Laurent
PHARMACEUTICALS

COVER PAGE FOR STATISTICAL ANALYSIS PLAN

Protocol Title: ESSOR: A DOUBL**E**-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, ADAPTIVE PHA**S**E 2/3 STUDY OF THE EFFICACY OF LAU-7b IN THE TREATMENT OF ADULT**S** WITH LONG C**O**VID AND MODE**R**ATE TO SEVERE SYMPTOMS

Document date: 28 Aug 2024

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STATISTICAL ANALYSIS PLAN (SAP)

For Phase II Portion

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, ADAPTIVE PHASE 2/3 STUDY OF THE EFFICACY OF LAU-7b IN THE TREATMENT OF ADULTS WITH LONG COVID AND MODERATE TO SEVERE SYMPTOMS

Protocol Number:	LAU-23-01 **Study Phase:** II
Trial Design:	Double-blind, randomized, placebo-controlled, multi-center Study with 2 study portions: Phase II Portion and Phase III Portion. This SAP only covers Phase II Portion (regimen-finding)
Medication/Dosage:	Subjects will be randomized in a 1:1:1 double-blinded fashion to 3 arms: Arm 1: 3 cycles Lau-7b 200 mg/day, once a day for 14 days/cycle Arm 2: 1 cycle Lau-7b 200 mg/day, 2 cycles placebo Arm 3: 3 cycles placebo
Population:	18 years and older, male/female subjects with LONG COVID and moderate to severe symptoms.
Estimated Enrollment:	Up to 270 subjects: 90 in each of the 3 arms
Study/Treatment Duration:	Duration of Study: 24 weeks, including a 12-week treatment period of 3 cycles (12-week core period), with 2-week treatment and 2-week follow-up per cycle, and one telehealth follow-up at Week 24. Study Period: from 20-Nov-2023 to 31-Aug-2024 (estimated)
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Version: Final

Date: 28-Aug-2024

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Date of Final Protocol (including all amendments)	V1.2 02-Oct-2023 V1.3 04-Jan-2024 V1.4 13-Feb-2024

Date of Final Plan: 28-Aug-2024

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

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LIST OF ABBREVIATIONS AND TERMS

Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CD40L	CD40 Ligand, CD154
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CXCL10	Interferon Gamma-induced Protein 10 (IP-10)
DPEMQ	DePaul Post-Exertional Malaise Questionnaire
ECG	Electrocardiogram
EDC	Electronic Data Capture
FACIT	The Functional Assessment of Chronic Illness Therapy
IFNγ	Interferon Gamma

Abbreviation	Definition
IFNL1	Interferon Lambda 1 (IL-29)
IFNL3	Interferon Lambda 3 (IL-28B)
IL-1β	Interleukin 1 Beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
IP	Intra-Peritoneal
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
ME/CFS	Myalgic Encephalomyelitis / Chronic Fatigue Syndrome
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MMRM	Mixed Model for Repeated Measures
PACS	Post-Acute COVID Syndrome
PASC	Post-Acute Sequelae of COVID/SARS-CoV-2
PCS	Physical Component Summary
PEM	Post-Exertional Malaise
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Abbreviation	Definition
SF-36	36-Item Short Form Survey
TEAE	Treatment Emergent Adverse Event
TNF-α	Tissue Necrosis Factor Alpha
WHODD	World Health Organization Drug Dictionary

Definition of Terms

Term	Definition
Alimentiv	Alimentiv Inc. – the CRO contracted to perform statistical planning, programming and analysis functions

1 BACKGROUND

SARS-CoV-2 is a novel coronavirus identified as the cause of the coronavirus disease 2019 (COVID-19). COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death. There is an accumulating body of knowledge confirming that a sizeable proportion of patients have persistent, relapsing or new symptoms occurring after an acute infection and interfering with their daily activities. This is named LONG COVID, it can cause a significant burden on patients and represents a very significant unmet medical need. There are likely multiple, potentially overlapping, causes of LONG COVID, including damage from original infection, lingering residual reservoirs of virus in the body, or a dysregulated immune-inflammatory response damaging small blood vessels or nerves.

LAU-7b (fenretinide oral capsules) is developed as a next generation, host-directed, broadly effective oral COVID-19 therapeutic with dual antiviral and inflammation-controlling activity.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of LAU-7b at reducing the overall disease burden in adults with LONG COVID (also named Post COVID-19 condition, Post-Acute COVID Syndrome (PACS), Post-Acute Sequelae of COVID/SARS-CoV-2 (PASC)).

2.2 Secondary Objectives

The secondary objectives of the study are:

1. To evaluate the safety and tolerability of LAU-7b.
2. To evaluate the efficacy of LAU-7b at improving daily usual activity level.
3. To evaluate the efficacy of LAU-7b at improving the Quality-of-Life.
4. To evaluate the efficacy of LAU-7b at alleviating LONG COVID symptoms.
5. To evaluate the efficacy of LAU-7b at preventing LONG COVID-related unplanned care visits including hospitalization.
6. To evaluate the efficacy of LAU-7b at preventing significant cardiovascular events.
7. To evaluate the activity of LAU-7b on a selection of systemic biomarkers, some depicting the control of inflammation.

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Design

This study (ESSOR) is a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study of LAU-7b for the treatment of LONG COVID in non-hospitalized adults with moderate to severe LONG COVID symptoms.

The primary goal of the study is to evaluate the efficacy of LAU-7b therapy + standard-of-care relative to placebo + standard-of-care at reducing the overall LONG COVID burden by improving multiple dimensions of quality-of-life and alleviating the symptoms.

The study will include two portions:

Phase II Portion (regimen-finding): subjects will be randomized in a 1:1:1 double-blinded fashion to 3 arms:

- Arm 1: 3 cycles LAU-7b 200 mg/day,
- Arm 2: 1 cycle LAU-7b 200 mg/day followed by 2 cycles placebo,
- Arm 3: 3 cycles placebo

Phase III Portion (confirmatory): subjects will be randomized in a 1:1 double-blinded fashion to 2 arms:

- Arm 1: LAU-7b – treatment regimen determined in Phase II Portion,
- Arm 2: placebo

The LAU-7b treatment regimen and sample size estimation of the distinct, self-sufficient Phase III Portion will be determined by the analysis results of the Phase II Portion and formal consultation with regulatory agencies and experts.

This SAP only covers the analysis plan of the Phase II Portion. The analysis of ESSOR's Phase III Portion will be described in a separate SAP.

3.1.1 Biomarker Sampling Sub-Study

The biomarker sampling sub-study is described in detail in Appendix 2 of the Protocol. Overall, it is for ESSOR subjects wishing to contribute blood at specific times during their participation to the study, more specifically at randomization (baseline) and after the first and third cycles of study treatment (Days 15 and 70). This will enable to see the time course of the levels of biomarkers. Lastly, since ESSOR subjects receiving only placebo will also be sampled, they will serve as a control for the subjects receiving 1 or 3 cycles of LAU-7b. The biomarker sampling sub-study will involve up to 100 subjects in total and will only be conducted during the Phase 2 portion of the ESSOR study.

The endpoints of biomarker sub-study and the analyses will be described in Section 6.5.3.

3.2 Primary Endpoint

The primary endpoint will be the overall functional health status at Week 12 compared to baseline. The overall functional health status is evaluated with the physical component summary (PCS) of the SF-36 questionnaire.

3.3 Secondary Endpoints

The secondary endpoints will be:

1. Safety: Incidence of AEs, SAEs as well as AEs leading to study medication discontinuation, from randomization through Week 12.
2. Efficacy: Proportion of subjects achieving a marked improvement (at least “much better”) in their ability to perform usual daily activities as measured with the Patient Global Impression of Change (PGI-Ci), from baseline to Weeks 4, 8 and 12.
3. Efficacy: Change from baseline in the FACIT-Fatigue scale (13-item), from baseline to Weeks 4, 8 and 12.
4. Efficacy: Change from baseline in the DePaul Post-Exertional Malaise Questionnaire (DPEMQ), from baseline to Week 12.
5. Efficacy: The overall functional health status evaluated with the PCS of the SF-36 questionnaire at Weeks 4 and 8, compared to baseline, analyzed along the primary endpoint with the repeated measure analysis of variance.
6. Efficacy: The other aspects of health status (mental, emotional, social...etc.) each evaluated with the SF-36 questionnaire at Weeks 4, 8 and 12, compared to baseline.
7. Efficacy: Proportion of subjects who judge to have regained their daily usual activity level of pre-causative-infection, from randomization through Weeks 4, 8 and 12.
8. Efficacy: Proportion of subjects achieving$\geqslant$25%, $\geqslant$50% or$\geqslant$75% improvement in the DALCI Score at Weeks 4, 8 and 12.
9. Efficacy: Change from baseline in the EQ-5D-5L score at Weeks 4, 8 and 12.
10. Efficacy: Proportion of subjects with relief of at least one core LONG COVID symptom for a minimum of 2 weeks. Relief means a reduction of severity from moderate to none, or severe to mild/none ($\geqslant$2-point Likert score change). From randomization through Week 12.
11. Efficacy: Time to relief of the first core LONG COVID symptom for a minimum of 2 weeks, among those symptoms present at baseline. From randomization through Week 12, censored at Week 12 if no symptoms are relieved by Week 12.

12. Efficacy: Proportion of subjects with a sustained clinical recovery, meaning a relief (as defined above) of all core LONG COVID symptoms, by Week 4, 8 and 12.
13. Efficacy: Change from baseline in the total number of LONG COVID symptoms (core and non-core) based on baseline inventory, at Weeks 4, 8 and 12.
14. Efficacy: Proportion of subjects with LONG COVID related unplanned medical visits (i.e., practitioner's office, urgent care, emergency room < 24h, hospitalization >24 hours) from randomization through Week 12.
15. Efficacy: Proportion of subjects deceased from any cause through Week 12.
16. Efficacy: Proportion of subjects with significant cardiovascular events (resulting in at least an acute care visit, a hospitalization, or an event-related death) through Week 12.

For the longer-term follow-up at Week 24, and separate from the analysis of the above endpoints:

17. Health and survival follow-up: Presence or not of LONG COVID symptoms, general health check-up, significant cardiovascular events and assessment of survival.

For the biomarker sampling sub-study:

18. Changes relative to baseline of measured biomarker values in plasma, serum or blood, by time point.
19. Explore correlations between the measured biomarkers values and effects on clinically relevant endpoints measured in the ESSOR study.

3.4 Randomization

All eligible subjects will be randomized (1:1:1) to receive in a blinded fashion, either:

- ARM 1: Cycles 1, 2 and 3: LAU-7b 200 mg per day (2 capsules of 100 mg each) once a day for 14 days followed by 14 days without capsule intake, per cycle.
- ARM 2: Cycle 1: LAU-7b 200 mg per day, once a day for 14 days followed by 14 days without capsule intake. Cycles 2 and 3: Matching placebo administered in the same fashion followed by 14 days without capsule intake, per cycle.
- ARM 3: Cycles 1, 2 and 3: Matching placebo administered in the same fashion per cycle, each followed by 14 days without capsule intake.

3.5 Blinding

The study will remain blinded, including sponsor's staff and Alimentiv 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 (e.g., final analysis) or partial unblinding (i.e., DSMB analysis for unblinded statistician and DSMB members).

3.6 Study Timeline and Schedule of Events

	Screening (within 7 days of randomization)	Randomization	In person first follow-up (15+/-2 days)	Telehealth Week 4 (28+/-3 days)[7]	Telehealth Week 8 (56+/-3 days)[7]	In Person Week 10 (70+/-2 days)*	In Person Week 12 (84+/-7 days)	Telehealth follow-up Week 24 168 +/-7 days)	Early termination
Visit number	1	2	3	4	5	*	6	7	n/a
Informed consent	X								
Inclusion/Exclusion criteria	X	X							
Demographics and Medical History with grading of causative COVID-19 infection	X								
LONG COVID symptom inventory, including core symptom severity (DALCI score [1])	X	X		X	X		X	X	X
Prior/Concomitant Meds including vaccination	X	X	X	X	X		X		X
Height (screening only[2]) and body weight	X						X		X
Vital signs	X						X		X
Pregnancy status and contraception check	X	X	X	X	X		X		X
Hematology and serum chemistry[3]	X								
Urinary pregnancy test for WOCBP[4]	X	X		X	X				
Biomarker sampling*		X	X			X			
SF-36 questionnaire		X		X	X		X		X
PGI-C				X	X		X		X
FACIT-Fatigue scale		X		X	X		X		X
DePaul Post-Exertional Malaise Questionnaire		X					X		X
Query return to pre-infection usual daily activity level				X	X		X		X
EQ-5D-5L questionnaire		X		X	X		X		X
Query unplanned care visits or hospitalization for COVID and significant cardiovascular events			X	X	X		X	X	X
Randomization[5]		X							
Study drug dispensing[6]		X							
Study treatment compliance check			X	X	X		X		X
Return of drug bottles with or without leftover							X		X
Adverse Events		X	X	X	X		X		X

* The biomarker sampling and the Week 10 visit are only applicable to subjects participating in the sub-study.
[1] According to Section 10.7 of the protocol
[2] Height measured if possible but self-reporting is accepted
[3] Hematology testing: *erythrocytes, hemoglobin, hematocrit, platelets, leucocytes, neutrophils, lymphocytes*. Serum Chemistry testing: *Creatinine, potassium, sodium, calcium, total bilirubin, glucose, alkaline phosphatase, AST, ALT*. Repeat of laboratory tests is allowed during the screening phase only if there are reasons for the Investigator to believe the results are not reliable or do not represent the status of the subject
[4] At the clinic for Screening and Randomization visits, at home for Weeks 4 and 8 visits.
[5] To be done once all inclusion/exclusion criteria are met, including satisfactory pre-study laboratory test results.
[6] Bottles for the 3 treatment cycles will be dispensed at once, along with a dosing calendar and/or a dosing diary (ePRO-based or paper-based) to record intake and help reconciliation.
[7] If necessary, the Weeks 4 and 8 telehealth calls can be spread over 2 sessions within 2 days of each other, to accommodate the subject's energy level.

4 DATA MANAGEMENT

4.1 Data Collection

Most data will be collected at the sites via an Electronic Data Capture (EDC) application.

Biomarker data for sub-study will be collected by clinical sites and be sent to Alimentiv in MS Excel data sheets.

4.2 Coding

Adverse Events (AE), Medical History (MH), and non-core LONG COVID symptoms are coded using MedDRA version 26.1. All Prior and Concomitant Medications (CM) are coded using WHO Drug Dictionary version B3GL 2023Q3.

5 CHANGE TO ANALYSIS AS OUTLINED IN THE PROTOCOL

5.1 Analysis model for Primary and key Secondary Efficacy Outcomes

To follow FDA's guidance about Clinical Outcome Assessments (COAs) (see Section 8), for the primary efficacy outcome, in addition to the planned analysis of the change from baseline to Week 12 of the PCS, the measured PCS scores will also be analyzed similarly, and the statistical model will include the PCS baseline score as a covariate adjustment.

For the key secondary efficacy outcomes, namely the SF-36, FACIT-F and EQ-5D-5L, in addition to the planned analysis of the change from baseline of the outcome, the measured outcome scores will also be analyzed similarly, and the statistical model will include the outcome's baseline score as a covariate adjustment.

5.2 Analysis of Covariance (ANCOVA) model for Secondary Efficacy Outcomes with Continuous Values

According to Section 12.5.2 of the Protocol, the secondary efficacy outcomes with continuous values will be analyzed using ANCOVA method.

Except for DPEMQ, all other secondary efficacy outcomes were collected at each visit, it is more proper to analyze them using a mixed model for repeated measures (MMRM). To be consistent, the mixed model will use the same covariates and same type of covariance structure of the primary efficacy analysis. Please see details in sections 6.5.1 and 6.5.2.

For DPEMQ results that are Yes/No flags, the Fisher's exact test and logistic regression analysis will be performed. Please see details in sections 6.5.2 and 7.3.4.

5.3 Assessments at Week 24

According to the protocol, health and survival follow-up at Week 24 is one secondary endpoint, including presence or not of LONG COVID symptoms, general health check-up, significant cardiovascular events and assessment of survival.

1. General health check-up data is not collected in EDC. The analysis will not be performed.
2. Survival data is not directly collected at Week 24. The Alive/Disease information at Week 24 will be determined based on subject's attendance of Week12/Week24 and the end date of AE with fatal outcome.

6 STATISTICAL METHODS

Descriptive summaries of continuous data will consist of the mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized with frequencies and percentages. All data will be listed by treatment arm, subject, and visit/time point, if applicable.

6.1 Sample Size

The primary measure of efficacy is the absolute change in the PCS of the SF-36 questionnaire from baseline to Week 12, LAU-7b compared to placebo-treated patients. The regimen-finding Phase 2 portion of this study is hypothesis generating. Therefore, no formal sample size calculation or statistical power estimation based on actual effect size have been done for the Phase 2 portion.

However, with the increased arm size from 68 to 90 subjects/arm, the study will have greater than 90% power to detect a 10-point difference in PCS between a treatment group and the placebo group at 5% two-sided significance level, assuming that the common standard deviation is 20.

The sample size was estimated according to the following assumptions:

- A t-test of the difference of the mean absolute change from baseline of the PCS of the SF-36 questionnaire of each group (active versus placebo) is used;
- The PCS result is a score between 0 and 100 and the difference from baseline (absolute change) is assumed to be normally distributed in each treatment group.

According to the results of the Phase 2 portion and after formal consultation with regulatory agencies and experts, the study protocol will be amended to expand and define the enrollment of subjects with LONG COVID in the distinct and self-sufficient confirmatory Phase 3 portion of the study. It will then be submitted for regulatory

approval, with a selection of endpoints benefiting from this initial part of the study, and a sample size estimated in order to ensure sufficient statistical power to make the results confirmatory and reach at least 90% power with a two-tailed test. The sample size estimation of the Phase 3 portion will be described in the separate SAP for the Phase 3 portion.

6.2 Analysis Population

6.2.1 Intent-To-Treat (ITT) Population

The intent-to-treat (ITT) population will include all subjects who are randomized to a treatment arm/group whether or not they actually received the study treatment.

The ITT population will be used for the primary analyses of all study endpoints, taking into consideration other analysis populations.

Regardless of the actual treatment regimen, all ITT subjects will be kept in their randomized treatment arm for the ITT analyses.

6.2.2 Per-Protocol (PP) Population

The per-protocol (PP) population will include all subjects randomized to a treatment group to whom the 3 cycles of study treatment and a minimum of 80% completion of the target doses of study treatment administered in accordance with the protocol (i.e., without major exclusionary protocol deviations as pre-identified prior to the database lock). For treatment compliance, please see calculations in section 7.1.11.2.

The PP population will serve as the basis for secondary analyses of all study endpoints.

6.2.3 Safety Population

The safety population will include all subjects who are randomized to a treatment group and receive at least one dose of study treatment.

This population will serve as the basis of analysis of all safety endpoints. All subjects will be kept in their treatment arms that they actually received for analysis.

6.2.4 Biomarker Population

The biomarker population will include all subjects randomized to a treatment group who consented for the biomarker sampling procedures and contributed the baseline biomarker samples and samples from at least one of the two on-study biomarker sampling time points.

6.3 Missing Data

6.3.1 Missing or Incomplete Date/Time

All missing or partial date/time values will not be imputed.

In the determination of following flags, the most conservative rules will be applied if the date/time values are missing or incomplete:

- Treatment-Emergent Adverse Event (TEAE)
  If AE start date/time is missing or incomplete, and there is no clear evidence showing the AE started before the first study treatment or after the last treatment, the AE will be considered as TEAE.
- Concomitant Medication
  If medication start/end date/time is missing or incomplete, and there is no clear evidence the medication stopped before the first study treatment or started after the last treatment, it is considered as concomitant medication.

6.3.2 Intercurrent Events

Intercurrent events are handled by treatment policy strategy, hypothetical, and composite event strategy based on the following table.

