2.0 SYNOPSIS

Name of Sponsor/Company: Biota Scientific Management Pty Ltd	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: Laninamivir Octanoate TwinCaps® Dry Powder Inhaler		
Name of Active Ingredient: Laninamivir Octanoate		
Title of Study: 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		
Investigators: 103 Principal Investigators recruited subjects in the study		
Study Centers: 103 study centers in 12 countries (Belgium, Bulgaria, Canada, Estonia, Germany, Hungary, Latvia, Mexico, New Zealand, South Africa, United Kingdom, and United States)		
Publication (Reference): None to date.		
Study Period: First subject enrolled: 10 June 2013 Last subject completed: 13 May 2014	**Phase of Development:** 2	
Objectives: **Primary Objective:** The primary objective of the study was to evaluate the efficacy of 2 dose levels of inhaled laninamivir octanoate (40 and 80 mg) delivered via TwinCaps® Dry Powder Inhaler (DPI) in adults with symptomatic presumptive influenza A or B infection. **Secondary Objectives:** • To evaluate the safety and tolerability of laninamivir octanoate • To evaluate the incidence of secondary bacterial infections and the use of antibiotics • To further evaluate the efficacy of laninamivir octanoate via secondary and exploratory efficacy endpoints • To evaluate the quantitative changes in virus shedding • To investigate the development of resistance to laninamivir by phenotypic and genotypic analyses • To investigate the impact of treatment of influenza with laninamivir octanoate on Quality of Life		
Methodology: Subjects were eligible to participate if they had symptomatic presumptive influenza A or B infection and were able to be randomized within 40 hours following the first symptom onset. Eligible subjects were randomly allocated to receive laninamivir octanoate 40 mg or 80 mg or placebo delivered by TwinCaps® DPI and were to receive their first dose within 44 hours of first symptom onset. The study drug (laninamivir octanoate or placebo) was administered in 2 dosing sessions: the first in the clinic on Day 1 and the second by the subject at home 12 to 18 hours after the first dosing session. In the case of the 40 mg group, all active compound was delivered during the first dosing session.		

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Subjects returned to the clinic on Days 3, 5, 8, and 15 for study assessments, and on Day 29 for a final study visit.

A pharmacokinetic (PK) substudy was conducted at selected sites. Samples for PK were collected on Day 1 (1 and 2.5 to 4 hours after the first dose), Day 2 (after the second dose; this was an optional visit), Day 3, Day 5, and Day 8.

A Data Monitoring Committee (DMC) monitored the data as it accumulated for potential, unexpected, or frequent adverse events (AEs) and laboratory abnormalities. It also reviewed AEs of clinically diagnosed bacterial infection. The first DMC meeting was conducted following enrollment of the first 50 subjects and then at a frequency determined by the DMC.

Number of Subjects (Planned and Analyzed):

Planned: As many as 900 subjects were to be randomized (in order to achieve 444 with laboratory-confirmed influenza). Actual: A total of 639 subjects were randomized (252 with laboratory-confirmed influenza); 248 subjects were analyzed for efficacy (Intent-to-Treat-Infected Analysis Set) and 634 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:

Male and female adults aged 18 to 64 years, inclusive, with symptomatic presumptive influenza A or B infection (defined as fever [≥38.0°C or ≥100.4°F] with at least 1 moderate systemic symptom and at least 1 moderate respiratory symptom), able to be randomized within 40 hours after onset of influenza illness, and, if female, not pregnant or breastfeeding. Subjects were not to have used antiviral treatment for influenza within 2 weeks, or received an influenza virus vaccine within 3 weeks of screening.

Test Product, Dose and Mode of Administration, Batch Number:

Laninamivir octanoate was delivered via Twincaps® DPI (a breath-actuated, single-use disposable inhaler). Subjects were to inhale either laninamivir octanoate 40 mg or 80 mg in 2 dosing sessions, 12 to 18 hours apart (2 TwinCaps® DPI per session). In the case of the 40 mg group, all active compound was delivered during the first dosing session (the second session contained placebo).

Duration of Treatment:

Two dosing sessions, 12 to 18 hours apart.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo was delivered via Twincaps® DPI. Subjects were to inhale placebo in 2 dosing sessions, 12 to 18 hours apart (2 TwinCaps® DPI per session).

Criteria for Evaluation:

Efficacy: Efficacy assessments included Influenza Intensity and Impact Questionnaire (Flu-iiQ™) and body temperature. The primary efficacy parameter was the time to alleviation of influenza symptoms (cough sore throat, nasal congestion, headache, feeling feverish, body aches and pains, and fatigue) and fever for ≥24 hours. The time of symptom alleviation was defined as the period from start of study drug to the start of the first 24-hour period in which influenza symptoms were scored as mild (1) or absent (0) and fever was absent (≤38.0°C). Secondary efficacy parameters included time to return to normal body temperature, time to alleviation of systemic and respiratory influenza symptoms, Flu-iiQ™ symptom domain scores, area under the curve (AUC) of the duration and severity of mean all Flu-iiQ™ symptom scores, and determination of dose-response relationship.

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Safety: Safety was evaluated by AEs, concomitant medications, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital signs, physical examination, electrocardiograms (ECGs), and spirometry.

Virology: virus shedding, antibody titers and resistance monitoring (blood samples and nasopharyngeal swabs)

Other: Quality of Life sections of the Flu-iiQ™

Exploratory: Pharmacokinetics

Statistical Methods:

Primary efficacy analysis performed on the Intent-to-Treat-Infected (ITT-I), Intent-to-Treat (ITT) and Per-Protocol (PP) Analysis Sets: A log rank test (non-parametric) for median time to alleviation stratified by geographic region, with associated upper and lower 95.02% confidence intervals (CIs). A bootstrap method was used to calculate the median difference between treatment groups for time to alleviation with associated upper and lower 95.02% CIs of the median difference. The generalised Wilcoxon test was presented as supplemental to the log rank test since it provided greater weighting towards earlier event differences. Kaplan-Meier survival distribution curves (survival distribution function versus for time to alleviation) were graphically displayed. Additionally, inverse failure probability curves (where failure probability was 1 minus survival probability) were also constructed.

Secondary efficacy analysis performed on ITT-I and ITT Analysis Sets: Time to event endpoints were analyzed using the same methodology as the primary variable with the exception of dose-response relationship, mean time to alleviation supplementary analysis and any sub-group analyses. The Flu-iiQ™ Total Domain Scores were initially analyzed, using a repeated measures analysis of variance model on scores assessed twice daily (AM and PM) up to Day 14, and secondly as a change from baseline at end of Days 1, 3, 5, 7 and 14. Area Under the Curve of Total Symptom Score (severity) Over Time ($AUC_{1 \text{ to } 14}$, $AUC_{1 \text{ to } 7}$ and $AUC_{7 \text{ to } 14}$) was summarized and analyzed using a two-way analysis of covariance model with treatment, geographical region, and baseline symptom score as fixed effects and time since onset (<24h, ≥24h) as a covariate. Proportion of Subjects with Complications Resulting from Influenza in each treatment group were presented for each study period (on-treatment, follow-up and overall) and compared using the Cochran-Mantel-Haenszel test stratified by geographic region. The homogeneity among strata for treatment effects was examined using the Breslow-Day test.

Quality of Life was analyzed using the same methodology as described for Flu-iiQ™ domain scores for total domains scores and changes from baseline, but gender and age were also included in the mixed model. The AUC was analyzed in the same way as for Flu-iiQ™ domain AUC.

Pharmacokinetic: Descriptive statistics on PK concentrations of laninamivir octanoate and its metabolite, laninamivir, were presented. A population PK model was developed and potential covariates (demographics, and laboratory and spirometry data) were formally tested using stepwise procedures.

Virology: Tabular summaries were presented. The viral load from double nasopharyngeal swabs was quantified by quantitative reverse-transcriptase polymerase chain reaction (expressed as log10 vp/mL) and qCulture as (expressed as log10 TCID50/mL) from samples collected. Viral load parameters were analyzed using the ITT-I Analysis Set based on a subset of subjects who were positive for the influenza virus at Day 1 (baseline). For quantitative viral culture data, supplemental analysis for the ITT-I Analysis Set was produced with samples beyond the established stability (more than 48 hours from sample

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collection to freezing) excluded from these summaries. The viral antibody titer ratio was presented by descriptive statistics.

Exploratory Analyses included time to alleviation of individual symptoms, partial response, symptom rebound, cumulative proportion of subjects whose body temperature/symptoms improved, and number of days for any moderate/severe, any severe symptoms or temperature ≥38.0°C.

Safety: Descriptive statistics were used to summarize AEs, laboratory data, vital signs, ECGs and spirometry**.**

Summary – Conclusions:

There was no notable imbalance of any characteristics or parameters between the 40 mg, 80 mg, and placebo groups at baseline.

Efficacy Results:

While the primary endpoint was not met, there were notable responses for some of the secondary endpoints, in particular virological activity, alleviation of systemic symptoms, return to normal body temperature, and secondary bacterial complications. Unexpectedly, and for reasons that are not clear, the response of the 80 mg dose could not be well differentiated from placebo whereas the 40 mg dose performed considerably better. All analyses were conducted on the ITT-I Analysis Set unless otherwise stated:

Primary outcome: Time to alleviation of Flu-iiQ™ influenza symptoms (cough, sore throat, nasal congestion, headache, body aches and pains, feeling feverish and fatigue) and fever for ≥24 hours. Median time to the alleviation of influenza symptoms and fever was similar between all 3 dose groups (102.3 hours, 103.20 hours, 104.10 hours in the 40 mg, 80 mg and placebo groups). The median differences in time were not statistically significant (log rank test p-values 0.251 and 0.818, respectively, and Wilcoxon test p-values 0.068 and 0.585, respectively).

Secondary outcomes:

Time to alleviation of Flu-iiQ™ respiratory domain symptoms was reduced in the 40 mg and 80 mg groups compared with placebo group (median time 84.00, 91.20, and 102.10 hours, respectively [40 mg and 80 mg versus placebo nominal p-values log rank test 0.061 and 0.441, respectively, and Wilcoxon test 0.041 and 0.458, respectively]).

Time to alleviation of Flu-iiQ™ systemic domain symptoms was reduced in the 40 mg and 80 mg groups compared with placebo group (median time 59.30, 75.25, and 78.80 hours, respectively [40 mg and 80 mg versus placebo nominal p-values log rank test 0.029 and 0.798, respectively, and Wilcoxon test 0.012 and 0.573, respectively]).

Time to return to normal body temperature was reduced in the 40 mg and 80 mg groups compared with placebo (median time 25.00, 29.15, and 44.30 hours, respectively [40 mg and 80 mg versus placebo nominal p-values log rank test 0.002 and 0.199, respectively, and Wilcoxin test 0.003 and 0.074, respectively]).

Area under the curve of the total symptom score for Days 1 to 14 was smaller for the 40 mg group (7.70) compared with the 80 mg (8.66) and placebo groups (8.78), reflecting lower severity scores for those in the 40 mg group.

Quality of Life: • The decrease in Flu-iiQ™ Quality of Life scores was slightly greater in the 40 mg group in the impact on emotions domain, suggesting a greater improvement in that domain for that group. As

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well, the percentage of subjects with worsening Quality of Life scores in the 14 days from baseline was smaller in the 40 mg group in each domain compared with placebo and the percentage of subjects with >1 unit of improvement was greater.

Secondary bacterial complications: the incidence in the use of antibiotics during the On-treatment Period (Day 1 to 15) was lower in the 40 mg group (1.9%) compared with the 80 mg and placebo groups (5.7%, and 6.6%, respectively), which was consistent with no secondary bacterial complications reported in the 40 mg group compared with 5.0% in the 80 mg group and 7.8% in the placebo group.

Virology: mean viral titers at Days 3, 5, and 8, were lower in the 40 mg group compared with placebo. The mean difference in titers was statistically significant at Day 3 (van Elteren test p-value <0.001 [qRT-PCR assay] and <0.018 [qCulture assay]).

Resistance (ITT Analysis Set): 4 post-baseline influenza virus isolates with neuraminidase (NA) gene sequence variants were considered to have a high potential for modulating inhibitor binding to NA and, therefore, susceptibility to inhibition by laninamivir. All 4 subjects were negative for influenza (qCulture) by Day 5, and had achieved symptom alleviation by Day 7 or earlier. The findings collectively indicated that these viral variants did not have a detrimental effect on the subjects' response to treatment. Based on the analysis performed to date, none of the other NA gene variant sequences identified among subjects in this study were likely to alter NA inhibition.

Exploratory outcomes:

Individual symptoms: there were reductions in time to alleviation of individual respiratory symptoms (cough, sore throat, nasal congestion) in the 40 mg group and a reduction in median time for cough in the 80 mg group compared with placebo. Likewise, there were reductions in median time to alleviation of individual systemic symptoms (headache, feverish, body aches and pains, and fatigue) in the 40 mg and 80 mg groups compared with placebo.

Safety Results:

Treatment with 40 mg or 80 mg of the study drug was well tolerated:

- The overall incidence of TEAEs during the On-treatment Period (Day 1 to 15) was similar across all 3 groups: 26.4% in the 40 mg group and 28.4% in the 80 mg group compared with 24.6% in the placebo group. The most frequently reported TEAE was bacterial bronchitis across the 3 groups. Across the 40 mg and 80 mg groups combined, the most frequently reported TEAEs compared with placebo were diarrhea, nasal congestion, cough, urinary tract infection and headache.
- The overall incidence of TEAEs considered related to study drug was low (4.4%); the incidence was higher in the 40 mg (5.2%) and 80 mg (5.7%) groups compared with placebo (2.4%). Diarrhea was the most frequently reported AE in both the 40 mg and 80 mg groups.
- The incidence of PSEs in the On-treatment Period was low (2.4%, 6.2%, and 6.6% of subjects in the 40 mg, 80 mg groups, and placebo groups, respectively).
- One subject in the 40 mg group was reported with 2 SAEs during the On-treatment Period and 2 subjects (1 each from the 80 mg and placebo groups) reported SAEs in the Follow-up Period. None of these SAEs were considered to be related to the study drug.
- In the Follow-up Period (Day 16 onwards), the overall incidence of TEAEs was 8.8% (56 of 634 subjects). There was no marked difference in the incidence across the groups.
- There were no remarkable differences in laboratory data, vital signs, physical examinations, ECG,

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or spirometry results across the 3 groups.

- No new safety signal was identified.

Conclusion:

The promising reduction in systemic influenza symptoms, the number of days influenza symptoms were recorded as severe, reduction in viral shedding as measured by both quantitative culture and quantitative RT-PCR, and the impact on secondary symptoms associated with the 40 mg dose of laninamivir octanoate are encouraging. Taken together with the extensive Japanese clinical experience of laninamivir octanoate 40 mg as approved for use in Japan, these data suggest that further development of the drug, including endpoint discussions with regulatory authorities, is warranted. There were no safety concerns after administration of either a 40 mg or 80 mg dose.