

**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	v2 (current)
This version publication date	02 December 2017
First version publication date	04 September 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Adverse events were reported for only the on-treatment period of the study in the original posting. Correcting to include AEs for the overall study.

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
Consent withdrawn by subject	3	7	3
Subject could not complete spirometry	1	-	-
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: 3 %

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	31 / 212 (14.62%)	27 / 211 (12.80%)	21 / 211 (9.95%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 212 (3.30%)	2 / 211 (0.95%)	3 / 211 (1.42%)
occurrences (all)	8	2	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 212 (3.77%)	6 / 211 (2.84%)	2 / 211 (0.95%)
occurrences (all)	8	6	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 212 (4.72%)	4 / 211 (1.90%)	6 / 211 (2.84%)
occurrences (all)	10	4	6
Nasal congestion			
subjects affected / exposed	9 / 212 (4.25%)	5 / 211 (2.37%)	3 / 211 (1.42%)
occurrences (all)	9	5	3
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	6 / 212 (2.83%)	6 / 211 (2.84%)	9 / 211 (4.27%)
occurrences (all)	8	7	9
Urinary tract infection			
subjects affected / exposed	1 / 212 (0.47%)	7 / 211 (3.32%)	1 / 211 (0.47%)
occurrences (all)	1	7	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: