12 centers), Canada, Spain, New Zealand (2 centers in each country), and Great Britain (1 center).

Pre-assignment

Screening details:

Randomisation stratified by onset of influenza-like illness (≤36 hours and >36 hours) and type of influenza test used for enrollment (rapid polymerase chain reaction (PCR) or rapid antigen test). Permuted block randomisation method used to obtain an approximate 1:1:1 ratio of subjects in the 3600 mg MHAA4549A, 8400 mg MHAA4549A, and placebo strata.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received single-dose placebo by intravenous (IV) administration.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received single-dose placebo by IV administration.

Arm title	MHAA4549A 3600 mg

Arm description:

Subjects received single-dose MHAA4549A, 3600 milligrams (mg), by IV administration.

Arm type	Experimental
Investigational medicinal product name	MHAA4549A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received single-dose MHAA4549A, 3600 mg, by IV administration.

Arm title	MHAA4549A 8400 mg

Arm description:

Subjects received single-dose MHAA4549A, 8400 mg, by IV administration.

Arm type	Experimental

Investigational medicinal product name	MHAA4549A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received single-dose MHAA4549A, 8400 mg, by IV administration.

Number of subjects in period 1	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg
Started	43	41	40
Completed	41	40	40
Not completed	2	1	0
Lost to follow-up	2	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received single-dose placebo by intravenous (IV) administration.	
Reporting group title	MHAA4549A 3600 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 3600 milligrams (mg), by IV administration.	
Reporting group title	MHAA4549A 8400 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 8400 mg, by IV administration.	

Reporting group values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg
Number of subjects	43	41	40
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 39.3 ± 10.8	 36.5 ± 12.5	 35.0 ± 13.6
Sex: Female, Male Units: Subjects			
Female	27	22	22
Male	16	19	18

Reporting group values	Total		
Number of subjects	124		
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	71		
Male	53		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received single-dose placebo by intravenous (IV) administration.	
Reporting group title	MHAA4549A 3600 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 3600 milligrams (mg), by IV administration.	
Reporting group title	MHAA4549A 8400 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 8400 mg, by IV administration.	

Primary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)[1]
End point description:	
An AE is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. The safety population included all subjects randomised to treatment.	
End point type	Primary
End point timeframe:	
Baseline to Day 100	

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: Data was not collected for this end point.

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	41	40	
Units: percentage of subjects				
number (not applicable)	30.2	39.0	30.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Hospitalisation for Influenza-Related Complications

End point title	Percentage of Subjects Requiring Hospitalisation for Influenza-Related Complications
End point description:	
Data was not collected for this outcome measure, since no subject was hospitalised for influenza-related complications.	
End point type	Secondary
End point timeframe:	
Baseline to Day 100	

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - No subject was hospitalised due to infection events.

[3] - No subject was hospitalised due to infection events.

[4] - No subject was hospitalised due to infection events.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalisation for Influenza-Related Complications

End point title	Duration of Hospitalisation for Influenza-Related Complications

End point description:

Data was not collected for this outcome measure, since no subject was hospitalised for influenza-related complications.

End point type	Secondary

End point timeframe:

Baseline to Day 100

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: days				
number (not applicable)				

Notes:

[5] - No subject was hospitalised due to infection events.

[6] - No subject was hospitalised due to infection events.

[7] - No subject was hospitalised due to infection events.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Antibiotics for Secondary Bacterial Respiratory Infections

End point title	Percentage of Subjects Requiring Antibiotics for Secondary Bacterial Respiratory Infections

End point description:

Subjects with antibiotic usage for secondary bacterial respiratory infections were identified by counting subjects with AEs containing the terms, "pneumonia, lung, myocarditis, ARDS (acute respiratory distress syndrome), otitis media, or respiratory." The intent-to-treat infected (ITTI) population included all randomised subjects who had an influenza A infection confirmed by central polymerase chain reaction

(PCR).

End point type	Secondary
End point timeframe: Baseline to Day 100	

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	35	31	
Units: percentage of subjects				
number (confidence interval 80%)	3.0 (0.32 to 11.28)	0 (0.00 to 6.37)	0 (0.00 to 7.16)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v MHAA4549A 3600 mg
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3031
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates (Wald)
Point estimate	-3.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-12.25
upper limit	6.19

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v MHAA4549A 8400 mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3324
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates (Wald)
Point estimate	-3.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-12.82
upper limit	6.76

Secondary: Percentage of Subjects with Complications of Influenza

End point title	Percentage of Subjects with Complications of Influenza

End point description:

Subjects with complications of influenza were identified by counting subjects with AEs containing the terms, "pneumonia, lung, myocarditis, ARDS (acute respiratory distress syndrome), otitis media, or respiratory." ITTI population included all randomised subjects who had an influenza A infection confirmed by central PCR.

End point type	Secondary

End point timeframe:

Baseline to Day 100

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	35	31	
Units: percentage of subjects				
number (confidence interval 80%)	3.0 (0.32 to 11.28)	0 (0.00 to 6.37)	0 (0.00 to 7.16)	

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v MHAA4549A 3600 mg
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3031
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates (Wald)
Point estimate	-3.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-12.25
upper limit	6.19

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v MHAA4549A 8400 mg

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3324
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates (Wald)
Point estimate	-3.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-12.82
upper limit	6.76

Secondary: Percentage of Subjects with Influenza A Relapse/Reinfection

End point title	Percentage of Subjects with Influenza A Relapse/Reinfection

End point description:

ITTI population included all randomised subjects who had an influenza A infection confirmed by central PCR.

End point type	Secondary

End point timeframe:

Baseline to Day 100

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	35	31	
Units: percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC) of MHAA4549A

End point title	Area Under the Concentration-Time Curve (AUC) of MHAA4549A[8]

End point description:

The AUC is a measure of the plasma concentration of the drug over time. It is used to characterise drug absorption. AUC was measured in micrograms times hours per milliliter (mcg*h/mL). Data was not collected for this outcome measure.

End point type	Secondary

End point timeframe:

Up to Day 100 (collections scheduled pre-dose [0 hours]; 60 minutes post-dose; and on Days 3, 5, 7, 30, and 100 post-dose; infusion duration = 2 hours)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was not collected for this end point.

End point values	MHAA4549A 3600 mg	MHAA4549A 8400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: mcg*h/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Data was not collected for this outcome measure.

[10] - Data was not collected for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of MHAA4549A

End point title	Maximum Serum Concentration (Cmax) of MHAA4549A[11]

End point description:

The pharmacokinetic (PK)−evaluable population included all subjects who received MHA4549A.

End point type	Secondary

End point timeframe:

Up to Day 100 (collections scheduled pre-dose [0 hours]; 60 minutes post-dose; and on Days 3, 5, 7, 30, and 100 post-dose; infusion duration = 2 hours)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was not collected for this end point.

End point values	MHAA4549A 3600 mg	MHAA4549A 8400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	37		
Units: mcg/mL				
arithmetic mean (standard deviation)	1050 (± 299)	2190 (± 581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of Symptoms of Influenza A Infection

End point title	Time to Alleviation of Symptoms of Influenza A Infection

End point description:

Time to alleviation of all 7 symptoms (i.e., nasal congestion, sore throat, cough, aches, fatigue, headaches, chills/sweats) was assessed using a rating scale of 0 (none), 1 (mild), 2 (moderate), or 3 (severe) for each symptom. The outcome was defined in two ways: time to a total symptom score of <=1 and time to a total symptom score of <=7. Resolution had to be maintained for 24 hours without use of symptom relief medications. For subjects who were enrolled with mild symptoms, the symptom score had to be reduced by one point during the study duration. ITTI population included all randomised

subjects who had an influenza A infection confirmed by central PCR.

End point type	Secondary
End point timeframe: Baseline to Day 14	

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	35	31	
Units: hours				
median (confidence interval 80%)				
Total Symptom Score of <=1	117.30 (108.62 to 157.15)	153.80 (125.52 to 175.23)	145.82 (132.98 to 156.68)	
Total Symptom Score of <=7	44.50 (27.23 to 58.65)	74.18 (64.32 to 87.98)	65.59 (44.12 to 87.23)	

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Total Symptom Score of <=1	
Comparison groups	Placebo v MHAA4549A 3600 mg
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7858
Method	Wilcoxon
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.62
upper limit	1.37

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Total Symptom Score of <=1	
Comparison groups	Placebo v MHAA4549A 8400 mg

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.517
Method	Wilcoxon
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.59
upper limit	1.36

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Total Symptom Score of <=7	
Comparison groups	Placebo v MHAA4549A 3600 mg
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0312
Method	Wilcoxon
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.45
upper limit	0.89

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Total Symptom Score of <=7	
Comparison groups	Placebo v MHAA4549A 8400 mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2044
Method	Wilcoxon
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.53
upper limit	1.04

Secondary: Percentage of Subjects with Influenza-Related Deaths

End point title	Percentage of Subjects with Influenza-Related Deaths

End point description:

The safety population included all subjects randomised to treatment.

End point type	Secondary

End point timeframe:

Baseline to Day 100

End point values	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	41	40	
Units: percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Day 100	
Adverse event reporting additional description:	
The safety population included all subjects randomised to treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received single-dose placebo by intravenous (IV) administration.	
Reporting group title	MHAA4549A 3600 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 3600 milligrams (mg), by IV administration.	
Reporting group title	MHAA4549A 8400 mg
Reporting group description:	
Subjects received single-dose MHAA4549A, 8400 mg, by IV administration.	

Serious adverse events	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Placebo	MHAA4549A 3600 mg	MHAA4549A 8400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 43 (9.30%)	7 / 41 (17.07%)	6 / 40 (15.00%)
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	2 / 43 (4.65%)	3 / 41 (7.32%)	3 / 40 (7.50%)
occurrences (all)	2	3	3
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 43 (2.33%)	3 / 41 (7.32%)	1 / 40 (2.50%)
occurrences (all)	1	3	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2016	Revised the study design to address operational constraints associated with subject enrollment and follow-up. Updated sections to be consistent with current company standards.
13 May 2016	Reduced the inclusion criteria enrollment window (from ≤ 120 hours) to "≤ 72 hours (3 days) between onset of influenza-like illness (as determined by the investigator) and start of study treatment."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported