



Clinical trial results:

An Open-Label, Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Intravenous Oseltamivir (Tamiflu®) in the Treatment of Infants Less Than One Year of Age With Influenza Infection

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-003003-54 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 28 January 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 26 April 2017 |
| First version publication date | 26 April 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | NP25138 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01053663 |
| 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, +41 616878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F.Hoffmann-La Roche, +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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 February 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 January 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This prospective, open-label, pharmacokinetic (PK)/pharmacodynamic (PD) and safety study was designed to define the PK of oseltamivir and oseltamivir carboxylate and evaluate the safety profile following intravenous (IV) administration of oseltamivir phosphate in infants less than 1 year of age with influenza. The study was also planned to evaluate viral load, viral shedding, and to evaluate all isolates for phenotypic and, where necessary, genotypic resistance.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 09 January 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | United States: 9 |
| Worldwide total number of subjects | 9 |
| 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) | 1 |
| Infants and toddlers (28 days-23 months) | 8 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2428 participants were prescreened; of which, 2419 failed the prescreening evaluation. The most common reasons for failing the prescreening evaluation included the following: negative influenza diagnosis, not meeting the age criterion, ability to tolerate/absorb oral medication, and inability to comply with the study procedures.

Period 1

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

Arms

| | |
|-----------|--------------------------------|
| Arm title | Oseltamivir - All Participants |
|-----------|--------------------------------|

Arm description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Oseltamivir |
| Investigational medicinal product code | RO0640796 |
| Other name | Tamiflu® |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received oseltamivir twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. The oseltamivir doses were based on participant's age.

| Number of subjects in period 1 | Oseltamivir - All Participants |
|---------------------------------|--------------------------------|
| Started | 9 |
| Completed | 3 |
| Not completed | 6 |
| Transferred to Another Hospital | 1 |
| Death | 2 |
| Poor IV Access | 1 |
| Negative Influenza Diagnosis | 1 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------|
| Reporting group title | Oseltamivir - All Participants |
| Reporting group description: Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses. | |

| Reporting group values | Oseltamivir - All Participants | Total | |
|--|--------------------------------|-------|--|
| Number of subjects | 9 | 9 | |
| Age categorical Units: Subjects | | | |
| Age continuous | | | |
| Here, 99999 represent data not estimable due to single participant analyzed. | | | |
| Units: days arithmetic mean standard deviation | 143.2 ± 82.9 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 2 | |
| Male | 7 | 7 | |

Subject analysis sets

| | |
|--|----------------------------------|
| Subject analysis set title | Oseltamivir: Age 91 to <365 Days |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses. | |
| Subject analysis set title | Oseltamivir: Age 31 to 90 Days |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses. | |
| Subject analysis set title | Oseltamivir: Age 0 to 30 Days |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses. | |

| Reporting group values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days |
|--|----------------------------------|--------------------------------|-------------------------------|
| Number of subjects | 7 | 1 | 1 |
| Age categorical Units: Subjects | | | |
| Age continuous | | | |
| Here, 99999 represent data not estimable due to single participant analyzed. | | | |
| Units: days | | | |
| arithmetic mean | 175 | 41 | 23 |
| standard deviation | ± 62 | ± 99999 | ± 99999 |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 0 | 0 |
| Male | 5 | 1 | 1 |

End points

End points reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Oseltamivir - All Participants |
|-----------------------|--------------------------------|

Reporting group description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) intravenously (IV) over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to less than (<) 365 days received 3 milligrams per kilogram (mg/kg); participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Oseltamivir: Age 91 to <365 Days |
|----------------------------|----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|----------------------------|--------------------------------|
| Subject analysis set title | Oseltamivir: Age 31 to 90 Days |
|----------------------------|--------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|----------------------------|-------------------------------|
| Subject analysis set title | Oseltamivir: Age 0 to 30 Days |
|----------------------------|-------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

Primary: Area Under the Concentration Versus Time Curve From Time Zero to Last Measurable Plasma Concentration (AUClast) of Oseltamivir and Oseltamivir Carboxylate on Day 1

| | |
|-----------------|--|
| End point title | Area Under the Concentration Versus Time Curve From Time Zero to Last Measurable Plasma Concentration (AUClast) of Oseltamivir and Oseltamivir Carboxylate on Day 1 ^[1] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) population included all treated participants who had at least one blood sample evaluable for drug concentration level. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1

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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|--|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 0 ^[2] | 1 | |
| Units: hour*nanograms/milliliter (h*ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 777 (± 162.8) | () | 494 (± 99999) | |
| Oseltamivir Carboxylate | 5200 (± 87.8) | () | 7510 (± 99999) | |

Notes:

[2] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 2

| | |
|-----------------|--|
| End point title | AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 2 ^[3] |
|-----------------|--|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 2

Notes:

[3] - 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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|--|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 1 | 0 ^[4] | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 988 (± 57.8) | 481 (± 99999) | () | |
| Oseltamivir Carboxylate | 7270 (± 42.2) | 5330 (± 99999) | () | |

Notes:

[4] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 4

| | |
|-----------------|--|
| End point title | AUClast of Oseltamivir and Oseltamivir Carboxylate on Day 4 ^[5] |
|-----------------|--|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here,

99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

Notes:

[5] - 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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 2 | 0 ^[6] | 1 | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 1520 (± 33.9) | () | 389 (± 99999) | |
| Oseltamivir Carboxylate | 3880 (± 98) | () | 2070 (± 99999) | |

Notes:

[6] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (C_{max}) of Oseltamivir and Oseltamivir Carboxylate on Day 1

| | |
|-----------------|--|
| End point title | Maximum Observed Plasma Concentration (C _{max}) of Oseltamivir and Oseltamivir Carboxylate on Day 1 ^[7] |
|-----------------|--|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1

Notes:

[7] - 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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 0 ^[8] | 1 | |
| Units: nanograms/milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 307 (± 315.7) | () | 203 (± 99999) | |
| Oseltamivir Carboxylate | 736 (± 55.5) | () | 871 (± 99999) | |

Notes:

[8] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 2

| | |
|-----------------|---|
| End point title | Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 2 ^[9] |
|-----------------|---|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 2

Notes:

[9] - 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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 1 | 0 ^[10] | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 419 (± 78.4) | 194 (± 99999) | () | |
| Oseltamivir Carboxylate | 1080 (± 43.6) | 1050 (± 99999) | () | |

Notes:

[10] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 4

| | |
|-----------------|--|
| End point title | Cmax of Oseltamivir and Oseltamivir Carboxylate on Day 4 ^[11] |
|-----------------|--|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome. Here, 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

Notes:

[11] - 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: No statistical analysis was planned for this open-label study.

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 2 | 0 ^[12] | 1 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Oseltamivir | 742 (± 31.1) | () | 189 (± 99999) | |
| Oseltamivir Carboxylate | 1370 (± 89.6) | () | 727 (± 99999) | |

Notes:

[12] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the Maximum Observed Plasma Concentration (Tmax) of Oseltamivir and Oseltamivir Carboxylate

| | |
|-----------------|---|
| End point title | Time to the Maximum Observed Plasma Concentration (Tmax) of Oseltamivir and Oseltamivir Carboxylate |
|-----------------|---|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 1 | 1 | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 1: Oseltamivir (n = 3, 0, 1) | 2.51 (± 55.4) | 9999 (± 9999) | 2 (± 99999) | |
| Day 1: Oseltamivir Carboxylate (n = 3, 0, 1) | 4.57 (± 32.5) | 9999 (± 9999) | 5.58 (± 99999) | |
| Day 2: Oseltamivir (n = 3, 1, 0) | 2.02 (± 1.4) | 2.13 (± 99999) | 9999 (± 9999) | |
| Day 2: Oseltamivir Carboxylate (n = 3, 1, 0) | 3.4 (± 47.8) | 4.3 (± 99999) | 9999 (± 9999) | |
| Day 4: Oseltamivir (n = 2, 0, 1) | 2.02 (± 1.2) | 9999 (± 9999) | 1.93 (± 99999) | |
| Day 4: Oseltamivir Carboxylate (n = 2, 0, 1) | 3.85 (± 6.7) | 9999 (± 9999) | 3.98 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Plasma Concentration (Clast) of Oseltamivir and Oseltamivir Carboxylate

| | |
|-----------------|---|
| End point title | Last Measurable Plasma Concentration (Clast) of Oseltamivir and Oseltamivir Carboxylate |
|-----------------|---|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 1 | 1 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 1: Oseltamivir (n = 3, 0, 1) | 5.58 (± 183) | 9999 (± 9999) | 2.76 (± 99999) | |
| Day 1: Oseltamivir Carboxylate (n = 3, 0, 1) | 505 (± 82.9) | 9999 (± 9999) | 503 (± 99999) | |
| Day 2: Oseltamivir (n = 3, 1, 0) | 8.22 (± 183.5) | 6.84 (± 99999) | 9999 (± 9999) | |
| Day 2: Oseltamivir Carboxylate (n = 3, 1, 0) | 849 (± 67.9) | 948 (± 99999) | 9999 (± 9999) | |
| Day 4: Oseltamivir (n = 2, 0, 1) | 66.2 (± 28.8) | 9999 (± 9999) | 10.7 (± 99999) | |
| Day 4: Oseltamivir Carboxylate (n = 2, 0, 1) | 1370 (± 89.6) | 9999 (± 9999) | 727 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time of the Last Measurable Plasma Concentration (Tlast) of Oseltamivir and Oseltamivir Carboxylate

| | |
|-----------------|---|
| End point title | Time of the Last Measurable Plasma Concentration (Tlast) of Oseltamivir and Oseltamivir Carboxylate |
|-----------------|---|

End point description:

PK population. Number of subjects analyzed = participants who were evaluable for this outcome, n = number of participants evaluable for specified categories. Here, 9999 represent data not available as no participant was evaluable at specified timepoint and 99999 represent data not estimable due to single participant analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose (Hour 0), 2, 3-4, 5-7, and 10-12 hours post-dose on Day 1 and Day 2, pre-dose (Hour 0), 2 and 4 hours post-dose on Day 4

| End point values | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days | |
|---|--|--------------------------------------|-------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 1 | 1 | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 1: Oseltamivir (n = 3, 0, 1) | 9.62 (± 24.7) | 9999 (± 9999) | 10.58 (± 99999) | |
| Day 1: Oseltamivir Carboxylate (n = 3, 0, 1) | 9.62 (± 24.7) | 9999 (± 9999) | 10.58 (± 99999) | |
| Day 2: Oseltamivir (n = 3, 1, 0) | 8.55 (± 51.1) | 6.47 (± 99999) | 9999 (± 9999) | |
| Day 2: Oseltamivir Carboxylate (n = 3, 1, 0) | 8.55 (± 51.1) | 6.47 (± 99999) | 9999 (± 9999) | |
| Day 4: Oseltamivir (n = 2, 0, 1) | 3.85 (± 6.7) | 9999 (± 9999) | 3.98 (± 99999) | |
| Day 4: Oseltamivir Carboxylate (n = 2, 0, 1) | 3.85 (± 6.7) | 9999 (± 9999) | 3.98 (± 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Greater Than or Equal to (\geq) 5-Fold Change in Neuraminidase Inhibition (NAI) Assay 50 Percent (%) Inhibitory Concentration (IC50) Values

| | |
|-----------------|---|
| End point title | Number of Participants With Greater Than or Equal to (\geq) 5-Fold Change in Neuraminidase Inhibition (NAI) Assay 50 Percent (%) Inhibitory Concentration (IC50) Values |
|-----------------|---|

End point description:

IC50 was defined as the concentration that causes 50% inhibition of viral activity. IC50 values were calculated using NAI assay. The 5-fold change was calculated as either ≥ 5 times change in the NAI IC50 visit value from the Reference value at a visit or ≥ 5 times change in the NAI IC50 Visit value from the Baseline value. Safety population included all participants who received at least one dose of IV study medication and had a safety assessment performed after initiation of treatment. Here, number of subjects analyzed = participants evaluable for this outcome measure, and n = participants evaluable for specified time-point, for each arm, respectively. Here, 9999 represent data not available as no participant was evaluable at specified timepoint.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days 1, 3, 4, 6, 15 | |

| End point values | Oseltamivir - All Participants | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days |
|-----------------------------|--------------------------------|----------------------------------|--------------------------------|-------------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 4 | 0 ^[13] | 1 |
| Units: participants | | | | |
| Day 1 (n=5, 4, 0, 1) | 1 | 1 | | 0 |
| Day 3 (n=1, 0, 0, 1) | 0 | 9999 | | 0 |
| Day 4 (n=3, 3, 0, 0) | 1 | 1 | | 9999 |
| Day 6 (n=1, 0, 0, 1) | 0 | 9999 | | 0 |
| Day 15 (n=1, 1, 0, 0) | 0 | 0 | | 9999 |

Notes:

[13] - No participant was evaluable for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Oseltamivir Resistance Mutation

| | |
|--|---|
| End point title | Number of Participants With Oseltamivir Resistance Mutation |
| End point description: | |
| Resistance was assessed by neuraminidase (NA) and hemagglutinin (HA) genes sequencing analysis, using Reverse Transcription Polymerase Chain Reaction (RT-PCR). Safety population. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Day 30 | |

| End point values | Oseltamivir - All Participants | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days | Oseltamivir: Age 0 to 30 Days |
|-----------------------------|--------------------------------|----------------------------------|--------------------------------|-------------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 7 | 1 | 1 |
| Units: participants | 1 | 1 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 30

Adverse event reporting additional description:

Safety population

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Oseltamivir - All Participants |
|-----------------------|--------------------------------|

Reporting group description:

Participants received oseltamivir (Tamiflu) twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. Oseltamivir doses were based on participant's age. Participants aged 91 to <365 days received 3 mg/kg; participants aged 31 to 90 days received 2.5 mg/kg; and participants aged 0 to 30 days received 2 mg/kg. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Oseltamivir: Age 91 to <365 Days |
|-----------------------|----------------------------------|

Reporting group description:

Participants aged 91 to <365 days received oseltamivir 3 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|-----------------------|--------------------------------|
| Reporting group title | Oseltamivir: Age 31 to 90 Days |
|-----------------------|--------------------------------|

Reporting group description:

Participants aged 31 to 90 days received oseltamivir 2.5 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Oseltamivir: Age 0 to 30 Days |
|-----------------------|-------------------------------|

Reporting group description:

Participants aged 0 to 30 days received oseltamivir 2 mg/kg twice daily (every 12 hours) IV over 5 or 6 days for a total of 10 doses. For participants who did not receive all 10 doses IV, treatment could be completed with oral oseltamivir suspension (twice daily). If medically necessary, participants were allowed to receive an additional 10 doses of IV or oral oseltamivir after the initial 10 doses.

| Serious adverse events | Oseltamivir - All Participants | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days |
|---|--------------------------------|----------------------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | 5 / 7 (71.43%) | 0 / 1 (0.00%) |
| number of deaths (all causes) | 3 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Cerebral Ischaemia | | | |

| | | | |
|--|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Multi–Organ Failure | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory Disorder | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Distress | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Respiratory Failure | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-------------------------------|--|--|
| Serious adverse events | Oseltamivir: Age 0 to 30 Days | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Cerebral Ischaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Multi–Organ Failure | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory Disorder | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Distress | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Oseltamivir - All Participants | Oseltamivir: Age 91 to <365 Days | Oseltamivir: Age 31 to 90 Days |
|---|--------------------------------|----------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | 4 / 7 (57.14%) | 0 / 1 (0.00%) |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 7 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cardiac disorders | | | |
| Sinus Bradycardia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nervous system disorders | | | |

| | | | |
|--|--|---|--|
| Brain Oedema subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 7 (14.29%) 1 | 0 / 1 (0.00%) 0 |
| Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 7 (14.29%) 1 | 0 / 1 (0.00%) 0 |
| General disorders and administration site conditions Application Site Vesicles subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 7 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Gastrointestinal disorders Abdominal Distension subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 | 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 | 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Pulmonary Hypertension subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 1 / 7 (14.29%) 2 | 0 / 1 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 7 (14.29%) 1 | 0 / 1 (0.00%) 0 |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 7 (14.29%) 1 | 0 / 1 (0.00%) 0 |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 7 (0.00%) 0 | 0 / 1 (0.00%) 0 |

| | | | |
|---|-------------------------------|--|--|
| Non-serious adverse events | Oseltamivir: Age 0 to 30 Days | | |
| Total subjects affected by non-serious adverse events | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Sinus Bradycardia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Brain Oedema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Application Site Vesicles | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal Distension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary Hypertension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|----------------------|--|--|
| Rash subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | | |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 08 April 2010 | <ul style="list-style-type: none">• Modified the requirements for the IV therapy duration and clarified the study population influenza diagnosis and duration of IV therapy• Provided an updated Assessments and Procedures schedule• Specified adverse events grading system |
| 14 May 2010 | <ul style="list-style-type: none">• Decreased the required number of IV doses to at least one and clarified that participants could have switched to oral dosing with oseltamivir after IV therapy was no longer medically necessary• Modified dosing in participants with moderate or severe renal impairment or who required continuous renal replacement therapy• Revised exclusion criteria and increased the flexibility of PK sampling |
| 19 September 2011 | <ul style="list-style-type: none">• Clarified the day of treatment completion depending on when dosing was started and whether one or two doses were received on Day 1• Revised the screening and eligibility text to allow flexibility to include data obtained from standard-of-care procedures prior to obtaining informed consent for study participation• Revised PK sample collection time-points |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|---|--------------|
| 28 January 2013 | The study was terminated prematurely after three influenza seasons. | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Low number of participants enrolled in the study at the time that the study was terminated limits conclusions that can be derived from the study data.

Notes: