Laurent
PHARMACEUTICALS

COVER PAGE FOR STATISTICAL ANALYSIS PLAN ADDENDUM

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: 29 Oct 2024

NCT number: 04417257

Statistical Analysis Plan

Addendum

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 29, 2024
Status:	Version 1.0

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Version of Final SAP	Version 1.0
Date of Final Plan	29-Sep-2023

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

Author:

[redacted] Date:

Reviewed by:

[redacted] Date:

Signature Approval Page
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Version of Final SAP	Version 1.0
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Reviewed by:

[redacted] Date:

[redacted] Date:

1. Introduction

This document is an addendum to the Statistical Analysis Plan (SAP) for protocol LAU-20-01, entitled “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”. The analyses as planned in the SAP were completed following database lock, and the results initially released on 14MAR2024.

The primary endpoint for this study is the proportion of patients requiring mechanical ventilation AND/OR deceased (all causes) by Day 60. Missing observations are treated as a non-response (i.e. patient not considered as alive and free of respiratory failure) for the primary analyses on ITT. Other imputations of missing data are included as sensitivity analyses.

Following the release of the results and review of the draft Clinical Study Report (CSR), the sponsor determined that the imputation method specified in the protocol (Section 12.7.1) and the SAP (Section 6.4.1) for handling missing data in the primary endpoint analysis was implausible from a clinical perspective. Specifically, treating all missing observations as non-response by assigning patients to the worst possible health status categories (i.e. not considered as alive and free of respiratory failure) was deemed overly conservative and unreflective of patients' actual health conditions. The sponsor hence proposed a revised approach to imputation for the primary analysis. The new method will treat missing observations as is, without any imputation, i.e. Including all patients with available health status/survival data at Day 60 for the primary analysis. Several additional analyses of efficacy outcomes were also requested for better understanding and interpretation of the data.

This SAP addendum serves to formally document the changes to the imputation method for the primary analysis of the primary endpoint, and the additional analyses as requested by the sponsor. For a complete description of the analysis for this study, please refer to the Statistical Analysis Plan (SAP), dated 29SEP2023.

2. Primary Endpoint Analysis

The primary analysis for the primary endpoint will treat missing observations as is without any imputation, i.e. Including all patients with available health status/survival data at Day 60 for the primary analysis. This is the complete case analysis.

The results from this approach will be presented as the primary analysis in the CSR, while the original analysis using the imputation method specified in the protocol and the SAP will still be included in the CSR, but referred to as the “former planned primary analysis”.

3. Additional Analyses

The updated imputation method is defined as follows:

- For the primary analyses on the intent-to-treat (ITT) population, missing observations will not be imputed.
- The original method, which assigned missing observations to non-response (health status 6-7), will continue to be reported as part of the CSR to ensure full transparency.
- The sensitivity and supplementary analyses will remain the same.
- The table numbering follows the ICH E3 guideline for CSR. Since both the pilot study and the extension study are included in the CSR, along with the additional tables described in this SAP addendum, the numbering rule is described as follows:
    - Main tables from the pilot study are numbered without any suffix.
    - Main tables from the extension study are numbered with the suffix “e”.
    - Additional tables described in this SAP addendum are numbered with “.1e” replacing the suffix “e”.
- The impacted tables to be differentiated from the main tables in the extension study are listed below:
    - Table 14.2.1.1**.1**e Primary Analysis: Proportion of Patients Requiring Mechanical Ventilation (includes ECMO) and/or Deceased by Day 60 – ITT;
    - Table 14.2.1.4**.1**e Supplemental Analysis: Proportion of Patients Requiring Mechanical Ventilation (includes ECMO) and/or Deceased by Day 60 Analyzed by Logistic Regression;
    - Table 14.2.3.1**.1**e Proportion of Patients Alive and Free of Respiratory Failure on Day 29 ITT;
    - Table 14.2.3.2**.1**e Proportion of Patients Alive and Free of Respiratory Failure on Day 29 PP;