



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 |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, + 41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 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 standard deviation | 65.7 ± 17.5 | 56.5 ± 18.2 | 59.8 ± 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 |
|-----------------|--|

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 (ITT_i) 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 | |

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: | |
| ITT 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 expressed as $\log_{10}(\text{viral particles/millilitre} \times \text{hour}) = \log_{10}(\text{vp/mL} \times \text{hour})$. 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: $\log_{10}(\text{vp/mL} \times \text{hour})$ | | | | |
| arithmetic mean (standard deviation) | 25.72 (\pm 15.92) | 21.99 (\pm 16.57) | 25.03 (\pm 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: | |
| ITT 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: | |
| ITT 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:

ITT_i 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: | |
| ITT 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: | |
| ITT _i 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:

AUC_{0-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 (C_{max}) of MHAA4549A

| | |
|-----------------|---|
| End point title | Maximum Serum Concentration (C _{max}) 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 t_{1/2}) of MHAA4549A

| | |
|-----------------|--|
| End point title | Elimination Half-Life (Terminal t _{1/2}) 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 occurrences (all) | 2 / 56 (3.57%) 2 | 4 / 55 (7.27%) 5 | 2 / 47 (4.26%) 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 56 (12.50%) 7 | 3 / 55 (5.45%) 3 | 0 / 47 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 4 | 4 / 55 (7.27%) 7 | 1 / 47 (2.13%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 3 | 4 / 55 (7.27%) 4 | 2 / 47 (4.26%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 2 / 55 (3.64%) 4 | 2 / 47 (4.26%) 2 |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 4 | 3 / 55 (5.45%) 3 | 1 / 47 (2.13%) 1 |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 5 / 55 (9.09%) 6 | 0 / 47 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 5 | 2 / 55 (3.64%) 2 | 4 / 47 (8.51%) 4 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 4 | 2 / 55 (3.64%) 3 | 2 / 47 (4.26%) 3 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 3 / 55 (5.45%) 7 | 2 / 47 (4.26%) 2 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 1 / 55 (1.82%) 1 | 3 / 47 (6.38%) 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 again 3-5 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