Clinical trial results:
A randomized, double-blind, placebo-controlled, phase 2a study in healthy volunteers to evaluate the efficacy and safety of MHAA4549A in an Influenza challenge model

Summary

EudraCT number	2013-001983-52
Trial protocol	GB
Global end of trial date	19 June 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	04 March 2016

Trial information

Trial identification

Sponsor protocol code	GV28985

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01980966
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the reduction in the area under the curve (AUC) of virus load from the nasopharyngeal mucosa in the MHAA4549A treatment group compared to placebo.

Protection of trial subjects:

This study was conducted according to Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the European Union (EU) Good Clinical Practice Directive (2005/28/EC), and any applicable local, state, and federal laws, as well as other applicable country laws. Participants were followed-up from the time they consented to participate in the study until the end of study. The safety of participants was ensured by monitoring of adverse events throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	European Union: 101
Worldwide total number of subjects	101
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 1 center in Europe between 14 October 2013 and 19 June 2014.

Pre-assignment

Screening details:

One hundred participants were planned, 101 participants were randomized and received the challenge virus at Retroscreen, and 100 participants received at least one dose of MHAA4549A.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants in Cohort 1-5 received matching placebo of MHAA4549A as a single intravenous infusion on Day 1. In addition, participants in Cohort 5 received matching placebo of Tamiflu as an oral capsule from Day 1 to Day 5.

Arm type	Placebo
Investigational medicinal product name	Tamiflu-matching placebo oral / MHAA4549A-matching placebo IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Participants in Cohort 1-5 received matching placebo of MHAA4549A as a single intravenous infusion on Day 1. In addition, participants in Cohort 5 received twice-daily doses of matching placebo of Tamiflu as an oral capsule from Day 1 to Day 5.

Arm title	MHAA4549A 400mg

Arm description:

Participants in Cohort 4 and Cohort 5 received MHAA4549A 400 mg as a single intravenous infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	MHAA4549A 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in Cohort 4 and Cohort 5 received MHAA4549A 400 mg as a single intravenous infusion on Day 1, 24-36 hours after viral inoculation.

Arm title	MHAA4549A 1200mg

Arm description:

Participants in Cohort 1 and Cohort 2 received MHAA4549A 1200 mg as a single intravenous infusion on Day 1.

Arm type	Experimental

Investigational medicinal product name	MHAA4549A 1200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in Cohort 1 and Cohort 2 received MHAA4549A 1200 mg as a single intravenous infusion on Day 1, 24-36 hours after viral inoculation.

Arm title	MHAA4549A 3600mg

Arm description:

Participants in Cohort 3 and Cohort 4 received MHAA4549A 3600 mg as a single intravenous infusion on Day 1.

Arm type	Experimental
Investigational medicinal product name	MHAA4549A 3600 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in Cohort 3 and Cohort 4 received MHAA4549A 3600 mg as a single intravenous infusion on Day 1, 24-36 hours after viral inoculation.

Arm title	Tamiflu

Arm description:

Participants in Cohort 5 received twice-daily doses of 75 mg Tamiflu as an oral capsule from Day 1 to Day 5. Also, participants in all the cohorts received twice-daily doses of Tamiflu from Day 7 to Day 11 to minimize risk of further transmitting the challenge virus.

Arm type	Active comparator
Investigational medicinal product name	Tamiflu 75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants in Cohort 5 received twice-daily doses of 75 mg Tamiflu as an oral capsule from Day 1 to Day 5. Also, participants in all the cohorts received twice-daily doses of Tamiflu from Day 7 to Day 11 to minimize risk of further transmitting the challenge virus.

Number of subjects in period 1	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg
Started	32	20	20
Completed	31	20	20
Not completed	1	0	0
Physician decision	1	-	-
AE observed after the challenge virus inoculation	-	-	-

Number of subjects in period 1	MHAA4549A 3600mg	Tamiflu
Started	21	8
Completed	20	8
Not completed	1	0

Physician decision	-	-
AE observed after the challenge virus inoculation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants in Cohort 1-5 received matching placebo of MHAA4549A as a single intravenous infusion on Day 1. In addition, participants in Cohort 5 received matching placebo of Tamiflu as an oral capsule from Day 1 to Day 5.	
Reporting group title	MHAA4549A 400mg
Reporting group description:	
Participants in Cohort 4 and Cohort 5 received MHAA4549A 400 mg as a single intravenous infusion on Day 1.	
Reporting group title	MHAA4549A 1200mg
Reporting group description:	
Participants in Cohort 1 and Cohort 2 received MHAA4549A 1200 mg as a single intravenous infusion on Day 1.	
Reporting group title	MHAA4549A 3600mg
Reporting group description:	
Participants in Cohort 3 and Cohort 4 received MHAA4549A 3600 mg as a single intravenous infusion on Day 1.	
Reporting group title	Tamiflu
Reporting group description:	
Participants in Cohort 5 received twice-daily doses of 75 mg Tamiflu as an oral capsule from Day 1 to Day 5. Also, participants in all the cohorts received twice-daily doses of Tamiflu from Day 7 to Day 11 to minimize risk of further transmitting the challenge virus.	

Reporting group values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg
Number of subjects	32	20	20
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	29.1	27.6	31.3
standard deviation	± 6.2	± 5.1	± 8.1
Gender categorical Units: Subjects			
Female	11	10	6
Male	21	10	14

Reporting group values	MHAA4549A 3600mg	Tamiflu	Total

Number of subjects	21	8	101
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	28.7	27	
standard deviation	± 7.7	± 7.7	-
Gender categorical Units: Subjects			
Female	10	2	39
Male	11	6	62

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants in Cohort 1-5 received matching placebo of MHAA4549A as a single intravenous infusion on Day 1. In addition, participants in Cohort 5 received matching placebo of Tamiflu as an oral capsule from Day 1 to Day 5.	
Reporting group title	MHAA4549A 400mg
Reporting group description:	
Participants in Cohort 4 and Cohort 5 received MHAA4549A 400 mg as a single intravenous infusion on Day 1.	
Reporting group title	MHAA4549A 1200mg
Reporting group description:	
Participants in Cohort 1 and Cohort 2 received MHAA4549A 1200 mg as a single intravenous infusion on Day 1.	
Reporting group title	MHAA4549A 3600mg
Reporting group description:	
Participants in Cohort 3 and Cohort 4 received MHAA4549A 3600 mg as a single intravenous infusion on Day 1.	
Reporting group title	Tamiflu
Reporting group description:	
Participants in Cohort 5 received twice-daily doses of 75 mg Tamiflu as an oral capsule from Day 1 to Day 5. Also, participants in all the cohorts received twice-daily doses of Tamiflu from Day 7 to Day 11 to minimize risk of further transmitting the challenge virus.	
Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent-to-treat (ITT) population, included all participants who were randomized and inoculated with the influenza virus, with participants allocated to the treatment arm associated with the regimen to which they were randomized.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population included all participants who were randomized, inoculated with influenza virus, and received at least one dose of study treatment. Participants were allocated to the treatment arm associated with the regimen actually received.	
Subject analysis set title	Pharmacokinetic population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic (PK) population included all participants who received MHAA4549A or Tamiflu, or both.	
Subject analysis set title	Intent-to-treat infected population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Intent-to-treat infected (ITTI) population included participants who were inoculated with influenza virus and had laboratory confirmed influenza infection.	

Primary: Median area under the curve of nasopharyngeal viral load by quantitative polymerase chain reaction

End point title	Median area under the curve of nasopharyngeal viral load by quantitative polymerase chain reaction
End point description:	
Influenza virus load in the nasopharyngeal samples was determined by quantitative polymerase chain reaction (qPCR assay). The area under the curve (AUC) was calculated by applying the trapezoid rule to the qPCR viral load measurements obtained three times per day for each participant from challenge	

virus inoculation until the morning of the day of discharge (Day 8). The trapezoidal rule is a numerical method that approximates the value of a definite integral. The ITTI population was the primary analysis population used for the efficacy analyses.

End point type	Primary

End point timeframe:

From the first assessment post dosing to the day of discharge (Day 8)

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: log10 viral copies per milliliter × hour				
median (full range (min-max))	458.05 (0 to 834.17)	247.23 (0 to 543.68)	444.43 (0 to 694.16)	11.3 (0 to 603.31)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: log10 viral copies per milliliter × hour				
median (full range (min-max))	57.4 (0 to 114.8)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0455
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-171.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-354.88
upper limit	-1.75

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.902
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	15.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-128.92
upper limit	179.54

Statistical analysis title	Placebo vs 3600 mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0051
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-323.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-463.75
upper limit	-116.75

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0558
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-374.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-719.38
upper limit	0

Secondary: Median area under the curve of nasopharyngeal viral load as measured

by cell culture (tissue culture infective dose 50% assay)	
End point title	Median area under the curve of nasopharyngeal viral load as measured by cell culture (tissue culture infective dose 50% assay)

End point description:

The AUC of nasopharyngeal viral load, as measured by tissue culture infective dose 50% (TCID50) cell culture assay was calculated by applying the trapezoid rule to the viral load measurements obtained three times per day for participant from challenge virus inoculation until the morning of the day of discharge (Day 8). The ITTI population was the primary analysis population used for the efficacy analyses.

End point type	Secondary

End point timeframe:

From the first assessment post dosing to discharge (Day 8)

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: log10 TCID50 × hour				
median (full range (min-max))	186.78 (0 to 443.56)	70.25 (0 to 245.94)	224.46 (0 to 344.28)	0 (0 to 327.04)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: log10 TCID50 × hour				
median (full range (min-max))	28.84 (0 to 57.68)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0087
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-127.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-203.51
upper limit	-40.58

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8742
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-4.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93.52
upper limit	75.33

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-149.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-229.11
upper limit	-68.51

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0558
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-170.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-385.88
upper limit	0

Secondary: Median peak viral load post dosing to the last day of quarantine (quantitative polymerase chain reaction)

End point title	Median peak viral load post dosing to the last day of quarantine (quantitative polymerase chain reaction)

End point description:

The median peak viral load post dosing to the last day of quarantine was measured by qPCR in ITTI population.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: log10 viral copies per milliliter				
median (full range (min-max))	6.38 (0 to 7.76)	5.08 (0 to 6.39)	6.36 (0 to 8.01)	1.45 (0 to 6.89)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: log10 viral copies per milliliter				
median (full range (min-max))	2.3 (0 to 4.6)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0187
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.37
upper limit	-0.35

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	1.12

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0024
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-3.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.25
upper limit	-1.23

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0947
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.37
upper limit	0.19

Secondary: Median peak viral load post dosing to the last day of quarantine (cell culture)

End point title	Median peak viral load post dosing to the last day of quarantine (cell culture)

End point description:

The median peak viral load post dosing to the last day of quarantine was measured by cell culture in ITTI population.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: log10 TCID50				
median (full range (min-max))	4.25 (0 to 6)	1.75 (0 to 4.5)	4 (0 to 5.75)	0 (0 to 4.75)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: log10 TCID50				
median (full range (min-max))	1.25 (0 to 2.5)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	-0.25

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	MHAA4549A 1200mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9578
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	1.25

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-3.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.25
upper limit	-1

Statistical analysis title	Placebo vs Tamiflu

Comparison groups	Placebo v Tamiflu
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.115
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	1.5

Secondary: Median duration of viral shedding from first positive detection after initiation of dosing until the assessment after the last positive (quantitative polymerase chain reaction)

End point title	Median duration of viral shedding from first positive detection after initiation of dosing until the assessment after the last positive (quantitative polymerase chain reaction)

End point description:

The median duration of viral shedding for participants who had measurable virus by qPCR was computed using Kaplan-Meier methodology in ITTI population. Only participants with detectable event were analyzed.

End point type	Secondary

End point timeframe:

From first positive detection after initiation of dosing until the assessment after the last positive

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	8	11	7
Units: hours				
median (full range (min-max))	113.7 (0 to 154.1)	103.8 (0 to 144.1)	119.9 (0 to 154.2)	71.7 (0 to 144)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: hours				
median (full range (min-max))	33.1 (0 to 33.1)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	5.15

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	MHAA4549A 1200mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.78

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	8.09

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	14.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.54
upper limit	141.31

Secondary: Median duration of viral shedding from first positive detection after initiation of dosing until the assessment after the last positive (cell culture)

End point title	Median duration of viral shedding from first positive detection after initiation of dosing until the assessment after the last positive (cell culture)

End point description:

The median duration of viral shedding for participants who had measurable virus by cell culture was computed using Kaplan-Meier methodology in ITTI population. Only participants with detectable event were analyzed.

End point type	Secondary

End point timeframe:

From first positive detection after initiation of dosing until the assessment after the last positive

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	7	11	6
Units: hours				
median (full range (min-max))	80.5 (0 to 128.8)	48.2 (0 to 120)	81.2 (0 to 128.8)	63.9 (0 to 96)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: hours				
median (full range (min-max))	33.1 (0 to 33.1)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	4.85

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.94

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	5.27

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	13.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	122.47

Secondary: Median duration of viral shedding from peak viral load (post dosing) until the assessment after the last positive (quantitative polymerase chain reaction)

End point title	Median duration of viral shedding from peak viral load (post dosing) until the assessment after the last positive (quantitative polymerase chain reaction)

End point description:

The median duration of viral shedding by qPCR from the peak viral load was estimated using Kaplan-Meier methodology in the ITTI population. Only participants with detectable event were analyzed.

End point type	Secondary

End point timeframe:

From peak viral load (post dosing) until the assessment after the last positive

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	8	11	7
Units: hours				
median (full range (min-max))	6.6 (0 to 7.8)	5.8 (0 to 6.4)	6.4 (0 to 8)	4.8 (0 to 6.9)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: hours				
median (full range (min-max))	4.6 (0 to 4.6)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	3.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.51
upper limit	9.8

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.3

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	7.76

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	8.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	72.12

Secondary: Median duration of viral shedding from peak viral load (post dosing) until the assessment after the last positive (cell culture)

End point title	Median duration of viral shedding from peak viral load (post dosing) until the assessment after the last positive (cell culture)

End point description:

The median duration of viral shedding by cell culture from the peak viral load was estimated using Kaplan-Meier methodology. Only participants with detectable event were analyzed.

End point type	Secondary

End point timeframe:

From peak viral load (post dosing) until the assessment after the last positive

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	7	11	6
Units: hours				
median (full range (min-max))	4.3 (0.8 to 6)	3.5 (0.8 to 4.5)	4.3 (0.8 to 5.8)	4 (0.8 to 4.8)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: hours				
median (full range (min-max))	2.5 (0.8 to 2.5)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	6.84

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.93

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	5.79

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	4.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	35.98

Secondary: Median duration of Grade 2 or worse symptoms from first assessment after dosing until the assessment after the last positive

End point title	Median duration of Grade 2 or worse symptoms from first assessment after dosing until the assessment after the last positive

End point description:

The median duration of Grade 2 or higher symptoms was estimated using Kaplan-Meier methodology in ITTI population. Only participants with detectable event were analyzed.

End point type	Secondary

End point timeframe:

From first assessment after dosing until the assessment after the last positive

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	3	4	6
Units: hours				
median (full range (min-max))	72 (0 to 88)	48 (0 to 72)	56 (0 to 96)	68 (0 to 96)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	0[1]			
Units: hours				
median (full range (min-max))	(to)			

Notes:

[1] - No participants had a detectable event which could be analysed in Tamiflu arm

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	7.4

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	3.62

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	2.47

Secondary: Median peak composite symptoms from first assessment after dosing to the last day of quarantine

End point title	Median peak composite symptoms from first assessment after dosing to the last day of quarantine

End point description:

The composite symptom score at each time point for a participant was derived by summing the 10 individual symptom scores for that participant at that time point. The individual symptoms were as follows: runny nose, stuffy nose, sneezing, sore throat, earache, malaise (tiredness), cough, shortness

of breath, headache, and muscle/joint ache or stiffness. The scores ranged from 0 to 3 and were scored as follows: 0 = absence of symptom; 1 = symptom just noticeable; 2 = symptom bothersome but does not prevent participation in activities, and 3 = symptom bothersome and interferes with activities.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: Score				
median (full range (min-max))	4 (0 to 16)	3 (0 to 11)	4 (2 to 14)	2 (0 to 14)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Score				
median (full range (min-max))	0.5 (0 to 1)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2375
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	1

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.79
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2174
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	1

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0664
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	0

Secondary: Median area under the curve of composite symptoms from the first

evaluation after dosing to the last day of quarantine	
End point title	Median area under the curve of composite symptoms from the first evaluation after dosing to the last day of quarantine

End point description:

The median AUC for symptom scores over time was calculated from the time of initiating drug administration in the ITTI population.

End point type	Secondary

End point timeframe:

Day 1 to Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	11	13	14
Units: score x hour				
median (full range (min-max))	207.68 (0 to 783.08)	87.51 (0 to 458.28)	192.1 (55.73 to 782.53)	37.7 (0 to 1214.31)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: score x hour				
median (full range (min-max))	8.14 (0 to 16.28)			

Statistical analyses

Statistical analysis title	Placebo vs 400mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 400mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-91.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-254.22
upper limit	44.48

Statistical analysis title	Placebo vs 1200mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 1200mg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8743
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-14.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-160.58
upper limit	116.82

Statistical analysis title	Placebo vs 3600mg MHAA4549A
Comparison groups	Placebo v MHAA4549A 3600mg
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2887
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-106.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-238.03
upper limit	40.79

Statistical analysis title	Placebo vs Tamiflu
Comparison groups	Placebo v Tamiflu
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0855
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-203.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-568.87
upper limit	8.27

Secondary: Incidence of treatment emergent adverse events

End point title	Incidence of treatment emergent adverse events

End point description:

An adverse event is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution. All treatment emergent adverse events (TEAEs) (i.e. AEs that occurred during or after dosing) were summarized for each treatment group in safety population.

End point type	Secondary

End point timeframe:

From the time of virus inoculation (one day prior to receiving study drug) until the participant completes (approximately up to 270 days) or discontinues the study

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	20	20	20
Units: Number	28	18	16	17

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Number	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Anti−Therapeutic Antibodies to MHAA4549A

End point title	Incidence of Anti−Therapeutic Antibodies to MHAA4549A

End point description:

Serum samples for Anti−Therapeutic Antibodies (ATA) analysis were obtained at Baseline, before dosing, and at multiple time points.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Day 29, Day 85 and Day 120

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[2]	20	20	20
Units: Number				
Positive for ATA	1	0	0	0
Negative for ATA	30	20	20	20

Notes:

[2] - Only those participants available at the specified time points were analyzed

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Number				
Positive for ATA	0			
Negative for ATA	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in forced expiratory volume in one second

End point title	Absolute change from Baseline in forced expiratory volume in one second

End point description:

Spirometry was conducted to evaluate lung function. Forced expiratory volume in one second (FEV1) is the amount of air exhaled at 1 second. Change from Baseline in FEV1 on last day of quarantine (Day 8) in safety population was reported. Baseline value was defined as the last value prior to inoculation with challenge virus.

End point type	Secondary

End point timeframe:

Baseline and Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	20	20	20
Units: Litres				
arithmetic mean (standard deviation)	0 (± 0.16)	0.08 (± 0.24)	-0.1 (± 0.2)	-0.12 (± 0.39)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			

Units: Litres				
arithmetic mean (standard deviation)	0.05 (± 0.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from Baseline in forced vital capacity

End point title	Absolute change from Baseline in forced vital capacity

End point description:

Spirometry was conducted to evaluate lung function. Forced vital capacity (FVC) is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. Change from Baseline in FVC on last day of quarantine (Day 8) in safety population was reported. Baseline value was defined as the last value prior to inoculation with challenge virus.

End point type	Secondary

End point timeframe:

Baseline and Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	20	20	20
Units: Litres				
arithmetic mean (standard deviation)	0.01 (± 0.33)	0.1 (± 0.34)	-0.21 (± 0.42)	-0.19 (± 0.49)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Litres				
arithmetic mean (standard deviation)	0.06 (± 0.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in forced expiratory volume in one second/forced vital capacity

End point title	Absolute change from baseline in forced expiratory volume in one second/forced vital capacity

End point description:

Spirometry was conducted to evaluate lung function. FEV1 is defined as the maximal amount of air that can be forcefully exhaled in one second and FVC is defined as the amount of air that can be forcibly

exhaled from the lungs after taking the deepest breath possible. Change from Baseline in FEV1/FVC on last day of quarantine (Day 8) in safety population was reported. Baseline value was defined as the last value prior to inoculation with challenge virus.

End point type	Secondary

End point timeframe:

Baseline and Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	20	20	20
Units: Percentage				
arithmetic mean (standard deviation)	-0.03 (± 4.85)	-0.05 (± 3.75)	1.51 (± 5.93)	1 (± 4.58)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage				
arithmetic mean (standard deviation)	0 (± 3.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in maximum mid-expiratory flow

End point title	Absolute change from baseline in maximum mid-expiratory flow

End point description:

Spirometry was conducted to evaluate lung function. The maximum midexpiratory flow (MMEF) is the average expiratory flow over the middle half of the FVC. FVC is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

End point type	Secondary

End point timeframe:

Baseline and Day 8

End point values	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	20	20	20
Units: Litres/second				
arithmetic mean (standard deviation)	0 (± 0.52)	0.07 (± 0.49)	0.03 (± 0.69)	-0.14 (± 0.48)

End point values	Tamiflu			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Litres/second				
arithmetic mean (standard deviation)	0.04 (± 0.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve of MHAA4549A in serum

End point title	Area under the curve of MHAA4549A in serum[3]

End point description:

Blood samples for PK analysis of MHA4459A levels were collected at pre-dose and at 30 minutes and 4 hours post end of infusion on Day 1, 24 hours post end of infusion on Day 2, 72 hours post end of infusion on Day 4, and on Day 8, Day 15, Day 29, Day 57, Day 85 and Day 120. AUC is defined as the area under the MHA4459A concentration-time curve as a measure of drug exposure. AUC (0-inf) is defined as the area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time. AUC (0-last) is defined as area under the concentration-time curve from time zero (predose) to the last time of measurable concentration.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose; Study Day 1 is equivalent to PK Day 0) to Day 120 (Study Day 120 is equivalent to PK Day 119)

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: The endpoint is applicable only for MHAA4549A arms.

End point values	MHAA4549A 400mg	MHAA4549A 1200mg	MHAA4549A 3600mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: day x microgram/millilitre				
geometric mean (geometric coefficient of variation)				
AUC(0-last)	1700 (± 21.2)	4940 (± 20.2)	17200 (± 19.5)	
AUC(0-infinity)	1760 (± 22.3)	5130 (± 23.3)	17700 (± 20.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of administration of the study drug until the completion of the study (approximately up to 270 days) or until the participant was discontinued from the study

Adverse event reporting additional description:

SAEs and non-serious AEs were collected for participants in the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants in Cohort 1-5 received matching placebo of MHAA4549A as a single intravenous infusion on Day 1. In addition, participants in Cohort 5 received matching placebo of Tamiflu as an oral capsule from Day 1 to Day 5.

Reporting group title	MHAA4549A 400mg

Reporting group description:

Participants in Cohort 4 and Cohort 5 received MHAA4549A 400 mg as a single intravenous infusion on Day 1.

Reporting group title	MHAA4549A 1200mg

Reporting group description:

Participants in Cohort 1 and Cohort 2 received MHAA4549A 1200 mg as a single intravenous infusion on Day 1.

Reporting group title	MHAA4549A 3600mg

Reporting group description:

Participants in Cohort 3 and Cohort 4 received MHAA4549A 3600 mg as a single intravenous infusion on Day 1.

Reporting group title	Tamiflu

Reporting group description:

Participants in Cohort 5 received twice-daily doses of 75 mg Tamiflu as an oral capsule from Day 1 to Day 5. Also, participants in all the cohorts received twice-daily doses of Tamiflu from Day 7 to Day 11 to minimize risk of further transmitting the challenge virus.

Serious adverse events	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	0 / 20 (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
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MHAA4549A 3600mg	Tamiflu	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	MHAA4549A 400mg	MHAA4549A 1200mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 32 (87.50%)	18 / 20 (90.00%)	16 / 20 (80.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Oropharyngeal pain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Cough			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Rhinorrhoea			

subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 32 (15.63%)	5 / 20 (25.00%)	4 / 20 (20.00%)
occurrences (all)	5	5	4
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 32 (9.38%)	5 / 20 (25.00%)	3 / 20 (15.00%)
occurrences (all)	3	5	3
Amylase increased			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	8 / 32 (25.00%)	6 / 20 (30.00%)	3 / 20 (15.00%)
occurrences (all)	8	6	4
Contusion			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Muscle strain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 32 (15.63%)	0 / 20 (0.00%)	3 / 20 (15.00%)
occurrences (all)	5	0	3
Presyncope			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Sinus headache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	2 / 32 (6.25%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Toothache			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Abdominal distension			

subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dental caries			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 32 (3.13%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Rash erythematous			
subjects affected / exposed	2 / 32 (6.25%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 32 (18.75%)	3 / 20 (15.00%)	2 / 20 (10.00%)
occurrences (all)	7	3	2

Nasopharyngitis			
subjects affected / exposed	0 / 32 (0.00%)	3 / 20 (15.00%)	1 / 20 (5.00%)
occurrences (all)	0	3	1
Respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lice infestation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Postoperative wound infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tracheitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vaginitis bacterial			
subjects affected / exposed	0 / 32 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	MHAA4549A 3600mg	Tamiflu	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	7 / 8 (87.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Chest discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	3 / 20 (15.00%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	3	
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 20 (20.00%)	2 / 8 (25.00%)	
occurrences (all)	4	2	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)	2 / 8 (25.00%)	
occurrences (all)	3	3	
Amylase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	6 / 20 (30.00%)	3 / 8 (37.50%)	
occurrences (all)	7	3	
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 20 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Sinus headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Ear pain			

subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 20 (15.00%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Dental caries			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Rash erythematous			

subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)	0 / 8 (0.00%)	
occurrences (all)	5	0	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Lice infestation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Postoperative wound infection			

subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Tracheitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 8 (0.00%)	
occurrences (all)	0	0	
Vaginitis bacterial			
subjects affected / exposed	1 / 20 (5.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Substantial amendment was done to change the Principal Investigator.
28 January 2014	Substantial amendment was done to change the Principal Investigator. In addition, this amendment corrected the instructions for the allocation of a replacement randomization number.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported