



Clinical trial results:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Inhaled Laninamivir Octanoate TwinCaps® Dry Powder Inhaler in Adults with Symptomatic Influenza A or B Infection

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2013-000582-36 |
| Trial protocol | GB HU EE BG LV BE DE FR |
| Global end of trial date | 13 May 2014 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 |
| This version publication date | 04 September 2016 |
| First version publication date | 04 September 2016 |
| Summary attachment (see zip file) | BTA51-350-201 Study Synopsis (bta51-350-201 synopsis.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | BTA51-350-201 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01793883 |
| WHO universal trial number (UTN) | U1111-1139-1560 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Biota Scientific Management Pty Ltd. |
| Sponsor organisation address | 2500 Northwinds Pkwy., Ste 100, Alpharetta, GA, United States, 30009 |
| Public contact | Clinical Development, Aviragen Therapeutics, Inc., info@aviragentherapeutics.com |
| Scientific contact | Clinical Development, Aviragen Therapeutics, Inc., info@aviragentherapeutics.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 | 11 March 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 May 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of two doses of inhaled laninamivir octanoate (40 and 80mg) delivered via TwinCaps® Dry Powder Inhaler (DPI) in adults with symptomatic presumptive influenza A or B infection.

Protection of trial subjects:

The study was performed in accordance with applicable regulatory and ethical guidelines including the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 June 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Belgium: 35 |
| Country: Number of subjects enrolled | Bulgaria: 95 |
| Country: Number of subjects enrolled | Estonia: 39 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Latvia: 8 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | Mexico: 29 |
| Country: Number of subjects enrolled | United States: 283 |
| Country: Number of subjects enrolled | New Zealand: 9 |
| Country: Number of subjects enrolled | South Africa: 117 |
| Worldwide total number of subjects | 639 |
| EEA total number of subjects | 194 |

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) | 639 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a multi-center study with sites in Belgium, Bulgaria, Estonia, Germany, Hungary, Latvia, United Kingdom, Canada, Mexico, United States, New Zealand and South Africa. The study period was 10 Jun 2013 - 13 May 2014.

Pre-assignment

Screening details:

A total of 639 subjects were randomized (213 in the 40 mg group, 214 in the 80 mg group and 212 in the placebo group).

Period 1

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

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 40 mg laninamivir octanoate |

Arm description:

40 mg dose consists of 2 laninamivir octanoate TwinCaps(R) DPI and 2 laninamivir actanoate matching placebo DPI

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Laninamivir octanoate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

40 mg laninamivir octanoate administered by inhalation

| | |
|--|-------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Laninamivir octanoate matching placebo administered by inhalation

| | |
|------------------|-----------------------------|
| Arm title | 80 mg Laninamivir octanoate |
|------------------|-----------------------------|

Arm description:

80 mg dose consists of 4 laninamivir octanoate TwinCaps(R) DPI

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Laninamivir octanoate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

80 mg laninamivir octanoate administered by inhalation

| | |
|---|-------------------|
| Arm title | Placebo |
| Arm description: | |
| Placebo dose consists of 4 laninamivir octanoate matching placebo DPI | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Laninamivir octanoate matching placebo administered by inhalation | |

| Number of subjects in period 1 | 40 mg laninamivir octanoate | 80 mg Laninamivir octanoate | Placebo |
|---|-----------------------------|-----------------------------|---------|
| Started | 213 | 214 | 212 |
| Completed | 201 | 204 | 204 |
| Not completed | 12 | 10 | 8 |
| Respiratory distress during spirometry | - | - | 1 |
| Subject could not complete spirometry | 1 | - | - |
| Consent withdrawn by subject | 3 | 7 | 3 |
| Subject was randomized in error | 1 | - | - |
| Subject met exclusion criteria #12 | 1 | - | - |
| Dosing error | - | 1 | - |
| Lost to follow-up | 5 | 1 | 3 |
| Subject unable to complete measurements | 1 | - | - |
| Protocol deviation | - | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------|
| Reporting group title | 40 mg laninamivir octanoate |
| Reporting group description: 40 mg dose consists of 2 laninamivir octanoate TwinCaps(R) DPI and 2 laninamivir actanoate matching placebo DPI | |
| Reporting group title | 80 mg Laninamivir octanoate |
| Reporting group description: 80 mg dose consists of 4 laninamivir octanoate TwinCaps(R) DPI | |
| Reporting group title | Placebo |
| Reporting group description: Placebo dose consists of 4 laninamivir actanoate matching placebo DPI | |

| Reporting group values | 40 mg laninamivir octanoate | 80 mg Laninamivir octanoate | Placebo |
|---|-----------------------------|-----------------------------|---------|
| Number of subjects | 213 | 214 | 212 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 38.5 | 39.2 | 39.3 |
| standard deviation | ± 11.95 | ± 12.49 | ± 12.6 |
| Gender categorical Units: Subjects | | | |
| Female | 119 | 128 | 115 |
| Male | 94 | 86 | 97 |

| Reporting group values | Total | | |
|--|----------------------------|--|--|
| Number of subjects | 639 | | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) | 0 0 0 0 0 0 | | |

| | | | |
|----------------------|-----|--|--|
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 362 | | |
| Male | 277 | | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | 40 mg laninamivir octanoate |
| Reporting group description: 40 mg dose consists of 2 laninamivir octanoate TwinCaps(R) DPI and 2 laninamivir actanoate matching placebo DPI | |
| Reporting group title | 80 mg Laninamivir octanoate |
| Reporting group description: 80 mg dose consists of 4 laninamivir octanoate TwinCaps(R) DPI | |
| Reporting group title | Placebo |
| Reporting group description: Placebo dose consists of 4 laninamivir actanoate matching placebo DPI | |
| Subject analysis set title | Intent-to-Treat-Infected (ITT-I) Analysis Set - 40 mg |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The ITT-I Analysis Set was the primary efficacy population and consisted of all ITT subjects with laboratory-confirmed influenza A or B infection by at least 1 virological method (qRT-PCR or qCulture) on either Day 1 or Day 3) | |
| Subject analysis set title | Intent-to-Treat-Infected (ITT-I) Analysis Set - 80 mg |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The ITT-I Analysis Set was the primary efficacy population and consisted of all ITT subjects with laboratory-confirmed influenza A or B infection by at least 1 virological method (qRT-PCR or qCulture) on either Day 1 or Day 3) | |
| Subject analysis set title | Intent-to-Treat-Infected (ITT-I) Analysis Set - Placebo |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The ITT-I Analysis Set was the primary efficacy population and consisted of all ITT subjects with laboratory-confirmed influenza A or B infection by at least 1 virological method (qRT-PCR or qCulture) on either Day 1 or Day 3) | |

Primary: Time to alleviation of influenza symptoms

| | |
|-------------------------------------|---|
| End point title | Time to alleviation of influenza symptoms |
| End point description: | |
| End point type | Primary |
| End point timeframe: Day 1 to 14 | |

| End point values | Intent-to-Treat-Infected (ITT-I) Analysis Set - 40 mg | Intent-to-Treat-Infected (ITT-I) Analysis Set - 80 mg | Intent-to-Treat-Infected (ITT-I) Analysis Set - Placebo | |
|----------------------------------|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 67 | 75 | 89 | |
| Units: hours | | | | |
| median (confidence interval 95%) | 102.3 (80.6 to 114.8) | 103.2 (89 to 138.3) | 104.1 (93 to 140.7) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Primary Efficacy Variable(s) - 80 mg to Placebo |
| Comparison groups | Intent-to-Treat-Infected (ITT-I) Analysis Set - Placebo v Intent-to-Treat-Infected (ITT-I) Analysis Set - 80 mg |
| Number of subjects included in analysis | 164 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.818 |
| Method | Logrank |

| | |
|---|--|
| Statistical analysis title | Copy of Primary Efficacy Variable(s) - 40 mg to... |
| Comparison groups | Intent-to-Treat-Infected (ITT-I) Analysis Set - Placebo v Intent-to-Treat-Infected (ITT-I) Analysis Set - 40 mg |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.251 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 - end of study (Day 29 or early termination)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Safety Analysis Set - 40 mg |
|-----------------------|-----------------------------|

Reporting group description:

All subjects who received study treatment were included in the evaluation of safety, regardless of whether the study was completed per protocol.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Safety Analysis Set - 80 mg |
|-----------------------|-----------------------------|

Reporting group description:

All subjects who received study treatment were included in the evaluation of safety, regardless of whether the study was completed per protocol.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Safety Analysis Set - placebo |
|-----------------------|-------------------------------|

Reporting group description:

All subjects who received study treatment were included in the evaluation of safety, regardless of whether the study was completed per protocol.

| Serious adverse events | Safety Analysis Set - 40 mg | Safety Analysis Set - 80 mg | Safety Analysis Set - placebo |
|---|-----------------------------|-----------------------------|-------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 212 (0.47%) | 1 / 211 (0.47%) | 1 / 211 (0.47%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 212 (0.47%) | 0 / 211 (0.00%) | 0 / 211 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumomediastinum | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 0 / 211 (0.00%) | 1 / 211 (0.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis bacterial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 212 (0.47%) | 0 / 211 (0.00%) | 0 / 211 (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 |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 1 / 211 (0.47%) | 0 / 211 (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 |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Safety Analysis Set - 40 mg | Safety Analysis Set - 80 mg | Safety Analysis Set - placebo |
|---|--------------------------------|--------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 56 / 212 (26.42%) | 60 / 211 (28.44%) | 52 / 211 (24.64%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 212 (2.36%) | 1 / 211 (0.47%) | 1 / 211 (0.47%) |
| occurrences (all) | 6 | 1 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 1 / 211 (0.47%) | 3 / 211 (1.42%) |
| occurrences (all) | 0 | 1 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 3 / 211 (1.42%) | 3 / 211 (1.42%) |
| occurrences (all) | 0 | 3 | 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 212 (3.30%) | 6 / 211 (2.84%) | 2 / 211 (0.95%) |
| occurrences (all) | 7 | 6 | 2 |
| Nausea | | | |
| subjects affected / exposed | 3 / 212 (1.42%) | 1 / 211 (0.47%) | 4 / 211 (1.90%) |
| occurrences (all) | 3 | 1 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 2 / 211 (0.95%) | 3 / 211 (1.42%) |
| occurrences (all) | 0 | 2 | 3 |
| Gastritis | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 212 (1.42%) 3 | 0 / 211 (0.00%) 0 | 0 / 211 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 212 (4.25%) | 3 / 211 (1.42%) | 5 / 211 (2.37%) |
| occurrences (all) | 9 | 3 | 5 |
| Nasal congestion | | | |
| subjects affected / exposed | 8 / 212 (3.77%) | 3 / 211 (1.42%) | 3 / 211 (1.42%) |
| occurrences (all) | 8 | 3 | 3 |
| Infections and infestations | | | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 4 / 212 (1.89%) | 6 / 211 (2.84%) | 9 / 211 (4.27%) |
| occurrences (all) | 5 | 7 | 9 |
| Sinusitis bacterial | | | |
| subjects affected / exposed | 0 / 212 (0.00%) | 5 / 211 (2.37%) | 2 / 211 (0.95%) |
| occurrences (all) | 0 | 5 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 212 (0.47%) | 5 / 211 (2.37%) | 0 / 211 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 212 (0.47%) | 0 / 211 (0.00%) | 3 / 211 (1.42%) |
| occurrences (all) | 1 | 0 | 3 |
| Oral herpes | | | |
| subjects affected / exposed | 3 / 212 (1.42%) | 0 / 211 (0.00%) | 1 / 211 (0.47%) |
| occurrences (all) | 3 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 12 November 2013 | <p>The sample size calculation in the original protocol assumed that approximately 70% of subjects would be confirmed as having influenza A or B infection, meaning that a total of 636 subjects would be required, in order to provide the target sample size of 444 influenza-infected subjects. However, of the first 105 subjects enrolled in this study, only 48 (45.7%) were confirmed as being infected with influenza. Additionally, the enrolment rate into the pharmacokinetic (PK) sub-study has been very low. In order to address this, Biota has made three key changes to the protocol:</p> <ul style="list-style-type: none">• Previously, subjects were eligible if they had either (a) a measured fever at screening or (b) they had a self-reported history of fever within the past 24 hours and they had taken anti-pyretic medication within 6 hours of screening. However, out of the first 105 subjects enrolled in this study, a subset of 42 subjects had a measured temperature of $\geq 38.0^{\circ}\text{C}$ at screening. Of those, 27 (64.3%) were confirmed as being infected with influenza, compared to 21/63 (33.3%) who did not have a measured fever at screening. This suggests that a measured fever at screening is strongly predictive of influenza infection. Consequently, for the remainder of the study, subjects will only be eligible if they have a measured fever at the screening visit.• To mitigate the risk of completing the study with fewer than the target number of influenza-positive subjects, the study will now aim to recruit up to 900 randomized or 444 laboratory-confirmed influenza infected subjects, whichever occurs first. This means that if the upper limit of 900 randomized subjects is reached first, the target sample size would still be achieved if approximately 50% of enrolled subjects have laboratory-confirmed influenza A or B infection.• The number of sites participating in the PK sub-study will be substantially increased, and the cap on the number of subjects who can participate in the sub-study has been removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The Sponsor ended recruitment in the study prior to attainment of the originally planned number of PCR-positive subjects (444 planned vs. 248 actual) for strategic reasons unrelated to any safety issues or interim data reviews.

Notes: