Clinical trial results:
A Phase 2 Randomized, Double-Blind Placebo-Controlled Trial of MHAA4549A, a Monoclonal Antibody in Combination With Oseltamivir Versus Oseltamivir for Treatment of Severe Influenza A Infection

Summary

EudraCT number	2014-000461-43
Trial protocol	IT GB HU DE CZ ES BE NL BG PL FR
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	30 May 2018
First version publication date	30 May 2018

Trial information

Trial identification

Sponsor protocol code	GV29216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02293863
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	23 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main safety objective of the trial was to evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in subjects with severe influenza A, focusing on serious and non-serious adverse events (AEs) as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters and anti-therapeutic antibodies. The main efficacy objective was to determine the time to normalization of respiratory function of subjects dosed with MHAA4549A in combination with oseltamivir compared to subjects dosed with placebo and oseltamivir.

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	14 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 3

Worldwide total number of subjects	158
EEA total number of subjects	83

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)	91
From 65 to 84 years	56
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 62 investigational sites in 17 countries.

Pre-assignment

Screening details:

Subjects with a diagnosis of influenza using a Sponsor-approved influenza test and one of the following markers of severity within 24 hours of admission were included in the study: 1. requirement for oxygen (O2) supplementation to maintain oxygen saturation level (SpO2) greater than (>) 92 %; 2. requirement for Positive Pressure Ventilation (PPV).

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 + Oseltamivir

Arm description:

Subjects received a single IV dose of placebo matched to MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single intravenous (IV) dose of placebo matched to MHAA4549A on Day 1.

Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received oseltamivir capsule either 75 mg or 150 mg twice daily (BID) orally for minimum of 5 days. Dosage and administration followed local prescribing information for oseltamivir.

Arm title	MHAA4549A 3600 mg + Oseltamivir

Arm description:

Subjects received a single low intravenous (IV) dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.

Arm type	Experimental
Investigational medicinal product name	MHAA4549A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Subjects received a single low (3600 milligrams [mg]) dose of MHAA4549A by IV infusion on Day 1.	
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received oseltamivir capsule either 75 mg or 150 mg twice daily (BID) orally for minimum of 5 days. Dosage and administration followed local prescribing information for oseltamivir.	
Arm title	MHAA4549A 8400 mg + Oseltamivir
Arm description:	
Subjects received a single high IV dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	
Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received oseltamivir capsule either 75 mg or 150 mg twice daily (BID) orally for minimum of 5 days. Dosage and administration followed local prescribing information for oseltamivir.	
Investigational medicinal product name	MHAA4549A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received a single high (8400 mg) dose of MHAA4549A by IV infusion on Day 1.	

Number of subjects in period 1	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir
Started	56	55	47
Completed	47	42	38
Not completed	9	13	9
Adverse event, serious fatal	4	6	4
Consent withdrawn by subject	3	3	1
Lost to follow-up	2	2	2
Reason not specified	-	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Oseltamivir
Reporting group description:	
Subjects received a single IV dose of placebo matched to MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	
Reporting group title	MHAA4549A 3600 mg + Oseltamivir
Reporting group description:	
Subjects received a single low intravenous (IV) dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	
Reporting group title	MHAA4549A 8400 mg + Oseltamivir
Reporting group description:	
Subjects received a single high IV dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	

Reporting group values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir
Number of subjects	56	55	47
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	65.7	56.5	59.8
standard deviation	± 17.5	± 18.2	± 17.9
Sex: Female, Male			
Units: Subjects			
Female	24	25	22
Male	32	30	25
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	13	20	8
Not Hispanic or Latino	37	28	34
Not Stated	6	7	5
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska native	1	0	1
Asian	4	0	2
Black or African American	1	1	0
White	45	44	39
Multiple	0	1	0
Unknown	5	9	5

Reporting group values	Total		
Number of subjects	158		
Age categorical			
Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: Subjects			
Female	71		
Male	87		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	41		
Not Hispanic or Latino	99		
Not Stated	18		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska native	2		
Asian	6		
Black or African American	2		
White	128		
Multiple	1		
Unknown	19		

End points

End points reporting groups

Reporting group title	Placebo + Oseltamivir
Reporting group description:	
Subjects received a single IV dose of placebo matched to MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	
Reporting group title	MHAA4549A 3600 mg + Oseltamivir
Reporting group description:	
Subjects received a single low intravenous (IV) dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	
Reporting group title	MHAA4549A 8400 mg + Oseltamivir
Reporting group description:	
Subjects received a single high IV dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.	

Primary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events[1]
End point description:	
An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Safety population included all randomised subjects who received study drug, with subjects grouped according to the treatment actually received.	
End point type	Primary
End point timeframe:	
From randomisation up to 60 days	

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: Only descriptive summary statistics were provided for primary safety outcomes per protocol.

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	55	47	
Units: percentage of subjects				
number (not applicable)	80.4	67.3	74.5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Anti-Therapeutic Antibodies (ATA) to MHAA4549A During and Following Administration of MHAA4549A

End point title	Number of Subjects With Anti-Therapeutic Antibodies (ATA) to

	MHAA4549A During and Following Administration of MHAA4549A[2]

End point description:

Reported are the number of subjects positive for ATAs at baseline, the number of subjects with treatment-induced ATAs and the number of subjects with treatment-enhanced ATAs. Here, "n" indicates the number of subjects analysed for this outcome measure. Safety population included all randomised subjects who received study drug, with subjects grouped according to the treatment actually received.

End point type	Primary

End point timeframe:

From randomisation up to 60 days

Notes:

[2] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	55	47	
Units: subjects				
Positive for ATAs at baseline (n= 56, 55, 47)	0	1	1	
Treatment-induced ATAs (n= 47, 43, 37)	0	0	0	
Treatment-enhanced ATAs (n= 47, 43, 37)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Normalisation of Respiratory Function

End point title	Time to Normalisation of Respiratory Function

End point description:

The time to normalisation of respiratory function was defined as the time to removal of the subject from oxygen (O2) supplementation in order to maintain a blood oxygen saturation level (SpO2) equal to or greater than 95% as measured by pulse oximetry. Intent-to-treat infected (ITTi) population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Primary

End point timeframe:

From randomisation up to 60 days

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: days				
median (confidence interval 80%)	4.28 (3.06 to	2.78 (2.52 to	2.65 (1.58 to	

6.60)	4.20)	4.52)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.605
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.83
upper limit	1.4

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2028
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.85
upper limit	1.51

Secondary: Percentage of Subjects by Clinical Status Using a Categorical Ordinal Outcome

End point title	Percentage of Subjects by Clinical Status Using a Categorical Ordinal Outcome

End point description:

The clinical status of subjects was defined by five mutually exclusive categories: 1. Death; 2. In the Intensive Care Unit (ICU); 3. Non-ICU hospitalisation, requiring supplemental oxygen (O2); 4. Non-ICU hospitalisation, not requiring supplemental oxygen (O2); 5. Not hospitalised. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary
End point timeframe: Days 1-7, 14 and 30	

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (not applicable)				
Day 1: Death	0.0	0.0	0.0	
Day 1: In ICU	42.6	38.5	43.2	
Day 1: Non-ICU, requiring supplemental O2	57.4	61.5	52.3	
Day 1: Non-ICU, not requiring supplemental O2	0.0	0.0	4.5	
Day 1: Not hospitalised	0.0	0.0	0.0	
Day 2: Death	0.0	0.0	2.3	
Day 2: In ICU	42.6	38.5	38.6	
Day 2: Non-ICU, requiring supplemental O2	40.7	51.9	31.8	
Day 2: Non-ICU, not requiring supplemental O2	11.1	7.7	20.5	
Day 2: Not hospitalised	5.6	1.9	6.8	
Day 3: Death	0.0	0.0	2.3	
Day 3: In ICU	37.0	32.7	34.1	
Day 3: Non-ICU, requiring supplemental O2	31.5	42.3	27.3	
Day 3: Non-ICU, not requiring supplemental O2	20.4	19.2	25.0	
Day 3: Not hospitalised	11.1	5.8	11.4	
Day 4: Death	0.0	0.0	2.3	
Day 4: In ICU	35.2	30.8	29.5	
Day 4: Non-ICU, requiring supplemental O2	25.9	21.2	18.2	
Day 4: Non-ICU, not requiring supplemental O2	22.2	36.5	29.5	
Day 4: Not hospitalised	16.7	11.5	20.5	
Day 5: Death	0.0	0.0	2.3	
Day 5: In ICU	27.8	26.9	27.3	
Day 5: Non-ICU, requiring supplemental O2	25.9	19.2	18.2	
Day 5: Non-ICU, not requiring supplemental O2	24.1	34.6	27.3	
Day 5: Not hospitalised	22.2	19.2	25.0	
Day 6: Death	1.9	1.9	2.3	
Day 6: In ICU	22.2	23.1	22.7	
Day 6: Non-ICU, requiring supplemental O2	22.2	15.4	15.9	
Day 6: Non-ICU, not requiring supplemental O2	27.8	34.6	25.0	
Day 6: Not hospitalised	25.9	25.0	34.1	

Day 7: Death	1.9	1.9	2.3	
Day 7: In ICU	18.5	21.2	20.5	
Day 7: Non-ICU, requiring supplemental O2	24.1	13.5	15.9	
Day 7: Non-ICU, not requiring supplemental O2	14.8	28.8	25.0	
Day 7: Not hospitalised	40.7	34.6	36.4	
Day 14: Death	1.9	3.8	6.8	
Day 14: In ICU	5.6	11.5	9.1	
Day 14: Non-ICU, requiring supplemental O2	7.4	3.8	6.8	
Day 14: Non-ICU, not requiring supplemental O2	14.8	3.8	4.5	
Day 14: Not hospitalised	70.4	76.9	72.7	
Day 30: Death	5.6	7.7	9.1	
Day 30: In ICU	1.9	3.8	4.5	
Day 30: Non-ICU, requiring supplemental O2	5.6	1.9	4.5	
Day 30: Non-ICU, not requiring supplemental O2	1.9	3.8	0.0	
Day 30: Not hospitalised	85.2	82.7	81.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Failure

End point title	Percentage of Subjects With Clinical Failure

End point description:

Clinical failure after 24 hours post-infusion of study drug was defined as progression to increased O2 requirement defined by an increase in oxygen supplementation from low flow oxygen (i.e., 2−6 liters per minute [L/min]) to high flow oxygen (i.e., > 6 L/min) or from oxygen supplementation alone to any positive pressure ventilation (PPV) or extracorporeal membrane oxygenation (ECMO), progression to ICU, prolonged ventilation or O2 support defined by > 2 weeks, or death. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

24 hours after end of infusion (infusion duration = approximately 120 minutes) up to Day 60

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)	14.8 (8.82 to 22.95)	25.0 (17.22 to 34.32)	22.7 (14.63 to 32.84)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3168
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	7.91
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-2.64
upper limit	18.47

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1905
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	10.19
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.15
upper limit	20.52

Secondary: Percentage of Subjects With Clinical Resolution of Abnormal Vital Signs

End point title	Percentage of Subjects With Clinical Resolution of Abnormal Vital Signs

End point description:

Description: Clinical resolution of abnormal vital signs was defined as meeting three out of five of the following criteria: 1. SpO2 ≥ 95% without supplemental O2; 2. Respiratory rate < 24 breaths per minute without supplemental O2; 3. Core temperature < 37.2 Celsius (C) immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36 C in subjects who are initially hypothermic; 4. Heart rate (HR) < 100 beats/minute; 5. Systolic blood pressure (SBP) >90 mmHg. Reported here is the percentage of subjects who had clinical resolution of at

least three out of five abnormal vital signs by the end of study. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

From randomization up to 60 days

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)	81.3 (62.88 to 92.90)	73.3 (53.60 to 87.82)	66.7 (44.10 to 84.58)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6043
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	-7.92
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-27.5
upper limit	11.66

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3865
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	-14.58

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-36.13
upper limit	6.97

Secondary: Percentage of Subjects Who Died Due to Any Cause

End point title	Percentage of Subjects Who Died Due to Any Cause

End point description:

ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

Days 14, 30 and 60

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)				
Day 14	1.9 (0.19 to 7.01)	3.8 (1.03 to 9.91)	6.8 (2.53 to 14.56)	
Day 30	5.6 (2.06 to 11.95)	7.7 (3.40 to 14.79)	9.1 (4.02 to 17.35)	
Day 60	7.4 (3.27 to 14.26)	9.6 (4.75 to 17.11)	9.1 (4.02 to 17.35)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Day 14

Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5379
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	1.99

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.57
upper limit	9.56

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Day 14	
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2189
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	4.97
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.12
upper limit	13.05

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Day 30	
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6594
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	2.14
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.04
upper limit	10.31

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Day 30	
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	3.54
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.24
upper limit	12.31

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Day 60	
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6849
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	2.21
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.28
upper limit	10.69

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Day 60	
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7633
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	1.68
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-7.38
upper limit	10.74

Secondary: Area Under Viral Load-Time Curve (AUEC) of Influenza A Virus

End point title	Area Under Viral Load-Time Curve (AUEC) of Influenza A Virus

End point description:

Influenza A viral load was measured by quantitative polymerase chain reaction (qPCR) in nasopharyngeal samples at multiple time points during the study. AUEC is the area under the viral load-time curve curve expressed as log10 (viral particles/millilitre x hour) = log10 (vp/mL x hour). ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

Immediately prior to MHAA4549A infusion and oseltamivir dosing on Day 1, immediately prior to oseltamivir dosing on Days 2 to 10, Days 14, 20, 25, 30, on day of discharge from hospital (up to Day 60), and at study completion (Day 60)

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	46	39	
Units: log10 (vp/mL x hour)				
arithmetic mean (standard deviation)	25.72 (± 15.92)	21.99 (± 16.57)	25.03 (± 13.48)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2407
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.73
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.41
upper limit	-1.06

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8339
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.49
upper limit	2.1

Secondary: Peak Influenza A Viral Load

End point title	Peak Influenza A Viral Load

End point description:

Influenza A viral load was measured by qPCR in nasopharyngeal samples at multiple time points during the study. Reported here is the peak Influenza A viral load expressed as log10 vp/mL. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

Immediately prior to MHAA4549A infusion and oseltamivir dosing on Day 1, immediately prior to oseltamivir dosing on Days 2 to 10, Days 14, 20, 25, 30, on day of discharge from hospital (up to Day 60), and at study completion (Day 60)

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	46	39	
Units: log10 vp/mL				
arithmetic mean (standard deviation)	5.70 (± 1.32)	5.37 (± 1.39)	5.28 (± 1.71)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.279
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.33

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.6
upper limit	-0.07

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1909
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.7
upper limit	-0.15

Secondary: Duration of Viral Shedding

End point title	Duration of Viral Shedding

End point description:

Influenza A viral load was measured by qPCR in nasopharyngeal samples at multiple time points during the study. Reported here is the duration of viral shedding. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

Immediately prior to MHAA4549A infusion and oseltamivir dosing on Day 1, immediately prior to oseltamivir dosing on Days 2 to 10, Days 14, 20, 25, 30, on day of discharge from hospital (up to Day 60), and at study completion (Day 60)

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: days				
median (confidence interval 80%)	4.00 (3.66 to 5.60)	4.63 (3.63 to 4.97)	4.60 (3.57 to 5.53)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7413
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.77
upper limit	1.32

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4763
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.99
upper limit	1.77

Secondary: Duration of Hospitalisation	
End point title	Duration of Hospitalisation
End point description:	
ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.	
End point type	Secondary
End point timeframe:	
From randomisation up to 60 days	

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: days				
median (confidence interval 80%)	8.95 (5.90 to 10.29)	7.65 (6.94 to 8.02)	6.69 (6.00 to 8.86)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8806
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.78
upper limit	1.32

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5447
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.8
upper limit	1.38

Secondary: Duration of Intensive Care Unit (ICU) Stay

End point title	Duration of Intensive Care Unit (ICU) Stay

End point description:

ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with

subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:
From randomisation up to 60 days

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: days				
median (confidence interval 80%)	4.66 (3.91 to 7.10)	6.60 (4.82 to 10.53)	5.29 (3.25 to 6.58)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4171
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.47
upper limit	1.03

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8322
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.61
upper limit	1.34

Secondary: Percentage of Subjects Using Antibiotics for Respiratory Infections	
End point title	Percentage of Subjects Using Antibiotics for Respiratory Infections
End point description:	
ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.	
End point type	Secondary
End point timeframe:	
From randomisation up to 60 days	

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)	13.0 (7.36 to 20.84)	11.5 (6.17 to 19.37)	11.4 (5.63 to 20.06)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	-1.42
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-10.61
upper limit	7.76

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8111
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	-1.6
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.48
upper limit	8.28

Secondary: Percentage of Subjects With Secondary Complications of Influenza

End point title	Percentage of Subjects With Secondary Complications of Influenza

End point description:

The following were considered secondary complications of influenza: pneumonia, including hospital-acquired pneumonia (HAP) and ventilation-acquired pneumonia (VAP), exacerbations of chronic lung disease, myocarditis, acute respiratory distress syndrome (ARDS), otitis media, or other related complications. ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

From randomisation up to 60 days

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)	13.0 (7.36 to 20.84)	15.4 (9.17 to 23.79)	13.6 (7.32 to 22.71)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7219
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	2.42

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.96
upper limit	11.8

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9225
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	0.67
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9.29
upper limit	10.64

Secondary: Percentage of Subjects Readmitted to Hospital Due to Any Cause

End point title	Percentage of Subjects Readmitted to Hospital Due to Any Cause

End point description:

ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.

End point type	Secondary

End point timeframe:

Days 30 and 60

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: percentage of subjects				
number (confidence interval 80%)	1.9 (0.19 to 7.01)	3.8 (1.03 to 9.91)	0 (0.00 to 5.10)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5379
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	1.99
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.57
upper limit	9.56

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3667
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in event rates
Point estimate	-1.85
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9.88
upper limit	6.18

Secondary: Duration of Ventilation	
End point title	Duration of Ventilation
End point description:	
ITTi population included all randomised subjects, who were confirmed to be influenza A infected, with subjects grouped according to the treatment assigned at randomisation.	
End point type	Secondary
End point timeframe:	
From randomisation up to 60 days	

End point values	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	44	
Units: days				
median (confidence interval 80%)	4.11 (2.72 to 5.32)	7.05 (1.92 to 13.12)	5.89 (4.13 to 13.07)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Oseltamivir v MHAA4549A 3600 mg + Oseltamivir
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7827
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.41
upper limit	1.07

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Oseltamivir v MHAA4549A 8400 mg + Oseltamivir
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2522
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.36
upper limit	0.96

Secondary: Area Under Serum Concentration-Time Curve from Time 0 to Infinity (AUC0-inf) of MHAA4549A

End point title	Area Under Serum Concentration-Time Curve from Time 0 to Infinity (AUC0-inf) of MHAA4549A[3]

End point description:

AUC0-inf is reported as day*microgram/millilitre (day*mcg/mL). Pharmacokinetic (PK)−evaluable population included all subjects, who received MHAA4549A and from whom evaluable PK samples were obtained.

End point type	Secondary

End point timeframe:

30 minutes (min) before & 60 min after end of MHAA4549A infusion (infusion duration = 120 min) on Day 1; immediately prior to oseltamivir dose on Days 2, 3, 5, 7; on Days 14, 30; on day of discharge (up to Day 60); at study completion (Day 60)

Notes:

[3] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: day*mcg/mL				
arithmetic mean (standard deviation)	11400 (± 4530)	26700 (± 9810)		

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[4]

End point description:

PK−evaluable population included all subjects, who received MHAA4549A and from whom evaluable PK samples were obtained.

End point type	Secondary

End point timeframe:

30 min before & 60 min after end of MHAA4549A infusion (infusion duration = 120 min) on Day 1; immediately prior to oseltamivir dose on Days 2, 3, 5, 7; on Days 14, 30; on day of discharge (up to Day 60); at study completion (Day 60)

Notes:

[4] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: mcg/mL				
arithmetic mean (standard deviation)	916 (± 294)	2220 (± 556)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-Life (Terminal t1/2) of MHAA4549A

End point title	Elimination Half-Life (Terminal t1/2) of MHAA4549A[5]

End point description:

PK−evaluable population included all subjects, who received MHAA4549A and from whom evaluable PK samples were obtained.

End point type	Secondary

End point timeframe:

30 min before & 60 min after end of MHAA4549A infusion (infusion duration = 120 min) on Day 1; immediately prior to oseltamivir dose on Days 2, 3, 5, 7; on Days 14, 30; on day of discharge (up to Day 60); at study completion (Day 60)

Notes:

[5] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: day				
arithmetic mean (standard deviation)	19.0 (± 4.91)	17.8 (± 3.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Clearance (CL_obs) of MHAA4549A

End point title	Observed Clearance (CL_obs) of MHAA4549A[6]

End point description:

PK−evaluable population included all subjects, who received MHAA4549A and from whom evaluable PK samples were obtained.

End point type	Secondary

End point timeframe:

30 min before & 60 min after end of MHAA4549A infusion (infusion duration = 120 min) on Day 1; immediately prior to oseltamivir dose on Days 2, 3, 5, 7; on Days 14, 30; on day of discharge (up to Day 60); at study completion (Day 60)

Notes:

[6] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: mL/day				
arithmetic mean (standard deviation)	288 (± 158)	350 (± 130)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Steady State Volume of Distribution (Vss_obs) of MHAA4549A

End point title	Observed Steady State Volume of Distribution (Vss_obs) of MHAA4549A[7]

End point description:

PK−evaluable population included all subjects, who received MHAA4549A and from whom evaluable PK samples were obtained.

End point type	Secondary

End point timeframe:

30 min before & 60 min after end of MHAA4549A infusion (infusion duration = 120 min) on Day 1; immediately prior to oseltamivir dose on Days 2, 3, 5, 7; on Days 14, 30; on day of discharge (up to Day 60); at study completion (Day 60)

Notes:

[7] - 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: PK results for MHAA4549A are only provided for the arms, which received MHAA4549A.

End point values	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	31		
Units: mL				
arithmetic mean (standard deviation)	6410 (± 3170)	7450 (± 2270)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation up to 60 days

Adverse event reporting additional description:

Safety Population included all randomised subjects, who received study drug, with subjects grouped according to the treatment actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo + Oseltamivir

Reporting group description:

Subjects received a single IV dose of placebo matched to MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.

Reporting group title	MHAA4549A 3600 mg + Oseltamivir

Reporting group description:

Subjects received a single low intravenous (IV) dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.

Reporting group title	MHAA4549A 8400 mg + Oseltamivir

Reporting group description:

Subjects received a single high IV dose of MHAA4549A on Day 1 and standard oseltamivir therapy for minimum of 5 days.

Serious adverse events	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 56 (14.29%)	11 / 55 (20.00%)	12 / 47 (25.53%)
number of deaths (all causes)	4	6	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Extubation			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ulcer			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute pulmonary oedema			

subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (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
Aspiration			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Suture rupture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Traumatic intracranial haemorrhage			

subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (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
Cardio−respiratory arrest			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (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

Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 56 (1.79%)	3 / 55 (5.45%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Septic shock			
subjects affected / exposed	2 / 56 (3.57%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			

subjects affected / exposed	0 / 56 (0.00%)	1 / 55 (1.82%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 55 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 55 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	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	Placebo + Oseltamivir	MHAA4549A 3600 mg + Oseltamivir	MHAA4549A 8400 mg + Oseltamivir
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 56 (50.00%)	26 / 55 (47.27%)	18 / 47 (38.30%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 56 (12.50%)	1 / 55 (1.82%)	4 / 47 (8.51%)
occurrences (all)	9	2	4
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 56 (5.36%)	4 / 55 (7.27%)	2 / 47 (4.26%)
occurrences (all)	3	8	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 56 (3.57%)	2 / 55 (3.64%)	3 / 47 (6.38%)
occurrences (all)	2	2	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 56 (3.57%)	3 / 55 (5.45%)	2 / 47 (4.26%)
occurrences (all)	2	3	2
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 56 (3.57%)	4 / 55 (7.27%)	2 / 47 (4.26%)
occurrences (all)	2	5	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 56 (12.50%)	3 / 55 (5.45%)	0 / 47 (0.00%)
occurrences (all)	7	3	0
Nausea			
subjects affected / exposed	4 / 56 (7.14%)	4 / 55 (7.27%)	1 / 47 (2.13%)
occurrences (all)	4	7	1
Constipation			
subjects affected / exposed	2 / 56 (3.57%)	4 / 55 (7.27%)	2 / 47 (4.26%)
occurrences (all)	3	4	2
Vomiting			
subjects affected / exposed	3 / 56 (5.36%)	2 / 55 (3.64%)	2 / 47 (4.26%)
occurrences (all)	3	4	2
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 56 (7.14%)	3 / 55 (5.45%)	1 / 47 (2.13%)
occurrences (all)	4	3	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 56 (5.36%)	5 / 55 (9.09%)	0 / 47 (0.00%)
occurrences (all)	3	6	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	4 / 56 (7.14%)	2 / 55 (3.64%)	4 / 47 (8.51%)
occurrences (all)	5	2	4
Hypophosphataemia			
subjects affected / exposed	4 / 56 (7.14%)	2 / 55 (3.64%)	2 / 47 (4.26%)
occurrences (all)	4	3	3
Hyperglycaemia			
subjects affected / exposed	1 / 56 (1.79%)	3 / 55 (5.45%)	2 / 47 (4.26%)
occurrences (all)	1	7	2
Hyperkalaemia			
subjects affected / exposed	1 / 56 (1.79%)	1 / 55 (1.82%)	3 / 47 (6.38%)
occurrences (all)	1	1	3

Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	3 / 55 (5.45%) 4	1 / 47 (2.13%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2014	More frequent review of safety data was facilitated by employing an Internal Monitoring Committee (IMC) in combination with a Scientific Oversight Committee (SOC) rather than a single Independent Data Monitoring Committee (iDMC). Allowing the inclusion of subjects diagnosed with influenza A as determined by a Sponsor-supplied rapid influenza test and/or local molecular test (PCR) allowed enrollment flexibility. Subjects on low-flow oxygen were to receive a daily trial off oxygen in the morning. Subjects to be fitted with pulse oximeter,and their SpO2 had to be checked once while on oxygen and then again3-5 minutes after turning off oxygen supplementation. Updated background clinical safety and efficacy data were added to provide investigators with the most current information concerning MHAA4549A.
20 March 2015	Added a high-dose arm (i.e., 8400 mg MHAA4545A). The addition of the 8400-mg treatment necessitated an adjustment in the infusion rate to 120 minutes for MHAA4549A and placebo. In addition, to mitigate any concerns with safety monitoring, the study design was expanded to include an initial safety assessment by the Internal Monitoring Committee and the Scientific Oversight Committee of a sentinel safety cohort consisting of the first 30 subjects enrolled or those subjects enrolled during the first influenza season, whichever occurs first. The time to normalization end point was adjusted operationally based on investigator feedback to allow greater flexibility to be in line with local standard course of clinical care. The sample size was adjusted to approximately 330 subjects. The MHAA4549A dosing rationale was updated to support the 8400-mg dose. The background clinical safety and efficacy summaries were updated with the most current data concerning MHAA4549A.
16 May 2016	Added an additional secondary endpoint to compare the clinical status of subjects using an ordinal outcome with 6 clinical statuses. Revised initial oseltamivir dosing from 8 hours to 12 hours after completion of study drug administration. Clarification to inclusion criteria of "any supplemental O2 to maintain oxygen saturation >92%". Clarification that subjects with a history of chronic lung disease with a documented SpO2 <95% off oxygen were excluded. Clarification of daily trial off oxygen.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported