Laurent
PHARMACEUTICALS

COVER PAGE FOR STATISTICAL ANALYSIS PLAN

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

Document date: 04 Aug 2021

NCT number: 04417257

Statistical Analysis Plan

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 or matching placebo
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 is 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:	August 4, 2021
Status:	Version 1.0

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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)
Date of Final Plan	04-Aug-2021

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

Author:

[redacted]

Reviewed by:

[redacted]

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Reviewed by:

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition
AE	Adverse Event
APR	Analysis Programming Requirements
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinical Significance
DMP	Data Management Plan - details of how data are managed throughout the trial
DMP	Data Management Plan
EDC	Electronic Data Capture (i.e. eCRF)
ITT	Intent-to-Treat
K-M	Kaplan Meier
LSMean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MMRM	Mixed Model Repeated Measures
MSL	McDougall Scientific Ltd - CRO contracted to perform the data management, statistical programming and analysis functions
NCS	Non-Clinical Significance
PD	Protocol Deviations
PP	Per Protocol
QoL	Quality-of-Life
SAEs	Serious Adverse Events
SAF	Safety
SAP	Statistical Analysis Plan
SDLC	Systems Development Lifecycle
SE	Standard Error
SOC	Standard-of-Care
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
WHODD	World Health Organization Drug Coding Dictionary managed by the Uppsala Monitoring Centre

1. Background

SARS-CoV2 is a novel coronavirus identified as the cause of the coronavirus disease 2019 (COVID-19) that began in Wuhan, China in late 2019, and rapidly qualified as a pandemic. No effective therapy currently exists for treatment. While most patients with COVID-19 disease are thought to have a favorable prognosis, older patients and those with chronic underlying conditions may have worse outcomes with hyper-inflammation in the lungs and rapid progression to acute respiratory distress syndrome (ARDS) that may result in a requirement for mechanical ventilation, thus creating an unsustainable burden for the health care system and a rapidly escalating crisis

One of the main mechanisms for ARDS is cytokine storm, a deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokines. Anti-inflammatory treatments that aggressively inhibit inflammation, such as corticosteroids, are less expected to have a significant benefit during the viral response phase of the disease, when the immune response is required for to effectively fight the infection and prevent its escalation to lung hyper-inflammatory phase that may require respiratory support. However, mild non-steroidal anti-inflammatory drug (NSAID)s (such as ibuprofen and acetaminophen) are useful for decreasing fever in coronavirus patients. Recent results from the RECOVERY clinical study with dexamethasone corticosteroid therapy in hospitalized COVID-19 patients showed a reduction in death incidence by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen without invasive mechanical ventilation. However, it did not reduce mortality in patients not receiving respiratory support at randomization.

LAU-7b is a novel once-a-day oral form of fenretinide that is under development by Laurent Pharmaceuticals for its ability to trigger the body's own resolution of inflammation without interfering with its immune response (a "pro-resolving" effect). LAU-7b is believed to act on the resolution phase of inflammation by endogenously modulating the metabolism of docosahexaenoic acid (DHA), an essential fatty acid involved in the process of healing and return to homeostasis after a pathogen attack or injury. Therefore, LAU-7b can be used as a balancing factor able to keep the inflammation process under control, complementing the action of typical anti-inflammatory drugs.

LAU-7b's lipid modulation activity was shown to be in conjunction with pro-resolving pathways of inflammation (MAPK/ERK, NF-kB, cPLA2), which also play a role in virus cellular entry, replication and avoidance of host defense system. By inhibiting these molecular pathways, LAU-7b may not only interfere with virus spread in the body, but also prevent the escalation of the pro-inflammatory response resulting during the infection process. Due to its antiviral properties and its pro-resolving effects on inflammation, LAU-7b is therefore being proposed as a therapeutic with potential to reduce COVID-19 disease severity, maintain a balanced immune-inflammatory response and prevent disease progression toward an Acute Respiratory Distress Syndrome, especially in patients at risk because of their age, underlying conditions, or both.

An independent Data and Safety Monitoring Board (DSMB) monitors the safety of this study and a DSMB charter is in use and described separately.

Additionally, a formal interim (futility) analysis is described in a separate document. The unblinded result based on the primary efficacy endpoint will be presented to the DSMB for recommendation to the sponsor with regards to whether the trial should be stopped.

2. Objectives

2.1. Primary Objective

To evaluate the efficacy of LAU-7b therapy + Standard-of-Care (SOC) relative to placebo + SOC in patients with COVID-19 disease with confirmed SARS-CoV-2 infection (target population).

2.2. Secondary Objective(s)

- To assess the safety of LAU-7b therapy in all patients who received at least one dose of the study medication (Safety Population), compared to placebo + SOC.
- To assess the efficacy of LAU-7b therapy at decreasing the rate of COVID-19 disease related aggravation in the target population (ITT population) (such as a worsening of one category on the ordinal scale, onset of severe categories on the ordinal scale, need for transfer to Intensive Care Unit (ICU), need for mechanical ventilation and death, among others), compared to placebo + SOC.
- To measure the impact of LAU-7b therapy on the time course of the COVID-19 disease in the target population, as depicted by mean ordinal scale change from baseline at each assessment time, and by time-to-event analyses (time to an improvement of one category on the ordinal scale, time to recovery (defined), time to ICU transfer, time to mechanical ventilation, and time to death), compared to placebo + SOC.
- To assess the antiviral activity of LAU-7b therapy as depicted by the time to attain an undetectable viral load representative of virology remission, compared to placebo + SOC.
- To assess the benefit of LAU-7b therapy on the Quality of Life, compared to placebo + SOC.

3. Study Design

RESOLUTION is a randomized, double-blind (patients, investigators and blinded study staff), placebo-controlled pilot study of LAU-7b against confirmed COVID-19 disease. All patients, hospitalized because of their health condition and aggravating factors, suspected or confirmed to be infected with SARS-CoV-2 virus, will undergo the SOC for their stage of COVID-19 disease at their institution. This design is appropriate for this phase of development as it caters to individuals at a greater risk of aggravation but do not yet require intensive care.

Up to approximately 240 patients will be recruited and randomized for the treatment phase of the study with the expectation that at least 200 patients complete the study as per protocol. Patients will be enrolled at approximately 15 centers in the United States of America and in Canada. Below is a schematic of the study structure:

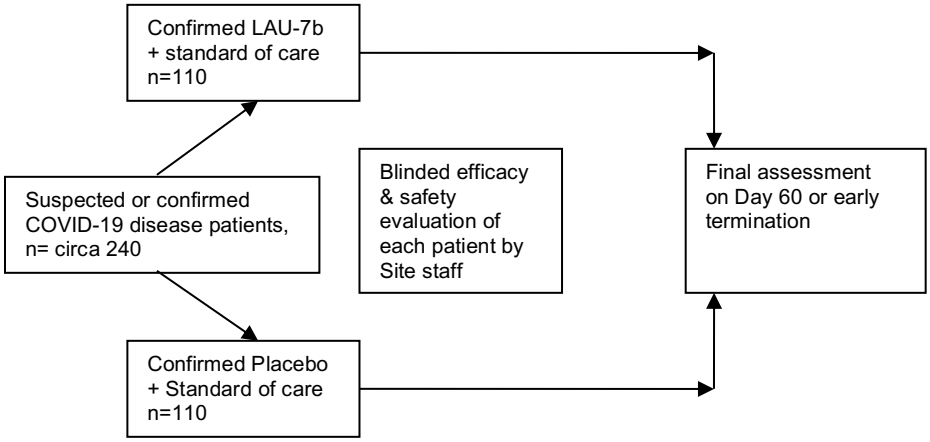


Figure 1: Overall structure of the study

Adult male and female patients 18 years and older, exhibiting a symptomatology typical of COVID-19 disease, suspected or confirmed to be positive for SARS-CoV-2 and admitted in the hospital for preventative reasons, will be offered to participate in this pilot interventional study. There is no time limit between the onset of symptoms, the start of hospitalization or the confirmation of SARS-CoV-2 infection, and the screening.

If agreeable, patients will be consented and eligibility will be confirmed. Eligible patients will be randomized (1:1) to receive in a blinded fashion, either LAU-7b 300 mg per day (3 capsules of 100 mg each), once a day for 3 days, or a matching placebo administered in the same fashion (the “Initial Treatment”).

Patients who receive a positive SARS-CoV-2 test result during Days 1-3, will continue the treatment with LAU-7b 200 mg per day (2 capsules of 100 mg each), once a day for the remaining 11 days, or a matching placebo administered in the same fashion, on top of SOC (the “Follow-up Treatment”).

For suspected cases, if the SARS-CoV-2 test result is negative or not received by pre-dose on Day 4, patient will be withdrawn from further treatment, will be assessed for safety at time of withdrawal only or until ongoing AE have resolved/stabilized and in any instances no later than Day 29, and will revert to SOC.

All eligible and confirmed patients will be treated and closely monitored for a period of up to 2 weeks or until early termination. The last day of follow-up will be on Day 60, or may correspond to early termination due to withdrawal or death, whichever comes first. An aggravation preventing oral intake of study medication in its intact form is not an early termination as the patients will continue to undergo the SOC and planned study assessment, whenever possible.

Dose and Administration

A study treatment consisting of up to fourteen (14) consecutive days of treatment with LAU-7b or placebo, administered as follows:

- Initial Treatment on Days 1-3: LAU-7b 300 mg per day (3 capsules of 100 mg each), or matching placebo, once a day for 3 days in the fed state, preferably the main meal of the day, followed by the
- Follow-up Treatment on Days 4-14: LAU-7b 200 mg per day (2 capsules of 100 mg each), or matching placebo, once a day in the fed state, preferably the main meal of the day. Only patients confirmed with SARS-CoV-2 infection no later than pre-dose on Day 4, will receive the Follow-up Treatment.
- The capsules should not be broken down to administer their content through a feeding tube if the patient is intubated and cannot ingest anymore the capsules intact.

3.1. Primary Outcome

The main efficacy variable is the 7-point ordinal scale of the patient status and the primary efficacy endpoint is the proportion of patients alive and free of respiratory failure on Day 29 (Ordinal scale scores 1-4 inclusively), compared between the active and control (placebo) arms of the study; all patients will undergo the SOC at their institution. The ordinal scale is presented below:

1) Not hospitalized, no limitations on activities
2) Not hospitalized, limitation on activities
3) Hospitalized, not requiring supplemental oxygen
4) Hospitalized, requiring supplemental oxygen
5) Hospitalized, on non-invasive ventilation or high flow oxygen devices
6) Hospitalized, on invasive mechanical ventilation or ECMO (extra-corporeal membrane oxygenation);
7) Death.

3.2. Secondary Outcomes

1) Safety: The safety of LAU-7b therapy will be assessed through the monitoring of treatment emergent adverse events and serious adverse events, vital signs including oxygen saturation and body temperature, symptom-directed physical examinations and safety laboratory tests. It is important to note that most of these assessments are also SOC for hospitalized patients with COVID-19 disease and changes from baseline can depict improvement or worsening of the condition.

2) Efficacy: Patient status on the 7-point ordinal scale on Days 14 and 29; compared between the active and control (placebo) arms of the study.

3) Efficacy: Rate of all-causes death, depicted by a change from baseline in the ordinal scale position to category 7 by Days 29 and 60, compared between the active and control (placebo) arms of the study.

4) Efficacy: Rate of COVID-19 disease-related aggravation, depicted by a change from baseline in the ordinal scale position of at least one category, compared between the active and control (placebo) arms of the study.

5) Efficacy: Rate of COVID-19 disease-related transfer to ICU, depicted by a change from baseline in the ordinal scale position to categories 5 or 6, compared between the active and control (placebo) arms of the study.

6) Efficacy: Rate of COVID-19 disease-related transfer to mechanical ventilation, depicted by a change from baseline in the ordinal scale position to category 6, compared between the active and control (placebo) arms of the study.

7) Efficacy: Mean change from baseline of the ordinal scale patient status as a function of assessment time, compared between the active and control (placebo) arms of the study.

8) Efficacy: Time to an improvement of one category on the ordinal scale patient status, compared between the active and control (placebo) arms of the study.

9) Efficacy: Time to recovery, defined here as a move from baseline to categories 2 or 1 on the ordinal scale patient status (first occurrence if more than one), compared between the active and control (placebo) arms of the study.

10) Efficacy: Time to mechanical ventilation, defined here as a move from baseline to category 6 on the ordinal scale patient status, compared between the active and control (placebo) arms of the study.

11) Efficacy: Time to death, defined here as a move from baseline to category 7 on the ordinal scale patient status, censored to Day 60 if it happens later than Day 60, compared between the active and control (placebo) arms of the study.

12) Efficacy: Duration of hospitalization (days) within the study period Days 1-60, compared between the active and control (placebo) arms of the study.

13) Efficacy: Time to attain an undetectable viral load through oropharyngeal swabs done at specified times, compared between the active and control (placebo) arms of the study. This is an optional endpoint for clinical sites able to obtain serial samples until discharge of patients.

14) Quality-of-Life: The change from baseline to Days 14, 29, 45 and 60 in the score obtained on the EQ-5D-5L survey, a well-documented scoring system that has been widely used and validated as a QoL assessment tool, compared between the active and

control (placebo) arms of the study, in patients reaching Days 14, 29, 45 and 60 and able to fill the questionnaire [redacted].

3.3. Safety Outcomes

Safety outcomes are described in section 4.2.

3.4. Randomization

Randomization will be stratified by clinical site and patients will be randomized in a 1:1 double-blinded fashion to either

- the LAU-7b + SOC (active) group or
- the placebo + SOC (control) group

3.5. Blinding

The study will remain blinded, including sponsor's staff and McDougall team members who are responsible for creating the programs to produce the outputs, until the end of the study (i.e. database lock), unless circumstances require unblinding (i.e. DSMB, interim safety analysis, futility analysis and final analysis).

3.6. Schedule of Events

	Screening Pre-randomization on Day 1	Randomization on Day 1	In-Hospital Days 2, 3, 4, 6, 7, 9, 10, 11, 13	In-Hospital Days 5, 8, 12	End-of–Hospital Stay or Day 14	Contacts in hospital after Day 14 or after discharge every 3 days up to Day 29	Contacts on Day 29 and Day 45	End-of-Study / Long term follow-up Day 60	Early termination due to (-) SARS-CoV-2 or else
Visit number	**0**	**1**	**2, 3, 4, 6, 7, 9, 10, 11, 13**	**5, 8, 12**	**n/a**	**variable**	**n/a**	**n/a**	**n/a**
Verification of ID and age	X								
Informed consent	X								
Inclusion/Exclusion criteria	X	X							
Demographics and Medical History	X								
Concomitant Meds	X			X	X	X	X		X
Standard of Care procedures									
Directed Physical Examination	X			X	X[3]				
Height, weight and Body Mass Index calculated[1]	X				X				
Vital Signs including respiratory rate, oxygen saturation and body temperature[2]	X	X	X	X	X				X
Oropharyngeal Swab (optional for certain sites)	X			X	X[3]				
COVID-19 symptom check	X	X	X	X	X	X	X	X	

	Screening Pre-randomization on Day 1	Randomization on Day 1	In-Hospital Days 2, 3, 4, 6, 7, 9, 10, 11, 13	In-Hospital Days 5, 8, 12	End-of–Hospital Stay or Day 14	Contacts in hospital after Day 14 or after discharge every 3 days up to Day 29	Contacts on Day 29 and Day 45	End-of-Study / Long term follow-up Day 60	Early termination due to (-) SARS-CoV-2 or else
Safety laboratory tests, including hematology with differentials[4], serum chemistry[5] and urinalysis[6]	X			X	X[3]				
Study-specific procedures									
Pregnancy Test for women (serum or urine)	X				X				X
Health status using Ordinal Scale	X		X	X	X	X	X	X	
QOL: EQ-5D-5L	X				X		X	X	
Randomization		X							
Dispensing of Initial Treatment		X							
Dispensing of Follow-up Treatment			X on Day 4 only						
Study drug verification[7]					X	X			
Open-ended safety questions				X	X[3]	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X

[1] Height only measured/estimated during Visit 0
[2] According to SOC, may be done on several occasions each day; for the purpose of data collection for the study, collect twice per day during hospitalization
[3] Will not be repeated if assessment done within 2 days from the discharge day
[4] Hematology: CBC, hemoglobin, hematocrit, differentials, platelets
[5] Serum Chemistry: Includes at a minimum creatinine, BUN, bilirubin, alkaline phosphatase, AST, ALT, albumin
[6] Urinalysis: According to SOC, could include pH, urobilinogen, protein, blood, bilirubin and glucose
[7] Verification will be done prior on discharge day, remaining study medication will be provided to Patient for at-home administration, where applicable.
[8] Contacts in hospital after Day 14 or after discharge will have a one-day window (i.e. ± 1 day on either side of the target visit day).

4. Data Management

4.1. Data Management

Data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall Scientific Ltd. All clinical research staff will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition, Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data have been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor, or the Sponsor delegate, and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

The responsible Data Manager will lock each subject's data files when all the criteria noted above are satisfied for that subject.

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at McDougall and are identified by the project code [redacted].

All data activities will be performed on validated computer systems as per 21CRF11 and kept under control, according to McDougall's SOPs. All programming will be performed in SAS version 9.4 or higher under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in [redacted] Canada.

4.2. Coding

Adverse Events (AEs) and Medical History will be coded using MedDRA version 23.

Concomitant medications will be coded using the most current version of WHODD at the beginning of coding, version March 1, 2020.

All coding will be approved by the sponsor prior to data base lock.

4.3. Missing Data

Primary outcome:

Missing observations will be treated as a non-response (i.e. patient not considered as alive or free of respiratory failure) for the primary analyses on intent-to-treat (ITT) population (See Section 6.4.1 Primary Analysis). This method of imputation will be considered as the primary method of imputation.

A worst-case scenario where all placebo patients with missing data will be considered as responders and all LAU-7b treated patients with missing data will be considered as non-responders will also be used for missing observation of the primary outcome.

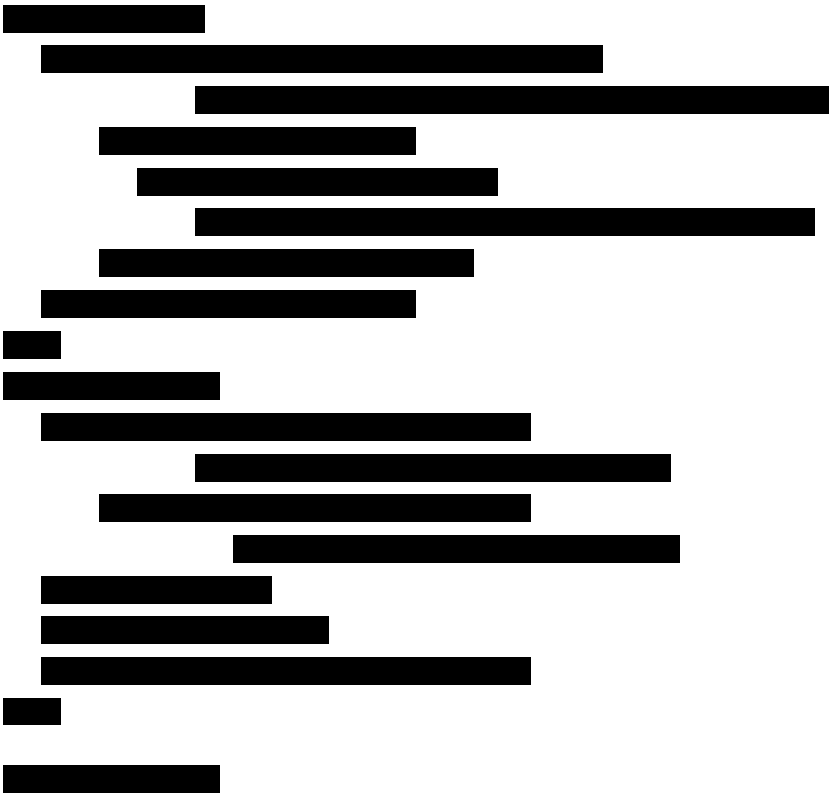
Additionally, a multiple imputation of the 7-point ordinal scale of the patient Health Status will be performed, in which the missing data will be predicted based on demographic and prognostic factors at baseline (age, gender, country, 7-point ordinal scale health status at baseline, diabetes, cardiovascular disease, chronic pulmonary conditions (COPD, asthma and emphysema), obesity, laboratory tests indicative of a higher risk of COVID-19-related complications) as well as the discharge status (completed or discontinued). Specifically, missing primary endpoint measurement based on health status data on Day 29 will be imputed using full

conditional specification (fcs) method with logistic regression based on missing at random (MAR) assumption. The imputation process involves 3 principal tasks (using random seed 12345 to ensure reproducibility of the results):

1) The missing data is imputed (estimated from observed data) using PROC MI to create 20 imputed datasets;

2) Each imputed dataset is then analyzed using the exact binomial test to obtain the estimates of binomial proportions of the primary endpoint in each treatment group, and the difference between these proportions;

3) The results from 20 imputed datasets are then pre-processed and combined using PROC MIANALYZE.



[redacted]

Secondary outcome:

No imputation will be performed explicitly.

5. Change to Analysis as Outlined in the Protocol

An additional secondary endpoint is added for secondary analysis per sponsor's request: the proportion of patients Alive and Free of Respiratory Failure on Day 14 (Section 6.4.2).

Subgroup analysis consisting of 3 subgroups is added per sponsor's request for analyzing the primary endpoint and 4 secondary endpoints described in 6.4.3.

No sensitivity analysis will be performed for any secondary endpoints because secondary endpoints are used for hypothesis generation and not testing.

Time to event endpoints in the presence of death as a competing event will be analyzed using an extension of Cox proportional hazards model. Accounting for the presence of a competing event such as death is deemed more suitable for some of the time to event endpoints and provide more reliable estimates on the treatment effect. Details are described in Section 6.4.2.

Body weight and BMI changes from screening will not be analyzed by any inferential statistical tests and will be summarized only by descriptive statistics. Body weight and BMI were not specified as study endpoints in the protocol.

The safety endpoint of looking at TEAEs related to COVID-19 is added to provide a more comprehensive safety profile for this COVID trial.

The protocol indicates that Chi-square will be used unless a certain cell falls below 5 counts. However, Fisher exact will provide superior precision based on permutation and it does not rely on any assumption of distribution. Therefore, Fisher exact will be used wherever applicable in this study.

6. Statistical Methods

6.1. Analysis Populations

6.1.1. The intent-to-treat (ITT) population

This is a modified ITT population as it will include all patients randomized to a treatment group who are randomized and receive at least one dose of the study drug. The ITT population will be used for the primary analyses of all study endpoints, taking into consideration the specific

populations described below. The patients will be kept in their randomized treatment arm for the analyses.

6.1.2. The per-protocol (PP) population

PP population will include all patients randomized to a treatment group to whom at least 12 days of study treatment are administered in accordance with the protocol (i.e. without major protocol deviations as pre-identified prior to the database lock) and without interruption triggering withdrawal from further treatment. The PP population will serve as the basis for secondary analyses of all study endpoints. The patients will be kept in the treatment arm that they actually received for the analyses.

6.1.3. The safety (SAF) population

SAF will include all patients randomized to a treatment group who received at least one dose of study drug treatment. This population will serve as the basis for analyses of all safety endpoints. The patients will be kept in the treatment arm that they actually received for the analyses.

6.2. Calculated Outcomes

The following are the key endpoints derived from the study data for analysis. Complete documentation of the calculations and data manipulation required to go from the clinical database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Alive and Free of Respiratory Failure on Day 29 (or other time point)

= Y if ordinal scale score ranges from 1 to 4, inclusively

= N if ordinal scale score ranges from 5 to 7, inclusively

All-causes Death by Day 29 (or other time point)

= Y if death of any cause occurs on or before Day 29 (or other time point)

= N otherwise

COVID-19 Disease-related Aggravation

= Y if a change from baseline in the ordinal scale position increases at least one category at any point in time from randomization up to Day 60

= N if a change from baseline shows no change or decreases by Day 60

COVID-19 Disease-related Transfer to ICU

= Y if a change from baseline in the ordinal scale position increases to categories 5 or 6 at any point in time from randomization up to Day 60

= N otherwise

COVID-19 Disease-related Transfer to Mechanical Ventilation

= Y if a change from baseline in the ordinal scale position increases to category 6 at any point in time from randomization up to Day 60

= N otherwise

Age (yr)

= year of consent date – birth year, if consent day is after or the same as birthday, or

= year of consent date – birth year – 1, if consent day is before birthday

BMI (kg/m^2) = 10000*weight (kg) / $[Height (cm)]^2$

First Dose Date, i.e. Date of first study treatment = Date of Visit 2 (typically Day 1 Randomization, but it can happen on Day 2, due to local process, actual Day to be used)

Study day of an event

= Date of the event – First Dose Date + 1, if it occurs on or after the first study treatment, or

= Date of the event – First Dose Date, if it occurs before the first study treatment.

Time since Last Intake (days) = Event date (i.e. date of AE leading to death, SAE onset, AE leading to discontinuation of the study) – Date of last intake of study drug

Duration of Study Drug Exposure (days) = Last dosing date – First Dose Date + 1 regardless of any interruptions in dosing. If the last dose date of study drug is missing, the patient's discontinuation or completion date will be used for analysis purpose.

Dosing Compliance (%) = 100 × ([total number of caps dispensed – caps returned (or known/reported to not have been taken)]/(caps expected to have been taken), where caps expected to have been taken = 3 per day * 3 days + 2 per day * 11 days = 31.

Change from Baseline = Assessment at post baseline Visit – Assessment at Baseline, where “Assessment” is the measurement or assessment of study endpoints (e.g. vital signs, lab results, etc.). Baseline is the last non-missing assessment prior to first study treatment.

Time to the first occurrence of Event = Date of the first occurrence of event (or censored date) – First Dose Date + 1

Time in hospitalization (days) = Date of hospital discharge - Date of hospitalization start (i.e. Day 1) + 1. Duration of rehospitalization in days, if any, will be added to the total duration.

Quality of Life Questionnaire EQ-5D-5L scoring: in short, the 5 dimensions will be combined into a 5-digit number, e.g. “21111” and compared with the location-dependent value sets (i.e. US value set) for extracting the scores.

Day 14: the actual Day 14 based on first dose date with +/- 1 day time window.

6.3. Interim Futility Analysis

This section is detailed in a separate document.

6.4. Analysis Methods

All calculations described in this SAP will be performed using SAS version 9.4 or higher resident on the Windows 2012R2 server at McDougall in [redacted], Canada.

6.4.1. Primary Outcome Analysis

The analysis of the primary outcome consists of three analyses, the primary analysis, the sensitivity analyses and the supplementary analysis.

Primary analysis:

Primary analysis is based on ITT population. The variable for primary analysis is Alive and Free of Respiratory Failure on Day 29, which is derived from the 7-point ordinal scale of the patient Health Status (Section 6.2 Calculated Outcomes):

$$\frac{\text{No. of patients alive and free of respiratory failure on Day 29}}{\text{Total number of patients in ITT in treatment arm}}$$

A Fisher exact test will be used to test the difference in proportion between the LAU-7b and Placebo groups. This will be performed using SAS FREQ procedure. The alpha level is 5% (one-sided, right-tailed).

Sensitivity analysis:

To allow plausible assumptions on missing data handling and evaluate their impacts on the primary analysis, sensitivity analyses will be using two imputation methods: worst scenario and multiple imputation (Section 4.3 Missing Data) based on ITT population. A Fisher exact test will be performed for the primary endpoint using each of the imputation methods.

Supplementary analysis:

There are two supplementary analyses: primary endpoint analyzed based on PP population and logistic regression based on ITT population for selecting prognostic factor(s) that is (are) statistically significant.

Supplementary analysis 1 – using PP population to represent the best (per the protocol) scenario and to supplement the primary analysis which represents the conservative condition based on the ITT population. Similarly, a Fisher exact test will be performed for the primary endpoint based on PP population.

Supplementary analysis 2 – using logistic regression to estimate treatment effect conditioned on the screened prognostic factors at baseline (i.e. age groups, gender, race, Heath Status Ordinal

score, comorbidities, country) - will also be performed using SAS LOGISTIC procedure and covariate selection will be performed based on p-value. Comorbidities are pre-specified at enrollment including:

1) Controlled or uncontrolled diabetes
2) Pre-existing cardiovascular disease, including hypertension
3) Pre-existing respiratory disease such as COPD, asthma, emphysema
4) Active smoker with a 20 pack-years of smoking
5) Obesity as depicted by BMI≥30
6) Laboratory tests indicative of a higher risk of COVID-19-related complications, such as troponin >1.5 ULN and/or CRP >1.5 ULN
7) Patient aged 70 years and older who, based on the judgment of the Investigator, at a higher risk of developing complications

Comorbidity that is present in all the patients or < 10% within an analysis population, or having missing values > 10% will not be included as it either does not confound the result or hinders the proper functioning of the model.

These prognostic factors will be screened in a stepwise fashion, and those that are considered significant at $p < 0.1$ level will be included/stay in the final model. Odds ratios with two-sided 95% CIs will be presented for the screened prognostic factors as well as the treatment groups in the final model.

6.4.2. Secondary Outcome Analysis

Secondary analysis related to efficacy endpoints is based on both ITT and PP population. No missing data will be imputed. A nominal alpha of 10% (two-sided) will be used for all comparisons. Covariates selected from the supplemental analysis using logistic regression will be included in secondary outcome analyses wherever applicable.

7-point Ordinal Scale of Health Status

Due to the ordinal nature of the ordinal scale health status data, the analysis adopts an ordinal logistic regression model to analyze the primary outcome, i.e. proportional odds cumulative logit model using PROC LOGISTIC, to evaluate the treatment effect. As such, the slope for each variable (e.g. treatment) is constant, while having different intercepts.

Specifically, the treatment group comparison will be based on health status on Day 14. The same model will also be applied for Day 29.

The proportional odds assumption will be tested based on the Chi-Square Score test at 10% significance level. Adjusted (common) odds ratio (OR: LAU-7b vs. placebo) and two-sided exact 90% CI will be provided as measures of strength of association and precision, respectively. The

null hypothesis of no treatment effect can be expressed as H_0: OR = 1 and will be tested at the ≤ 0.1 level using goodness-of-fit likelihood ratio test.

The SAS pseudo code is described below:

[redacted]

where endpoint denotes the health status on either Day 14 or 29 (in a separate model), and at baseline, respectively. The odds ratio, 90% confidence interval, and p-value for LAU-7b vs. Placebo will be reported.

In case of not meeting the proportional odds assumption, the supporting p-value from the Wilcoxon rank sum test will be provided.

Time to Event

All time-to-event endpoints will be analysed using Kaplan-Meier (K-M) method to compare treatment effect in the two groups. Depending on whether there is a competing risk, the Cox regression will be used with the extension to account for competing risk, conditional on the selected covariates.

Time-to-event endpoints in the presence of death as a competing risk will be analysed using Fine and Gray's (1999) extension of the Cox regression that models the cumulative incidence function. These time-to-event endpoints include:

- Time to the first improvement of at least one category on the ordinal scale health status, compared between the two treatment groups. If health status is not improved (remains stable or aggravates) by Day 60, it will be censored at Day 60 (including subjects discharged but were re-hospitalized prior to the first phone contact).
- Time to recovery, defined here as a move from baseline to categories 2 or 1 on the ordinal scale health status (first occurrence if more than one). If health status does not reach categories 2 or 1 by Day 60, it will be censored at Day 60 (including subjects discharged but were re-hospitalized prior to the first phone contact).

Per the protocol, health status records the worst status of the previous day and the previous day is entered on the CRF. However, site staff have recorded the worst score of the discharge day for the day of discharge in reality, due to the reason that there is no "following day" to retrospectively record the score for the day of discharge. As such, a health status score of 2 or 1 is often recorded 3 days after the discharge day on the first phone contact assessment, rendering the typical time to event calculation not accurate. Therefore, the calculation is clarified as follows:

- If a health status of 2 or 1 is recorded prior to or on the discharge date the typical calculation is adopted:

  Date of the first occurrence of event (or censored date) – First Dose Date + 1

- If no such score of 2 or 1 is recorded prior to or on the discharge date, the calculation is:

  Date of hospital discharge (or censored date) + 1 – First Dose Date + 1

because the hospital discharge event implies that the health status of the subject moves to a 2 or 1, and conservatively adding 1 more day to it will ensure a more precise estimation of the time to recovery or first improvement.

However, some patients may be readmitted to the hospital prior to the first phone contact day soon after the first discharge. These subjects, if no score of 2 or 1 is further recorded, cannot be assumed being recovered and will be censored at Day 60.

The pseudo SAS code is described as follows (So et al., 2014):

[redacted]

where `eventcode=1` designates the event of interest (`Status=1`). Variable Status is expected to have 3 values: 0 for censored observations, 1 for patients who experienced the event of interest (e.g. recovery), and 2 for patients who died before the event of interest occurs. The `hazardratio` statement requests the subdistribution hazard ratio for each pair of the treatment groups.

Other time-to-event endpoints in the absence of a competing risk will adopt Kaplan Meier method to compare the two treatment groups using a log-rank test. Cox regression will also be used to compare treatment effect conditional on the selected covariates. These endpoints include:

- Time to mechanical ventilation, defined here as a move from baseline to category 6 on the ordinal scale health status, compared between the active and control (placebo) arms of the study. If health status does not reach category 6 by Day 60, it will be censored at the last available health status assessment. If category 6 is skipped and the subject dies (category 7), it is considered an event. Patients with missing observations (e.g. withdrew consent, lost to follow-up before reaching category 6) will be censored at their last available assessment, if they did not need mechanical ventilation while on study.

- Time to death, defined here as a move from baseline to category 7 on the ordinal scale health status, censored to Day 60 if it happens later than Day 60. Subjects are also censored at the last available visit where the patient is alive if no further ordinal scale health status assessment is available.

- Time to attain an undetectable viral load through oropharyngeal swabs done at specified times, compared between the active and control (placebo) arms of the study. If the viral load remains detectable, it will be censored at Day 14. Patients with missing observations (e.g. withdrew consent, lost to follow-up) will also be censored at Day 14 , if they did not have a swabs with undetectable virus while on study. This is an optional endpoint for clinical sites able to obtain serial samples until discharge of patients. If there is insufficient data for such analysis, the viral load measurements will be tabulated by treatment group and visit, and if available, this time to event endpoint will be presented descriptively (e.g. mean, median, standard deviation, etc.).

The K-M summary table for the time to event endpoint includes:

- Event-free survival (EFS) status (i.e. Number of Events, and Censored)

- Kaplan-Meier estimate of EFS in days (i.e. n, Q1, Median with 95% CI, and Q3)

- Probability of EFS (95% CI) at Day 14, 29, 45 and 60.

- P-value from a log-rank test over treatments as strata

The Cox regression (with/without competing risk) table will report odds ratio comparing treatment groups, 95% CI and the associated p-value.

Duration of Hospitalization

Duration of hospitalization (days) will be obtained from hospital charts, cumulated up to Day 60, will be tabulated by treatment and the means of the two treatment groups will be compared using a t-test. If the data is deem not normally distributed using a Kolmogorov-Smirnov test at 5% level, a Wilcoxon rank sum test will be used instead. Rehospitalization and discharge dates will be provided as an external document by the sponsor and duration of rehospitalization in days, if any, will be added to the total duration.

Rate-related Endpoints

Rate-related endpoints throughout the study will be summarized by treatment groups, and Clopper-Pearson confidence interval at 95% confidence level will be provided. A Chi-square (or Fisher's exact) test will be performed for each rate-related endpoint to compare whether there is a statistically significant difference between the two treatment arms. These endpoints include:

- Rate of all-causes death, depicted by a change from baseline in the ordinal scale position to category 7 by Days 29 and 60

- Rate of COVID-19 disease-related aggravation, depicted by a change from baseline in the ordinal scale position of at least one category
- Rate of COVID-19 disease-related transfer to ICU, depicted by a change from baseline in the ordinal scale position to categories 5 or 6
- Rate of COVID-19 disease-related transfer to mechanical ventilation, depicted by a change from baseline in the ordinal scale position to category 6
- In addition, the proportion of patients Alive and Free of Respiratory Failure on Day 14 (calculated similarly to the Primary Outcome) will be compared between treatment groups.

Quality of Life

The scored Quality of Life (QoL) data will be analyzed using MMRM with change from baseline to Day 14, 29, 45 and 60 as the outcome variable, treatment as fixed effect, time point and EQ-5D-5L score at baseline and selected covariates as covariates, with treatment * timepoint interaction term included. Missing data of the quality-of-life endpoint will not be included. Least squares means will be reported for each timepoint. Comparisons between the two treatment groups on each time point will be estimated by least-squared means. Covariance structure will be using UN if converged, otherwise, AR(1) and CS will be tested in order for the appropriateness of repeated measures:

[redacted]

The estimates of QoL include:

- Least Squares Mean (LSMean) difference between two treatment groups with 95% CI for the effect, Standard Error (SE), and the p-value.
- Estimates of change from baseline to Day 14, 29, 45 and 60 from the MMRM

Change from Baseline of Health Status

The same MMRM model from QoL analysis will be adopted for change from baseline of health status with all available measurements included from each patient. Same statistics from the model as QoL will be reported.

Safety Endpoints

Safety endpoints will be based on SAF population and summarized using only descriptive statistics. The body weight and BMI will be analyzed descriptively in the same way as other safety endpoints, e.g. Vital Signs.

Continuous data will be summarized via PROC MEANS – number of subjects, mean, standard deviation, median and range, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

6.4.3. Subgroup Analysis

The primary statistical analysis of the primary efficacy outcome as described in section 6.4.1 will be performed in the following subgroups at baseline:

- Severity at entry (Health status using Ordinal Scale)
- Age groups (18-44, 45-69, ≥70 years of age)
- Number of comorbidities (1, 2, ≥ 3)

The Fisher exact test will be done on both the ITT and PP populations within each subgroup. Note that the p-values reported for subgroup analyses are not adjusted for multiple comparisons.

Subgroup analyses will also be performed on the following secondary efficacy outcomes based on the ITT and PP populations, using the corresponding statistical methods described in section 6.4.2.

- Rate of all-causes death
- Rate of COVID-19 disease-related transfer to mechanical ventilation
- Time to recovery (defined as a move from baseline to categories 2 or 1)
- Duration of hospitalization

7. Results

All data collected in the clinical database will be at a minimum listed by subject and treatment group in data listings. Summary tables will summarize the data by treatment group if not otherwise stated. Key outcomes which help to define the study subjects or illustrate a safety or efficacy outcome will be tabulated and/or graphed as well.

The organization of the Tables and Listings will be guided by the ICH E3 – Structure and Content of Clinical Study Reports.

7.1. Study Subjects

7.1.1. Patient Disposition

Patient disposition will be summarized for the total enrolled population and by treatment group. The following data will be presented for:

- The number of patients who were screened and randomized;
- The number of patients who were confirmed positive for SARS-CoV-2;
- The number and proportion of patients in each analysis population;
- The number and percentage of patients who completed the study;
- The number and percentage of patients who did not complete the study drug treatment as per protocol and the associated reasons;
- The number and percentage of patients who discontinued prematurely from the study participation (follow-up) and the associated reasons;

Data listings for subject disposition and end of study information, including any additional textual reasons where applicable, will be provided.

Major and critical protocol deviations (PD) will be summarized by pre-specified groups based on the PD tracking log using counts and percentages. All protocol deviations will be presented in by-subject data listing.

7.1.2. Eligibility

The failed eligibility criteria and waiver information, if any, will be listed by subject for the total enrolled population.

7.1.3. Patient Characteristics

7.1.3.1. Demographic and Other Baseline Characteristics

Demographics, i.e. age, sex, race, ethnicity and childbearing potential if females, and baseline vital signs, i.e. height (cm), weight (kg), BMI (kg/m^2), pulse rate (beats/min), respiratory rate (breaths/min), blood pressure (mmHg), O_2 saturation (%) and type of oxygen supplementation if not room air will be summarized. Baseline comorbidities will also be included in this table; eligibility-determining comorbidities and factors will also be tabulated.

The demographics and baseline characteristics summary will be presented for ITT and PP populations. All demographics and baseline characteristics data will be listed.

No inferential analyses will be performed.

7.1.3.2. Medical History

Medical history and COVID-19 symptoms at screening will be summarized by MedDRA System Organ Class and Preferred Term, by treatment group and will be listed by subject based on SAF population.

Medical history and COVID-19 symptoms at screening listings will be presented by patient and will include also year of onset/ended and current ongoing (Yes or No) status.

7.1.4. Study Drug Exposure and Compliance

Duration of study drug exposure and dosing compliance will be summarized descriptively by treatment group based on SAF, alongside the counts and percentages of patients whose compliance are <80% or ≥80%.

Duration of study drug exposure and dosing compliance will be listed, and study drug dispensation information will be listed separately.

7.2. Efficacy Outcomes

All efficacy endpoints will be summarized by treatment groups for ITT and PP populations.

7.2.1. Primary Outcome

The analysis of the primary outcome consists of three analyses, the primary analysis, the sensitivity analysis and the supplementary analysis. Refer to section 7.4.1 for details of statistical methods.

Additionally, a summary table of health status as categorical variable by visit and shift from baseline will be presented. A row that pools category 1 – 4 on each visit will be included in the table.

Health status assessment using ordinal scale results will be listed by subject.

7.2.2. Secondary Outcomes

For the efficacy endpoint: Patient status on the 7-point ordinal scale on Days 14 and 29, the following summary table will be presented:

- A summary table for each of the two days of model statistics (see section 7.4.2 for details)

For each of the following endpoints:

1) Efficacy: Rate of all-causes death by Day 29 and 60
2) Efficacy: Rate of COVID-19 disease-related aggravation
3) Efficacy: Rate of COVID-19 disease-related transfer to ICU
4) Efficacy: Rate of COVID-19 disease-related transfer to mechanical ventilation
5) Efficacy: the proportion of patients Alive and Free of Respiratory Failure on Day 14 (calculated similarly to the Primary Outcome).

a summary table will be presented:

- Overall rate by treatment arm and the p-values from the Chi-square (or Fisher's exact) test will be presented

For each of the following efficacy endpoints:

1) Mean change from baseline of the ordinal scale patient status as a function of assessment time

2) Quality-of-Life: The change from baseline to Day 14, 29 and 45

two summary tables will be presented:

- A summary table of model statistics from MMRM (see section 6.4.2)
- A summary table of change from baseline by each visit

For each of the following efficacy endpoints:

1) Efficacy: Time to the first improvement of at least one category on the ordinal scale patient status.

2) Efficacy: Time to recovery

3) Efficacy: Time to mechanical ventilation

4) Efficacy: Time to death

5) Efficacy: Time to attain an undetectable viral load through oropharyngeal swabs done at specified times (if data is insufficient, this endpoint will be summarized descriptively and refer to section 6.4.2 for details)

two summary tables and a corresponding plot will be presented:

- A K-M summary table by treatment groups (see section 6.4.2 for details);
- A K-M plot with survival curves comparing the two treatment groups;
- A Cox regression table reporting adjusted odds ratio, 95% CI and p-value for treatment vs. placebo.

For the efficacy endpoint: Duration of hospitalization (days) within the study period Days 1-60, compared between the active and control (placebo) arms of the study, a summary table will be presented:

- A summary table by treatment groups and supporting P-value

7.3. Safety Outcomes

The safety profile will primarily be analysed by means of descriptive statistics and qualitative analysis. All summary tables and listings in the section are based on the SAF population.

7.3.1. Adverse Events (AEs)

AEs will be classified as pre-treatment AEs and TEAEs. Pre-treatment AE are those that started after consent signature and before the first dose of study drug and did not increase in severity. TEAE are those that increased in severity or that was appeared at or after the first dose of study drug and before or at the last follow-up, on Day 60, or earlier if follow-up is early terminated. For AEs with missing or incomplete start dates, if there is no clear evidence that the AEs started before or after the first dose of study drug, then the AEs will be classified as TEAEs.

All Treatment Emergent Adverse Events (TEAEs) will be summarized according to primary System Organ Class and Preferred Term based on MedDRA coding. The summaries will focus on the counts of subjects and also the number of events, for each System Organ Class and Preferred Term.

The summaries for TEAEs will be:

1) the number and percent of subjects/events for all TEAEs;
2) the number and percent of subjects for all TEAEs by strongest causality relationship to study drug;
3) the number and percent of subjects/events for all TEAEs related to COVID-19;
4) the number and percent of subjects for all TEAEs by maximum severity;
5) the number and percent of subjects/events for all TEAEs leading to treatment discontinuation;
6) the number and percent of subjects/events for all serious TEAEs;
7) the number and percent of subjects/events for all fatal TEAEs.

For these summaries, patients with multiple events will be counted only once per preferred term. AEs will also be summarized by severity and relationship to study drug. At each level of summarization, the event with the highest level of severity or strongest drug relationship will be presented.

All AEs will be listed by subject. SAEs, early discontinuation from the study due to AE and AE related to COVID-19 will be listed separately. These listings will include treatment, patient's age, duration of follow-up, amount of study drug received, and time since last intake.

7.3.2. Concomitant Medication

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced and categorized as the following:

- Prior medication: Any medication that started before the first dose of study drug, independently of when it ended.

- Concomitant medication: Medication continued or newly received at or after first dose of study drug to the last follow-up on Day 45 or earlier if early-terminated.

A given medication can be classified using the above, in one or more categories. If a medication has a missing or partial missing start/end date or time and cannot be determined whether was taken before the first dose of study drug, or concomitantly, it will be considered as prior and concomitant.

All concomitant medications collected in EDC will be coded based on WHODD and will be tabulated by the therapeutic class (ATC level 2) and chemical subgroup (ATC level 4). Prior medications and concomitant medications will be summarized descriptively based on the SAF population. The number and percentage of coded medications and subjects who used medications will be presented.

All medications will be listed.

7.3.3. Body Measurements and Vital Signs

Body measurements and vital signs (height, weight, BMI, blood pressure, temperature, heart rate, and oxygen saturation and respiration rate) will be presented based on SAF population at each time point using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Change from baseline values for each variable will also be presented by treatment group. Type of oxygen supplementation will be tabulated by treatment group.

The number and percentage of patients that meet the abnormal criteria for with shift changes from baseline of the vital signs during the TEAE period will be presented by treatment group. The specific changes of interest are:

- Diastolic Blood Pressure ≤45 mmHg and decrease from baseline ≥10 mmHg, Diastolic Blood Pressure ≥110 mmHg and increase from baseline ≥10 mmHg;
- Systolic Blood Pressure ≥160 mmHg and increase from baseline ≥20 mmHg, Diastolic Blood Pressure ≤45 mmHg and decrease from baseline ≥10 mmHg;
- Temperature ≤35^{o}C and ≥38^{o}C
- Heart rate ≤50 bpm and decrease from baseline ≥20 bpm, heart rate ≥120 bpm and increase from baseline ≥20 bpm;
- Oxygen saturation values and respiratory rate determined by the Investigator to be clinically abnormal (and reported as an AE). More specifically, the incidence of oxygen saturation being 92% or lower when measured in patient stabilized on room air, will be presented by treatment group.

All vital signs results will be listed, including the clinical significance by visits.

7.3.4. Clinical Laboratory Assessments

Hematology, biochemistry and some urinalysis (i.e. pH, specific gravity) data will be presented in SI units as mean values with variability and (absolute) change from baseline in each laboratory parameters.

Shift-tables for all treatment groups will be made for hematology and biochemistry presenting baseline and post-dose laboratory values categorized as “Low”, “Normal” and “High” according to the reference range. Shift-table for urinalysis will be based on clinical assessments, i.e. “Normal”, “Abnormal, NCS” and “Abnormal, CS”.

Lab results will be listed by lab panels. Abnormal lab results including the clinical significance for each lab panel will be listed separately.

7.3.5. Directed Physical Examination (Symptom- and Disease-Driven)

Directed physical examinations are performed according to the Schedule of Events, and is symptom- or disease-driven. After screening, any clinically significant abnormal findings in physical examination are reported as AEs.

Physical examination results, i.e.

Normal

Abnormal, CS

Abnormal, NCS

will be presented for SAF population and summarized for shift from baseline to each post baseline visit. All findings of physical exams will be reported in a listing, including the clinical significance information.

7.3.6. Electrocardiogram (ECG)

ECG will be presented in a listing by subject.

7.4. Other Analyses

7.4.1. SARS-CoV-2 Infection Confirmation

This information will be presented in a listing by subject.

7.4.2. Pregnancy Test

For female patients, the urine (or serum) pregnancy test: performed / not performed, date, type of pregnancy test and result will be listed.

7.4.3. Open Ended Safety Questions

Open ended safety questions and answers will be listed by subject.

8. Reference

Fine, Jason P., and Robert J. Gray. "A proportional hazards model for the subdistribution of a competing risk." *Journal of the American statistical association* 94.446 (1999): 496-509.

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So, Ying, Guixian Lin, and Gordon Johnston. "Using the PHREG procedure to analyze competing-risks data." *SAS Global Forum*. 2014.