Laurent
PHARMACEUTICALS

COVER PAGE FOR STATISTICAL ANALYSIS PLAN FOR INTERIM SAMPLE SIZE RE-ESTIMATION/FUTILITY ANALYSIS

Protocol Title: RESOLUTION: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE II/III STUDY OF THE EFFICACY AND SAFETY OF LAU-7b IN THE TREATMENT OF ADULT HOSPITALIZED PATIENTS WITH COVID-19 DISEASE

Document date: 03 Oct 2023

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Statistical Analysis Plan

For
Interim Sample Size Re-Estimation/Futility Analysis

Protocol #:	LAU-20-01
Protocol Title:	Resolution: A Double-Blind, Randomized, Placebo-Controlled, Phase II/III Study Of The Efficacy And Safety Of LAU-7b In The Treatment Of Adult Hospitalized Patients With COVID-19 Disease
Project Code:	[Enter Project Code]
Study Phase:	II/III
Trial Design:	Multicentre, randomized, double-blind (patients, investigators and blinded study staff), placebo-controlled Phase II/III study of LAU-7b for the treatment of COVID-19 disease in patients at a higher risk than the general COVID-19 disease population to develop complications while hospitalized
Study Drugs:	LAU-7b (fenretinide) oral capsules or matching placebo
Patients:	In the pilot Phase 2 portion, a total of 232 patients were randomized; in the Phase 3 extension study, 264 additional patients with a Health Status score 3 or 4 at the baseline, aged >= 18 years of age, with confirmed COVID-19 will be enrolled, with sample size re-estimation /futility analysis to optimize sample size or stop the trial early.
Treatment Period:	Study drug is administered once daily for up to 14 days
Sponsor Contact:	Jean-Marie Houle Laurent Pharmaceuticals Inc. [redacted]
Analysis Contact:	Guowei Zhong Alimentiv Inc. [redacted]
Date:	October 3, 2023
Status:	Final

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Date of Final Protocol (including all amendments):	16-Apr-2020 (Version 1.0) 11-May-2020 (Version 1.1) 31-May-2020 (Version 1.2) 15-Jun-2020 (Version 1.3) 18-Oct-2020 (Version 1.4.2) 05-May-2022 (Version 2.3) 04-Aug-2023 (Version 2.4)
Date of Final Plan	03-Oct-2023

I have reviewed the Addendum for the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

Author:

[redacted] Date:

Reviewed by:

[redacted] Date:

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Reviewed by:

[redacted] Date:

[redacted] Date:

1. Introduction

This document describes the process/procedures to be followed for the interim sample size re-estimation for protocol Resolution: A Double-Blind, Randomized, Placebo-Controlled, Phase II/III Study Of The Efficacy And Safety Of LAU-7b In The Treatment Of Adult Hospitalized Patients With COVID-19 Disease.

As stated in the protocol, an interim sample size re-estimation will occur once 42% (112) of the 264 planned patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early. The aim of this interim analysis is to ensure that the study extension is adequately powered and self-sufficient to be confirmatory.

This document describes the scope and approach for the analysis.

2. Interim Analysis Efficacy Endpoint

When 112 patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early, a formal sample size re-estimation based on the primary efficacy endpoint derived from the 7-point Ordinal Scale data will be carried out and reported to the DSMB for formulation of a recommendation to the Sponsor.

The endpoint is defined as proportion of patients requiring mechanical ventilation (includes extra-corporeal membrane oxygenation-ECMO) AND/OR deceased (all causes) by Day 60 (Ordinal scale scores 6-7 inclusively):

$$\frac{\text{No. of patients requiring mechanical ventilation AND/OR deceased by Day 60}}{\text{No. of patients within a given arm}}$$

At the data snapshot, subjects who are enrolled in the study but have not yet reached Day 60 will not be included in the interim analysis. Subjects who discontinue before Day 60 will be considered having mechanical ventilation AND/OR deceased by Day 60. If the pattern of discontinuation before Day 60 is severely imbalanced between the two treatment groups, additional analysis such as complete case analysis will be performed to estimate the conditional power. The additional information will be provided to, and considered by, the DSMB in making the recommendation to the sponsor.

3. Interim Analysis Population

The 112 patients that have either completed the Day 60 primary endpoint assessment or terminated their study participation early.

4. Sample Size Re-estimation Procedure and Decision Rule

Given that the interim analysis is to be performed at 42% of the initial sample size (264 subjects), the targeted power is 90%, and the maximum allowable sample size is set at 1.75 times of the initial sample size (462 subjects), the conditional power cut-off value (CPmin) is calculated to be 38.6%. If the conditional power (CP) is between 38.6% and 90%, the number of subjects per treatment arm will be increased, up to the maximum allowable sample size for this study (462), to recover the targeted power of 90%.

To evaluate the CP against the promising zone, the following parameters at the interim analysis are taken:

$$n_1 = n_{1t} + n_{1c}$$

$$P_{1t} = \#\text{ of responders} / \#\text{ of subjects in treatment arm}$$

$$P_{1c} = \#\text{ of responders} / \#\text{ of subjects in SOC arm}$$

$$Z_1 = \frac{|P_{1t} - P_{1c}|}{\sqrt{\frac{P_{1t} \times (1 - P_{1t})}{n_{1t}} + \frac{P_{1c} \times (1 - P_{1c})}{n_{1c}}}}$$

Where number 1 indicates interim analysis, n_1 is the # of subjects included in the interim analysis (i.e. 112) P_{1t} is the response rate for the treatment arm, P_{1c} is the response rate for the SOC arm and Z_1 is the Z statistic at the interim.

The CP can be calculated using the Mehta and Pocock, 2009 equation 6 as follows:

$$CP = 1 - \phi\left(\frac{Z_\alpha\sqrt{n_2} - Z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{Z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$

Where $Z_\alpha = Z_{0.025}$, $n_2 = 264$, ϕ is the cumulative distribution function and $\tilde{n}_2$ = 152 (264 – 112).

If CP is ≥ planned power of 90%, the recommendation is to continue with the planned sample size of 264.

If CP is found to be within the promising range of 38.6% and 90%, the recommendation is to continue the trial with the sample size increased to n_2^*, which can be obtained as follows:

$$n_2^* = \max\left(\min(n_1 + \tilde{n}_2', n_{max} = 462), n_1 = 264\right)$$

where $\tilde{n}_2'$ is the incremental sample size calculated as

$$\text{ceil}\left(\frac{n_1}{{z_1}^2} \times \left(\frac{Z_\alpha \times \sqrt{n_2} - Z_1 \times \sqrt{n_1}}{\sqrt{n_2 - n_1}} + Z_\beta\right)^2\right)$$

and $Z_\beta = Z_{0.9}$.

If CP is < CPmin, a non-binding recommendation of “stop for futility” is to be issued. However, it will be at the sponsor’s discretion to continue the trial with the planned sample size without breaching the protocol or data integrity.

Since sample size re-estimation occurs only when the interim conditional power falls in the pre-specified “promising” range, and the study will not stop for efficacy regardless of the conditional power, the overall alpha will be protected, and the final analysis will be carried out using conventional tests, without the need for weighing the stage 1 and 2 results or adjusting the alpha value.

Note that the promising zone will be re-calculated based on the actual number of subjects included in the sample re-estimation.

5. Data cut-off Time

The data cut-off time is when 112 patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early. The data logic checks (DLC) will be performed to ensure data quality and queries will be issued as needed prior to the analysis.

6. Unblinding

The data transfer and analysis after interim database lock will be tested in a blinded fashion using the dummy treatment code. The dummy treatment code will be used by the blinded statistician and programmers in the production of the SDTM datasets, alongside the output deliverables (for testing purpose only).

Upon completion, the data sets and programs will be sent to the dedicated unblinded statistician at Alimentiv Inc., and the randomization list that uncovers the actual treatment assignment will be provided to the unblinded statistician and incorporated into the data. The unblinded statistician will perform the analysis and generate the output deliverables in an unblinded fashion. In case of any communication between the blinded and unblinded parties, the communication (e.g. emails) should be kept in a blinded fashion, i.e. not in any way reveal the treatment assignment or the unblinded results.

Unblinded results and output deliverables, together with the results of additional analysis in the case of uneven discontinuation pattern for the two treatment groups, will be password protected and communicated to the dedicated unblinded members of the DSMB upon completion by the unblinded statistician. If the conditional power is below the promising zone, the futility criteria will be deemed met and a recommendation to stop further enrollment will be communicated to the DSMB. The communication plan from the DSMB is to report one of the three following statements based on the results: 1) “carry on with the original sample size”; 2) “increase sample size to XXX”

or 3) “Stop the study for futility”. The recommendation shall be conveyed to the sponsor by the DSMB.

7. Results and Deliverables

Results will be tabulated comparing the rates between the treatment arm and placebo and the recommendation will be presented in the format indicated in section 8.

The unblinded interim efficacy results will be provided to the DSMB.

8. Report format

Proportion of Ordinal scale scores 6-7				
Treatment	Placebo	Conditional Power	Recommendation	Z1
x.x% (p_{1t}/n_{1t})	x.x% (p_{1c}/n_{1c})	xx.xx%	1) Carry on with the original sample size; 2) Increase sample size to XXX; 3) Stop the study for futility.	x.xxxx