Laurent
PHARMACEUTICALS

COVER PAGE FOR STATISTICAL ANALYSIS PLAN FOR INTERIM FUTILITY ANALYSIS

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

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Statistical Analysis Plan

For
Interim Futility Analysis

Protocol #:	LAU-20-01
Protocol Title:	Resolution: A Double-Blind, Randomized, Placebo-Controlled, Pilot Phase II Study Of The Efficacy And Safety Of LAU-7b In The Treatment Of Adult Hospitalized Patients With COVID-19 Disease
Project Code:	
Study Phase:	II
Trial Design:	Multicentre, randomized, double-blind (patients, Investigators and blinded study staff), placebo-controlled Phase II 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
Patients:	Up to approximately 240 patients aged >= 18 years of age, with confirmed COVID-19 and at least one of the predefined co-morbidities
Treatment Period:	Study drug will be administered once daily for up to 14 days
Sponsor Contact:	Jean-Marie Houle Laurent Pharmaceuticals Inc. [redacted]
Analysis Contact:	Guowei Zhong McDougall Scientific Ltd. [redacted]
Date:	February 22, 2021
Status:	Final

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Date of Final Protocol:	18-Oct-2020 (Version 1.4.2)
Amendments:	N/A
Date of Final Plan	N/A

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

Author:

[redacted]

Reviewed by:

[redacted]

1. Introduction

This document describes the process/procedures to be followed for the interim futility analysis for protocol RESOLUTION – LAU-20-01: A double-blind, randomized, placebo-controlled, pilot phase II 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, a formal futility analysis is proposed to prematurely stop the trial for futility if there are major safety or efficacy concerns. The aim of this futility analysis/stopping rule is to ensure that there is a high probability of stopping the study when there is a true underlying excess risk of disease deterioration with the use of the investigational product, and a low probability of stopping the study when there is no such risk.

This document describes the scope and approach for the analysis.

2. Interim Futility Analysis Endpoint

When approximately 50 patients per arm are available for health status/efficacy data from Day 29, a formal futility analysis 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 the proportion of patients alive and free of respiratory failure, corresponding to Ordinal Scale scores of 1 to 4 inclusively, on Day 29:

$$\frac{\text{No. of patients alive and free or respiratory failure on Day 29}}{\text{No. of patients with available data on Day 29}}$$

3. Interim Futility Analysis Population

All patients enrolled in the study, who received a minimum of one dose of study medication, and with available health status data on Day 29 at the data cut-off time are included in the analysis.

4. Study Stopping Rule

The study will be stopped for futility if the observed investigational product rate is numerically lower than the observed control (placebo) arm rate. Based on the protocol, assuming that the true underlying control arm (placebo) rate is 78% and using a normal approximation when comparing proportions, it is estimated that when using this rule:

a. the probability of stopping the study is ~5% if the true underlying investigational product rate is 90%.

b. the probability of stopping the study is ~50% if the true underlying investigational product rate is 78% (equal to the assumed true underlying control arm rate).

c. the probability of stopping the study is ~91% if the true underlying investigational product rate is 66%.

5. Data cut-off Time

The data cut-off time is when approximately 50 patients per arm will be available for health status/efficacy data from Day 29. 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 will be carried out strictly in a blinded fashion. The dummy treatment code will be used by the blinded statistician and programmers in the production of the SDTM datasets, alongside the output deliverables.

Upon completion, the data sets and programs will be sent to the dedicated unblinded statistician at McDougall Scientific, 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 will be password protected and communicated to the dedicated unblinded members of the DSMB upon completion. The recommendation regarding whether the trial should be stopped based on the unblinded result from the DSMB shall be provided to the sponsor. The stopping rule is to stop the trial if the proportion of patients alive and free of respiratory failure in the treatment arm is numerically lower than in the placebo arm.

7. Results and Deliverables

Results will be tabulated comparing the rates between the treatment arm and placebo. A listing detailing the health status scale by patient on Day 29 will be provided.

The interim futility analysis results will be provided to the DSMB, along with the safety outcomes as described in the DSMB charter.