Intercurrent events	Strategy	Descriptions
1. Treatment non-compliance or interruption	Treatment Policy Strategy	1. For non-compliant, temporary or permanent interruptions of study treatment (e.g. due to an adverse event other than death, subject personal choice, PI decision...etc.), data collected will be analyzed as if treatment had continued normally throughout the study.
2. Use of disallowed drugs after randomization		2. If a subject is given disallowed medication (see Protocol Section 9.4.1) after enrollment, their safety will be analyzed as normal and efficacy data will be analyzed as normal in the Intention-to-

3. Start of other LONG COVID treatments after randomization		Treat population, excluded from the Per-Protocol population. 3. If a subject starts other LONG COVID treatments after randomization, their safety will be analyzed as normal and efficacy data will be analyzed as normal in the Intention-to-Treat population, excluded from the Per-Protocol population.
4. Study discontinuation for any reason other than death	Hypothetical Strategy	4. Efficacy outcome following treatment discontinuation for any reasons other than death will be estimated by the maximum likelihood in the MMRM.
5. Study discontinuation due to death	Composite Event Strategy	6. Efficacy outcome following discontinuation due to death will be estimated using last observation carried forward (LOCF).

The missing data imputation and sensitivity analysis (see section 6.3.3) will be performed after the handling of intercurrent events.

6.3.3 Missing of Primary Endpoint

At week 12, both the measured PCS score and the absolute PCS change from baseline will be the co-primary endpoints. They will be analyzed based on a mixed model for repeated measures (MMRM). The missing value of PCS at Week 12 will be handled by MMRM, no extra imputation will be performed.

Sensitivity analyses will be detailed in section 6.5.1.1.

6.4 Calculated Outcomes

The following are key endpoints derived from data captured at the sites via the EDC system. Complete documentation of the calculations and data manipulation required to go from the CRF database to the analysis database are contained in the specification documents of SDTM and ADaM.

Endpoint	Definition / Calculation	Comment
Study Day 1	= Date of the first study dose = Cycle 1 Day 1	
Study Day of an Event	= Date of the Event – Date of C1D1 + 1, if the event is on or after C1D1, or = Date of the Event – Date of C1D1, if the event is before C1D1	
Baseline value	= Value reported prior to the first study dose or in the case of late entries of patient reported outcomes, no later than Day 4	If multiple values collected prior to the first study dose, non-missing value closest to the date/time of the first study dose is considered baseline. If no non-missing record prior to the first study dose, the earliest non-missing assessment no later than Study Day 4 will be set as Baseline.
Change from Baseline	= Value collected at time point (Visit) – Baseline value	
Time in Trial (days)	= Study completion/withdrawal date – date of informed consent date + 1 day	
Time on Treatment (days)	= Date of the last study dose – date of the first study dose + 1 day	

Endpoint	Definition / Calculation	Comment
Age (years)	= Informed Consent Year – Birthdate Year, if consent date is on or after birthday, = Informed Consent Year – Birthdate Year – 1, if consent date is before birthday	
Age Group	= “18 - 44” = “45 - 54” = “>= 55”	
Treatment Emergent Adverse Event (TEAE)	= No if onset date/time of the AE is before the date/time of the first study dose, or after Week 12 follow-up, or after study completion/early withdrawal = Yes otherwise	Notes: According to conservative rule, all AEs that cannot be determined as started before study treatment or after Week 12/study completion/withdrawal will be considered as TEAE

Endpoint	Definition / Calculation	Comment
SF-36 Domain Scores and Component Summaries	Eight SF-36 functional scales (domain scores) will be calculated from the answers of all SF-36 questions. Physical Component Summary (PCS) and Mental Component Summary (MCS) will be derived from the domain scores using the physical and mental factor coefficients from the 1990 general US population.	Visit-Level variable. Please see reference #1.
Total Number of Core Symptoms	Count of core symptoms with answer Yes for “Did this symptom occur?”	Visit-level variable
DALCI Non-Burdensome Score	= sum of the Likert scores of all core symptoms with severity No Symptom (Likert score 0) or Mild (Likert score 1)	Visit-level variable
DALCI Burdensome Score	= sum of the Likert scores of all core symptoms with severity Moderate (Likert score 2) or Severe (Likert score 3)	Visit-level variable
DALCI Total Score	= DALCI Non-Burdensome Score + DALCI Burdensome Score	Visit-level variable

Endpoint	Definition / Calculation	Comment
DALCI Improvement Relative to Baseline (%)	= 100 * (Baseline DALCI burdensome Score - DALCI burdensome Score at Visit) / Baseline DALCI burdensome Score	Visit-level variable
Time to Relief of First Core LONG COVID Symptom for a Minimum of 2 Weeks	= Time to first achieving relief of anyone of the 7 Core LONG COVID symptom = Start date of the first achieving relief of anyone symptom – Date of the first study dose + 1 Here “relief” is defined as symptom’s severity reduction >= 2-point Likert score from baseline and maintained for a minimum of 2 weeks This variable is censored at Week 12 if no symptom is relief before Week 12	Subject-level variable

Endpoint	Definition / Calculation	Comment
FACIT Fatigue Scale	Fatigue is based on FACIT-F of 13 items with a summed score range from 0 to 52. For the following questions, keep the individual item scores: • I have energy • I am able to do my usual activities For all the remaining questions, subtract the individual item score by 4 to calculate the reverse score. Sum all individual item scores, multiply by 13 and divide by number of items answered to obtain the fatigue subscale score.	Visit-level variable, detailed calculations are described in ADaM Spec
DPEMQ PEM Flag	= Yes, frequency score >= 2 (about half of the time) with severity score >= 2 (moderate) in at least one question from Q1 to Q5, = No, otherwise	Visit-level variable
EQ-5D-5L Summary Index	= value calculated from a formula estimated for Canadian population. Please see Appendix E.	Visit-level variable, detailed calculations are described in Appendix E and ADaM Spec

Endpoint	Definition / Calculation	Comment
Had LONG COVID related unplanned medical visits	= Yes, if the subject had at least one Unplanned Care Visit or Hospitalization record with reason “LONG COVID” = No, otherwise	Subject-level variable
Had significant cardiovascular events during study	= Yes, if the subject had unplanned care visit or hospitalization for Significant Cardiovascular event, = Yes, if the subject had CV-related AE leading to death = No, otherwise.	Subject-level variable
The systematic inflammation index (SII),	Will be calculated at randomization and Day 70 as (N × P)/L, where N, P and L represent absolute neutrophil counts, platelet counts and lymphocyte counts, and the difference from randomization compared between treatment groups.	Visit-level variable

6.5 Analysis Methods

In general, all calculations and analyses will be performed using SAS version 9.4 at Alimentiv Inc. in Toronto, Canada. Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, and ranges, while categorical data will be presented as counts and percentages via PROC FREQ for the descriptive displays.

The following sections described the analysis models that will be used to perform the analysis of the primary and secondary efficacy endpoints. All safety outcomes will be tabulated as descriptive statistics by treatment arms including 95% confidence intervals of the AE occurrence percentages; no statistical inferences will be provided.

In addition to the change from baseline scores, SF-36, FACIT-F, EQ-5D-5L will be analyzed by their raw scores.

6.5.1 Primary Efficacy Analysis

The primary efficacy assessment is the physical component summary (PCS) of the SF-36 questionnaire. It is measured at various time points during the study period. The PCS value at visit and its absolute change from baseline score will be descriptive tabulated.

For primary efficacy analysis, the PCS absolute change from baseline will be analyzed based on a mixed model for repeated measures (MMRM), including all PCS assessments up to Week 12 or treatment discontinuations. The absolute change from baseline in PCS will be the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and patient as a random effect with adjustments for baseline PCS, gender, age group, screening COVID vaccination status (vaccinated, unvaccinated), COVID-19 severity at screening, baseline BMI, and baseline DALCI total score.

SAS procedure PROC MIXED will be used to construct the regression model. SAS codes of following general format will be used:

[redacted]

Variable VISIT is the post-baseline visits (Week 4, 8, 12, and early termination), D_PCS is the change score of PCS at those visits, B_PCS is the PCS score at baseline, TREAT is treatment arm, variables SEX, AGEGROUP, VACYN, COVSEV, B_BMI, and B_DALCI are covariates gender, age group, screening COVID vaccination status, causative COVID-19 severity, BMI at baseline, and DALCI total score at baseline. SUBJID (subject) is random effect. Type is the covariance structure of the R matrix. Unstructured covariance (UN) will be used as default type, other covariance matrices i.e. AR(1), CS …, will be used if the model with UN does not converge.

Model assumptions will be checked by examining the distribution of the residuals for normality and testing the homogeneity of the variance.

For the primary efficacy analysis, the treatment difference will be tested by comparing the estimated mean (LS Mean) for change from baseline at Week 12. Each LAU-7b study arm will be compared with the placebo arm and LAU-7b study arms will be compared to each other. Since the Phase 2 portion is for hypothesis generation and the sample size was not based on statistical power, the statistical tests will be performed and reported without adjusting for multiple comparisons.

6.5.1.1 Missing PCS and Sensitivity Analysis

For the primary efficacy analysis, the missing value of PCS at Week 12, not related to intercurrent events, will be handled by MMRM model. No additional imputation will be performed.

For missing data handling related to intercurrent events, please see section 6.3.2 for details.

A sensitivity analysis will be performed to allow plausible assumptions on missing data handling and evaluate their impacts on the primary analysis. The missing value of PCS at Week 12 will be imputed using the last non-missing PCS value before Week 12, i.e., Last Observation Carried Forward (LOCF) method.

The same mixed model of the primary analysis will be used to conduct the two sensitivity analyses.

6.5.1.2 Sensitivity Analysis for Questionnaire Errors

In EDC system, the first ePRO version of SF-36 had translation errors on some questions pertaining to secondary domains (not the PCS). Eighteen subjects entered data before the mistake was fixed. After the update of the EDC, those subjects re-answered correlated questions. Those data will be included in the final primary and secondary analysis related to these secondary domains of SF-36.

Sensitivity analyses for the relevant SF-36 endpoints will be performed with exclusion of those 18 subjects.

6.5.2 Secondary Efficacy Analyses

All secondary analyses will be performed without adjustment for multiplicity as these are considered supportive.

The following statistical analyses will be performed for:

Mixed Model for Repeated Measures (MMRM)

The mixed model will be same as the primary efficacy analysis with minor adjustment for the covariates depending on the corresponding response variable. It will be applied to following secondary efficacy endpoints:

- Change from baseline in the FACIT-Fatigue scale (13-item), from baseline to Weeks 4, 8 and 12.
- The overall functional health status evaluated with the PCS of the SF-36 questionnaire at Weeks 4 and 8, compared to baseline, analyzed along the primary endpoint with the repeated measure analysis of variance.
- The other aspects of health status (mental, emotional, social...etc.) each evaluated with the SF-36 questionnaire at Weeks 4, 8 and 12, compared to baseline.
- Change from baseline in the EQ-5D-5L score at Weeks 4, 8 and 12.

Time-to-Event Analysis

- Time to the first relief of a core LONG COVID symptom for a minimum of 2 weeks, among those burdensome symptoms present at baseline. From randomization through Week 12, censored at Week 12 or early termination if no symptoms are relieved by Week 12/early termination.

Cox proportional hazards model will be conducted and the p values with hazard ratios (with 95% CLs) will be provided. Proportional hazards assumption will be verified. If the assumption is failed, a stratified analysis will be conducted by adding STRATA statement into the SAS procedure.

SAS codes of following general format will be used for Cox model:

[redacted]

Variable TTE is the Time to the first Relief of a core symptom. CENS is the censor flag.

Additionally, Kaplan-Meier (KM) methods will be used to produce graphical presentations of the time to the first relief of a core LONG COVID symptom. Following SAS codes will be used to perform the KM analysis:

[redacted]

[redacted]

Analysis of Proportions

- Proportion of subjects achieving a marked improvement (at least "much better") in their ability to perform usual daily activities as measured with the Patient Global Impression of Change (PGI-Ci), from baseline to Weeks 4, 8 and 12.
- Proportion of subjects with PEM (based on DPMEQ) at Week 12
- Proportion of subjects who judge to have regained their daily usual activity level of pre-causative-infection, from randomization through Weeks 4, 8 and 12.
- Proportion of subjects achieving≥25%, ≥50% or≥75% improvement in the DALCI burdensome Score at Weeks 4, 8, 12 and 24.
- Proportion of subjects with relief of at least one core burdensome LONG COVID symptom for a minimum of 2 weeks. Relief means a reduction of severity from moderate to none, or severe to mild/none (≥2-point Likert score change). From randomization through Week 12.
- Proportion of subjects with a sustained clinical recovery, meaning a relief (as defined above) of all core LONG COVID symptoms, by Week 4, 8 and 12.
- Proportion of subjects with LONG COVID related unplanned medical visits (i.e., practitioner's office, urgent care, emergency room < 24h, hospitalization >24 hours) from randomization through Week 12.
- Proportion of subjects deceased from any cause through Week 12.
- Proportion of subjects with significant cardiovascular events (resulting in at least an acute care visit, a hospitalization or an event-related death) through Week 12.
- Health and survival follow-up: significant cardiovascular events and assessment of survival.

Variables will be tabulated by Visit for the three treatment arms. Fisher's Exact test will be performed to compare each LAU-7b arm with the placebo arm and to compare two LAU-7b arms. If data applicable, logistic regression will be conducted. SAS codes of following general format will be used:

[redacted]

"VAR" is the categorical variable at visit, "B_VAR" is its value at baseline.

ANOVA Model

ANOVA model will be applied to following secondary efficacy endpoints:

- Change from baseline in the total number of LONG COVID symptoms based on baseline inventory, at Weeks 4, 8 and 12.

SAS codes of following general format will be used:

[redacted]

Here D_COUNT is the total number of LONG COVID symptoms change from baseline.

6.5.3 Exploratory Analysis

6.5.3.1 Biomarker Analysis

All biomarker data (at visit measurements and change from baseline) will be summarized.

The scatter plots of all biomarkers will be displayed and the correlation coefficient between biomarkers will be calculated.

MMRM will also be applied to analyze the biomarkers selected based on the summary results. The mixed model will have similar covariates as the primary analysis.

The correlation between biomarkers and efficacy endpoints may also be calculated if applicable. The selection of biomarkers and efficacy endpoints will be based on the analysis results of the main study.

7 RESULTS

All data collected in EDC and as external datasets will be at a minimum listed.

All data of screen failures captured by EDC system will be displayed in listings separated from enrolled subjects. Summaries may also be provided if data applicable.

7.1 Study Subjects

All subject data collected at baseline will be analyzed for ITT population.

7.1.1 Patient Disposition

All enrolled subjects will be accounted for. A summary of subjects by treatment arm will be provided. All early discontinuations will be summarized by primary reason of discontinuation, alongside the following data:

- The number of subjects who were screened and randomized;
- The number and proportion of subjects in each analysis population;
- The number and percentage of subjects who completed the study;
- The number and percentage of subjects who discontinued prematurely from the study and the associated reasons;
- The number and percentage of subjects who attended each follow-up visit.

7.1.2 Protocol Deviations

Any deviations from protocol will be fully documented in the source documentation and be provided to Alimentiv Inc before database lock.

Major protocol deviations will be summarized by the category of deviation reasons.

Protocol deviations will be presented in by-subject data listing.

7.1.2.1 Disallowed Medications

The concomitant use of medications that may potentially act as modulators of intracellular ceramide levels or ceramide cytotoxicity, sphingolipids transport, or p-glycoprotein “MDR1” or “MRP1” drug/lipid transporters, such as: cyclosporine A or analogue; verapamil; tamoxifen or analogue; ketoconazole, chlorpromazine and thioridazine; RU486 (mifepristone); indomethacin; or sulfinpyrazone is prohibited.

Subjects that use disallowed medications after randomization to any clinically significant extent or start other LONG COVID treatments after randomization will be considered as having major protocol deviation and will be excluded from PP population.

7.1.3 Eligibility

Eligibility criteria are assessed at screening (Visit 1) and verified before randomization (Visit 2). All failed inclusion/exclusion criteria will be listed.

7.1.4 Demographics and Screening Characteristics

Demographics (age, sex, ethnicity, and race), screening visit body measurements (height, body weight, and calculated BMI), and vital signs (body temperature, heart rate, respiratory rate and blood pressures) will be summarized.

7.1.5 Causative COVID-19 Infection and LONG COVID Diagnosis Confirmations

Date of COVID-19 infection as reported by patient, severity of causative COVID-19 episode, and date of LONG COVID diagnosis will be listed.

Severity of causative COVID-19 episode will be summarized. This variable will be used as a covariate in the primary efficacy analysis and secondary analysis with MMRM. See section 6.5.1.

7.1.6 COVID-19 Vaccination Status

COVID-19 vaccination status collected in EDC will be listed.

COVID-19 vaccinated (yes/no) will be summarized and be used as a covariate in the primary efficacy analysis and secondary analysis with MMRM.

7.1.7 Non-Core LONG COVID Symptoms

Non-core LONG COVID symptoms will be summarized by MedDRA SOC and Preferred Term.

All non-core LONG COVID symptoms will be listed, including symptom term, start/end dates, ongoing (yes/no), and severity.

7.1.8 Medical History

Medical history will be coded using MedDRA and presented in a by-treatment table by System Organ Class and Preferred Term.

7.1.9 Hematology and Serum Chemistry

Hematology and serum chemistry are scheduled at screening visit. All laboratory data will be listed. This is distinct from the hematologic biomarkers assessed at specific times during study.

All unscheduled lab test data, if available, will be listed.

7.1.10 Study Medication Dispensing and Returning

Study drug is dispensed to all randomized subjects after randomization (Visit 2). The drug bottles are returned to clinical sites at Week 12 (Visit 7) or Early Termination.

All drug dispensing/returning data will be listed.

7.1.11 Study Treatment Exposure and Treatment Compliance

On each of the 14 days of study treatment portion of each cycle, the subject will self-administer once-a-day two capsules and enter administration data into dosing diary. Treatment exposure and compliance will be calculated based on the drug administration data in the dosing diary. Exceptionally, in the absence of usable diary data, the treatment exposure and compliance may be derived from Investigational Product reconciliation counts (returned treatment bottles).

7.1.11.1 Treatment Exposure

For each cycle, the treatment duration between the first and the last dosing dates will be calculated regardless of any interruptions in dosing.

A subject's Treatment Exposure will be the sum of treatment durations of the 3 cycles.

Treatment Exposure will be descriptively summarized by treatment group.

7.1.11.2 Treatment Compliance Rate and Compliance

Based on missing treated days, treatment compliance rate will be calculated based on actual treated days:

$$\text{Compliance Rate (\%)} = \frac{Actual\ Treated\ Days}{Expected\ Treatment\ Days}\ x\ 100\%$$

Here Expected Treatment Days is according to study design:

= 3 x 14 = 42 days for subjects who completed 3 cycles, or

= planned treatment days up to end of study for early withdrawals, considering 14 days for a full cycle and treatment during for early terminated cycle.

Actual Treated Day = Expected Treatment Days – total missing days, including interruption during treatment period and early stop at the end of cycle, except for the last cycle of early withdrawals, for whom the days after early termination will not be counted as missing days.

After compliance rate is calculated, a subject's treatment compliance (yes/no) can be determined according to 80% rule:

Compliance = Yes, if compliance rate >= 80%

= No if compliance rate < 80%

Treatment compliance rate and compliance will be summarized by treatment groups.

7.2 Primary Efficacy Outcomes

Descriptive statistics for the SF-36 PCS, as well as change from baseline, will be summarized by visit for the three treatment arms. The statistical inferences and estimates of the measured SF-36 PCS scores and their change from baseline (p values and LS means) from the mixed model analyses will also be presented for Week 12. Please see details in Section 6.5.1.

Primary efficacy analysis will be performed for both ITT and PP populations.

7.2.1 Sensitivity Analysis Outcomes

The mixed model will be rerun for SF-36 data with LOCF imputation. See section 6.5.1.1.

The mixed model will be rerun for SF-36 relevant secondary domains data with the exclusion of 18 subjects. See section 6.5.1.2.

The statistical inferences and estimates of the measured SF-36 PCS scores and their change from baseline (p values and LS means) from the mixed model will also be presented for Week 12.

7.3 Secondary Efficacy Outcomes

All secondary efficacy outcomes will be analysed for both ITT and PP populations.

7.3.1 36-Item Short Form Survey (SF-36)

7.3.1.1 SF-36 Measured PCS And Change from Baseline to Weeks 4 and 8

The statistical inferences and estimates of change from baseline (p values and LS means) from the primary efficacy model will be presented for Weeks 4 and 8.

7.3.1.2 SF-36 Domain Scales

SF-36 domain scales: General Health (GH), Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP). Vitality (VT), Social functioning (SF), Role-Emotional (RE), and Mental Health (MH) at each visit and their change from baseline will be descriptively summarized by visit.

7.3.2 Patient Global Impression of Change (PGI-C)

Key secondary endpoint PGI-C will be assessed at post-treatment visits Week 4, Week 8, and Week 12. The 7-level categorical results (from “Very much improved” to “Very much worse”) will be summarized by visit. The proportion of each category at each visit will be presented.

For each pair of two treatment arms, Fisher’s Exact Test will be performed, and the p value will be presented.

Logistic regression will also be performed if data applicable. To perform the analysis, PGI-C answer will be re-classified to two categories: Marked Improvement (including Very much improved and Much improved) and Other (including all other answers).

7.3.3 The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

FACIT Fatigue Scale will be calculated and all valid visit values and their changes from baseline will be summarized by visit.

The measured scores and their change from baseline at Weeks 4, 8, and 12 will also be estimated from a MMRM which includes the same covariates of the primary efficacy model.

7.3.4 DePaul Post-Exertional Malaise Questionnaire (DPEMQ)

At each visit, the proportions of subjects with PEM will be tabulated.

For each pair of two treatment arms, Fisher’s Exact Test will be performed, and the p value will be presented.

Logistic regression analyses will be conducted with PEM (yes/no) as response variable and with the same covariates of the primary efficacy model.

7.3.5 Daily Activity Level

At each visit, the proportion of subjects who judge to have regained the daily usual activity level that the subject had prior to being infected by COVID-19 will be tabulated.

For each pair of two treatment arms, Fisher’s Exact Test will be performed, and the p value will be presented.

Logistic regression analysis will be conducted with “regained the daily usual activity level (yes/no)” as response variable and with same covariates of the primary efficacy model.

7.3.6 EQ-5D-5L Score

EQ-5D-5L summary index will be calculated based on the questionnaire answers. All raw answers, VAS health score, derived summary index will be summarized by visit.

For summary index, the index value at Weeks 4, 8, and 12 visits and its Change from Baseline at Weeks 4, 8, and 12 will also be estimated from a MMRM which includes the same covariates of the primary efficacy model.

7.3.7 LONG COVID Symptoms and DALCI Score

At each visit, the severity of each of the 7 core LONG COVID Symptoms (Fatigue, Post-exertional malaise, Trouble sleeping, Cognitive problems, Mental health symptoms, Shortness of breath, and General pain and discomfort) will be assessed. DALCI scores (non-burdensome, burdensome, and total) will be calculated based on the severity of all 7 symptoms.

Following results will be summarized by visit:

- Severity of each core symptom
- DALCI total score (a numeric value from 0 to 21) and its change from baseline
- Total number of core symptoms
- Proportion of subjects achieving $\geqslant$25%, $\geqslant$50% or $\geqslant$75% improvement in the DALCI burdensome Score, by visit
- Proportion of subjects with all core symptoms with severity Likert score decreased >= 2-point from baseline (sustained recovery)

Following endpoint will be summarized:

- The proportion of subjects with at least one core symptom with severity Likert score decreased >= 2-point from baseline for a minimum of 2 weeks, from randomization through Week 12 (relief of a core eligibility-defining symptom).

P values from Fisher's Exact test will be presented for above endpoints about proportion. The results of Logistic Regression model, if performed, will be presented.

The time to the first relief of a core LONG COVID symptom will be tabulated by treatment arm. Cox model results, including parameter estimates, p values, and hazard ratios with 95% CLs, will be presented. In additional, the KM estimates of median, 25th percentile, and 75th percentile of the time of relief will be presented. KM curves of the three treatment arms will be provided.

7.3.8 Unplanned Care Visits and Hospitalization

All unplanned care visits and hospitalization reported in EDC will be listed, including type, dates, and reason of visit.

Proportion of subjects with LONG COVID related unplanned medical visits will be tabulated by treatment arm. Fisher's Exact test and Logistic Regression analysis will be performed.

Proportion of subjects with significant cardiovascular events (resulting in at least an acute care visit, a hospitalization or an event-related death) will be tabulated by treatment arm. Fisher's Exact test and Logistic Regression analysis will be performed.

7.3.9 Death

All deaths reported in EDC database will be presented in data list.

Proportion of subjects deceased from any cause through Week 12 will be tabulated. Fisher's Exact test and Logistic Regression analysis, if applicable, will be performed.

7.3.10 Long-Term Follow-up at Week 24

The presence (yes/no) of each LONG COVID core symptom will be tabulated. Fisher's Exact test and Logistic Regression analysis will be conducted if data applicable.

DALCI burdensome Score at Week 24 will be descriptively summarized. Proportion of subjects achieving≥25%, ≥50% or≥75% improvement of DALCI burdensome Score at Week 24 will be tabulated. Fisher's Exact test and Logistic Regression analysis will be conducted if data applicable.

The proportion of subjects who had unplanned care visit(s) and/or hospitalization(s) between Week 12 and Week 24, because of significant cardiovascular events will be summarized by treatment arm. Fisher's Exact test and Logistic Regression analysis, if applicable, will be performed.

Proportion of subjects deceased from any cause through after Week 24 will be summarized if applicable.

7.4 Exploratory Outcomes

7.4.1 Biomarker Outcomes

Descriptive statistics for the biomarkers, as well as change from baseline, will be summarized by visit for the three treatment arms.

7.5 Safety Outcomes

All safety outcomes will be analysed for the Safety Population.

7.5.1 Adverse Events

An AE is any untoward medical occurrence (which does not necessarily have to have a causal relationship with this treatment). An AE can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the study drug. This includes any occurrence that was new in onset or aggravated in severity or frequency from the screening condition.

Adverse events will be collected from the time of informed consent until the Week 12 in person follow-up, or until early termination or death, whichever occurs first.

SPECIAL REPORTING INSTRUCTIONS:

In the case of the ESSOR study, to avoid doubling of data entry between the AE log and the LONG COVID symptom log, all the LONG COVID symptoms (core and noncore) will only be entered in the LONG COVID symptom log even if they appear or worsen after the initial inventory at baseline and after the first dose, because the LONG COVID symptoms are an efficacy endpoint, as well as being a safety endpoint. However, upon judgement from the Investigator, if a LONG COVID symptom appears or worsens after the initial inventory and is unexpected and/or exceeds in severity the normal LONG COVID evolution, then the said LONG COVID symptom shall also be entered on the AE log.

Any AE that occurs from the first dose of study treatment (or prior to the first dose of study treatment and worsening after first dose of study treatment) until the Week 12 follow-up, or until early termination or death, whichever occurs first, will be considered as a Treatment-Emergent Adverse Event (TEAE).

Summaries of AEs will be prepared by treatment arm, and include:

- Brief summary of all AEs - include the total number of AEs, TEAEs, Treatment-Emergent Serious Adverse Events (TESAEs), TEAEs leading to death, and TEAEs leading to study treatment withdrawn,
- TEAEs by MedDRA System Organ Class and Preferred Term,
- TEAEs by MedDRA System Organ Class, Preferred Term, and strongest relationship to study treatment,
- TEAEs by MedDRA System Organ Class, Preferred Term, and maximum severity,
- Serious TEAEs by MedDRA System Organ Class and Preferred Term,

- TEAEs leading to treatment discontinuation,
- Fatal TEAEs

All these summaries will include the counts and frequencies of events, as well as the 95% confidence intervals of the frequencies, and of subjects who had events.

All AEs will be listed by subject. Death and other SAEs will be listed separately.

7.5.2 Body Measurements and Vital Signs

Body measurements (body weight, height, and BMI) and vital signs (heart rate, respiratory rate, temperature, and blood pressures) are measured at screening and Week 12 visit.

All measurements will be summarized by visit. At Week 12, the absolute change and % change from baseline will also be summarized.

Body Weight and BMI Change from Baseline to Week 12 will also be analyzed using ANCOVA model with Baseline Body Weight (or Baseline BMI), Gender, Age Group, screening COVID vaccination status, screening COVID-19 severity, and DALCI total score at baseline as covariates. These analyses will be conducted for Safety population, overweight subgroup, and obese subgroup.

All body measurements and vital signs will be listed.

7.6 Other Outcomes

7.6.1 Prior and Concomitant Medications

Any medication used in the study until Week 12 follow-up or early termination will be recorded in the eCRF. These medications are placed into one or both of following groups:

- **Prior Medication**: Medication started before the first study dose, independently of when it ended,
- **Concomitant Medication**: At least one dose after the first dose of study treatment up to the Week 12 follow-up or early termination

According to conservative rule, all medications that cannot be determined whether was taken before the first dose of study treatment, or concomitantly, it will be considered as both prior and concomitant.

A summary of all Concomitant Medications will be presented in tabular form by therapeutic drug class (ATC Level 2 coding term) and chemical subgroup (ATC Level 4 coding term) using the World Health Organization Drug Dictionary (WHODD).

All prior and concomitant medications will be presented in by-subject data listings.

7.6.2 Pregnancy Test

For female subjects with childbearing potential, urinary pregnancy test will be performed at the clinic or by the subject at home. The results must be negative at screening, before randomization, and prior to the start of treatment Cycles 2 and 3.

All pregnancy status, contraception check, and test kits dispensing data will be listed.

8 Reference

1. Ware JE, Kosinski M, Dewey JE, How to Score Version 2 of the SF-36 Health Survey. Lincoln, RI: QualityMetric Incorporated, 2000.
2. FDA, Patient-Focused Drug Development, Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments, June 2022
3. FDA, Patient-Focused Drug Development Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making, April 2023
4. Nancy Devlin, Bram Roudijk, Kristina Ludwig, Value Sets for EQ-5D-5L,Springer, 2022

APPENDIX A: 36-Item Short Form Survey (SF-36)

Choose one option for each questionnaire item.

1. In general, would you say your health is:
   - ○ 1 – Excellent
   - ○ 2 – Very good
   - ○ 3 – Good
   - ○ 4 – Fair
   - ○ 5 – Poor

2. **Compared to one year ago,** how would you rate your health in general **now?**
   - ○ 1 – Much better now than one year ago
   - ○ 2 – Somewhat better now than one year ago
   - ○ 3 – About the same
   - ○ 4 – Somewhat worse now than one year ago
   - ○ 5 – Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 – Not at all
- ○ 2 – Slightly
- ○ 3 – Moderately
- ○ 4 – Quite a bit
- ○ 5 – Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ○ 1 – None
- ○ 2 – Very mild
- ○ 3 – Mild
- ○ 4 – Moderate
- ○ 5 – Severe
- ○ 6 – Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ○ 1 – Not at all
- ○ 2 – A little bit
- ○ 3 – Moderately
- ○ 4 – Quite a bit
- ○ 5 – Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 – All of the time
- ○ 2 – Most of the time
- ○ 3 – Some of the time
- ○ 4 – A little of the time
- ○ 5 – None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

APPENDIX B: Patient Global Impression of Change (PGI-C)

Overall, how would you rate the change in your ability to perform daily usual activities since you started the study?

☑ *Check one box only:*

[1] ☐ Very Much Improved

[2] ☐ Much Improved

[3] ☐ Minimally Improved

[4] ☐ No Change

[5] ☐ Minimally Worse

[6] ☐ Much Worse

[7] ☐ Very Much Worse

APPENDIX C: The Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX D: DePaul Post-Exertional Malaise Questionnaire (DPEMQ)

For each symptom below, please circle one number for frequency and one number for severity: Please complete the chart from left to right.

Symptoms	Frequency: Throughout the **past 6 months**, how **often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					Severity: Throughout the past **6 months**, **how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**				
1. Dead, heavy feeling after starting to exercise	0	1	2	3	4	0	1	2	3	4
2. Next day soreness or fatigue after non-strenuous, everyday activities	0	1	2	3	4	0	1	2	3	4
3. Mentally tired after the slightest effort	0	1	2	3	4	0	1	2	3	4
4. Minimum exercise makes you physically tired	0	1	2	3	4	0	1	2	3	4
5. Physically drained or sick after mild activity	0	1	2	3	4	0	1	2	3	4

For each question below, choose the answer which best describes your PEM symptoms.

6. If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?	Yes			No		
7. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal physical effort?	Yes			No		
8. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal mental effort?	Yes			No		
9. If you feel worse after activities, how long does this last?	< 1 h	2-3 h	4-10h	11-13 h	14-23 h	> 24h
10. If you do not exercise, is it because exercise makes your symptoms worse?	Yes			No		

APPENDIX E: EQ-5D-5L Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

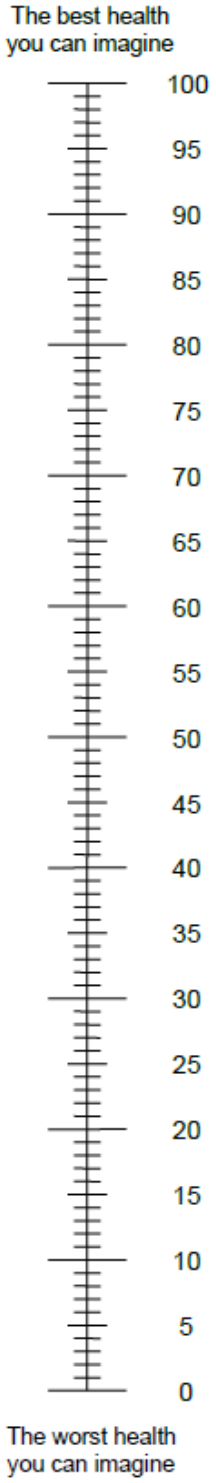
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



For Canadian population, following formula is used to calculate EQ-5D-5L Summary Index:

Summary Index = [redacted]

Here MO. SC, UA, PD, AD are the Likert scores of 5 dimensions: Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. MO45, SC45, UA45, PD45, and AD45 are indicator variables based on the 5-dimension scores:

XX45 = 1 if XX value is 4 or 5; = 0 otherwise, here XX = MO, SC, UA, PD, or AD.

Num45 is the total number of dimensions with value 4 or 5.

Summary Index can only be calculated when all 5-dimension values are not missing.