Laurent PHARMACEUTICALS

COVER PAGE FOR PROTOCOL

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

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CLINICAL TRIAL PROTOCOL

LAURENT PHARMACEUTICALS INC.

PROTOCOL NO: LAU-23-01

Study 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

Sponsor: Laurent Pharmaceuticals Inc.

Sponsor address: [redacted] Montréal (Québec) [redacted] Canada

Protocol Date: Feb 13th, 2024

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Signature Page for Sponsor:

Product: LAU-7b
Study No. LAU-23-01

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

Approved by the following:

Larry Lands, MD, PhD
Chief Medical Adviser
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Date

Jean-Marie Houle, B.Sc.Pharm., M.Sc., PhD
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Laurent Pharmaceuticals Inc.
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Date

Hong Chen
Study Statistician
Senior Director, Statistics and Principal Statistician
Alimentiv Inc.
[redacted]

Date

Signature Page for Investigator:

Product: LAU-7b
Study No. LAU-23-01

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

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with all relevant local regulations, the current International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP), and with the principles of the most recent version of the Declaration of Helsinki.

Signed:

_____	_____	_____
Principal Investigator Name (Print in block capital letters)	Signature	Date

_____
Institution Name

_____
City and Province + Postcode

1 SYNOPSIS

Note:	This synopsis does not contain all details and therefore cannot be used as a guide for the operational conduct of the study.
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
Investigational Product	LAU-7b (fenretinide) oral capsules
Sponsor	Laurent Pharmaceuticals Inc.
Study Objectives	**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)) **Secondary objectives:** 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 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.
Study Rationale	SARS-CoV-2 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. COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death. Furthermore, and in parallel, 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[i]. There is still no unanimous definition of what constitutes LONG COVID symptoms since they are quite numerous but in general there is a notion of timing/presence of symptoms after 4 weeks post-infection[ii], and/or presence of symptoms 12 weeks or more post-infection[iii], and not explained by an alternative etiology including a COVID re-infection.

[i] Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023).
[ii] US Department of Health and Human Services, https://www.covid.gov/longcovid
[iii] Health Canada, https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms/post-covid-19-condition.html

Study Rationale (cont'd)	While a number of therapeutic tools were progressively discovered and adopted for the prevention or treatment of COVID-19, consisting of vaccines, virus-directed antivirals and neutralizing antibodies, there is no approved disease-modifying medication for the prevention or treatment of LONG COVID; these patients are treated with currently available symptomatic therapies. LAU-7b is developed as a next generation, host-directed, broadly effective oral COVID-19 therapeutic with dual antiviral and inflammation-controlling activity. LAU-7b is currently being evaluated in hospitalized subjects with moderate-to-severe COVID-19 in a Phase 3 confirmatory study on the basis of a positive efficacy signal in the pilot Phase 2 portion of the study. Results from the Phase 2 portion showed 100% reduction in the risk of progression to mechanical ventilation and death by Day 60 in LAU-7b-treated hospitalized moderate-to-severe COVID-19 subjects, relative to placebo. Subjects on LAU-7b tended to recover more rapidly and leave hospital faster. LAU-7b was well-tolerated, with safety comparable to placebo. Fenretinide, the active pharmaceutical ingredient of LAU-7b, works by modulating host cell membrane lipids composition and fluidity, and de-novo cell lipogenesis. SARS-CoV-2 must reprogram host cellular lipid metabolism to favor its entry and replication, a mechanism shared by all lipid-enveloped viruses. Because it acts on the host rather than the virus, fenretinide has potential for a broad-spectrum antiviral activity regardless of mutations, as already demonstrated in vitro on multiple SARS-CoV-2 variants (including Delta and Gamma) and the MERS-CoV. Broader antiviral potential of fenretinide was demonstrated in preclinical testing against Dengue fever, Zika virus, respiratory syncytial virus, and HIV, via a mechanism also involving lipid modulation. Fenretinide was also shown to trigger certain membrane phospholipid metabolic pathways involved in the resolution phase of inflammation, a natural mechanism that keeps the inflammatory response under control without inducing immune-suppression (a "pro-resolving" effect). LAU-7b inflammation-controlling effects were demonstrated in a variety of preclinical models of acute and chronic inflammation of the respiratory system (ARDS, septic shock, cystic fibrosis and allergic asthma). Even more relevant for its potential benefit against LONG COVID neurological and psychiatric symptoms, fenretinide has shown ability to cross the blood-brain barrier and exert inflammation-controlling effect in multiple preclinical models of neuro-inflammation: A mouse model of spinal cord injury[iv], two animal models of ALS[v], [vi], and a mouse model of depression and blood-brain-barrier (BBB) dysfunction[vii]. Tissue distribution study in rats showed excellent blood-brain penetration with brain fenretinide concentrations equal or higher compared to plasma. Interestingly, fenretinide is used clinically to treat children and adults with glioblastomas and astrocytoma, at high doses, indicative of adequate brain penetration. Furthermore, fenretinide demonstrated in several in vitro studies an effect on abrogation of macrophage polarization to M1 phenotype that produces pro-inflammatory cytokines and promoting

[iv] Lopez-Vales R, Redensek A, Skinner TA, Rathore KI, Ghasemlou N, Wojewodka G, DeSanctis J, Radzioch D, David S. Fenretinide promotes functional recovery and tissue protection after spinal cord contusion injury in mice. J. Neuroscience. 2010 Mar 3; 30(9): 3220–6.

[v] Skinner TA. Molecular and neurological effects of fenretinide on Amyotrophic Lateral Sclerosis. MSc Thesis, McGill University, Montreal, 2008.

[vi] Orienti I, Armida M, Dobrowolny G, Pepponi R, Sollazini G, Pezzola A, Casola I, Musaro A, Popoli P and Potenza RL. Fenretinide Beneficial Effects on Amyotrophic Lateral Sclerosis associated SOD1^{G93A} Mutant Protein Toxicity: In Vitro and In Vivo Evidences. Neuroscience 2021 Oct 1; 473(1): 1-12.

[vii] Li T, Zheng LN and Han XH. Fenretinide attenuates lipopolysaccharide (LPS)-induced blood-brain barrier (BBB) and depressive-like behavior in mice by targeting Nrf-2 signaling. Biomedicine & Pharmacotherapy 125(2020) 1-10.

Study Rationale (cont'd)	M2 phenotype producing anti-inflammatory cytokines, as well as reducing microglial activation [viii], [ix]. This adaptive Phase 2/3 study (ESSOR) will assess the potential benefit and safety of LAU-7b against LONG COVID in non-hospitalized subjects with some moderate-to-severe symptoms. This study is a logical extension of investigating LAU-7b as a potential therapeutic against various phases of COVID-19, and it aims to evaluate its efficacy at reducing the overall disease burden in adults with LONG COVID, improving multiple dimensions of Quality-of-Life and alleviating the symptoms, together with the need for COVID-related unplanned care including hospitalization, and the prevention of significant cardiovascular events and survival. While biomarkers for LONG COVID are not yet fully established [x, xi] and considering that there is no known disease-modifying treatment for LONG COVID yet, it is appropriate and desirable to monitor an array of biomarkers susceptible to change upon administration of LAU-7b, earmarked as a potential disease-modifying LONG COVID treatment [xii]. A biomarker sampling sub-study was first introduced in Protocol Version 1.3 on a voluntary basis. In this Protocol Version 1.4, biomarkers will be sampled from all new randomized subjects at all (up to 6 sites) participating clinical sites (the biomarker sampling sub-study is described in details in Appendix 2). Due to its antiviral properties and its inflammation-controlling effects in the lungs and brain, two of the most affected organs by the post-COVID syndrome, LAU-7b is therefore being proposed as a potential disease-modifying medication for the treatment of LONG COVID.
Study Endpoints	[redacted] **<u>Primary endpoint:</u>** The overall functional health status evaluated with the physical component score (PCS) of the SF-36[xiii] questionnaire at Week 12 compared to baseline (screening), with covariate adjustments for baseline PCS, gender, age group, COVID vaccination status (vaccinated, unvaccinated), COVID-19 infection severity. Other prognostic factors may be considered in exploratory analysis. This will be analyzed with a repeated measure analysis of variance (MMRM). **<u>Secondary and exploratory endpoints</u>**: 1. Safety: Incidence of AEs, SAEs as well as AEs leading to study medication discontinuation, from randomization through Week 12 (see specific reporting instructions in Protocol Section 11.1.1).

[viii] Cao Y, Lin Y, Sun Y, Liu W, Shao Y and Zheng C. (2021) Fenretinide regulates macrophage polarization to protect against experimental colitis induced by dextran sulfate sodium, Bioengineered, 12:1, 151-161.
[ix] Dong X, Feng Y, Xu D, Zhang M, Wen X, Zhao W, Hu Q, Zhang Q, Fu H and Ping J. Targeting macrophagic 17b-HSD7 by fenretinide for the treatment of nonalcoholic fatty liver disease. Acta Pharmaceutica Sinica B 2023;13(1):142e156
[x] Conti V et al. Long COVID: Clinical Framing, Biomarkers, and Therapeutic Approaches. J. Pers. Med. 2023, 13, 334. https://doi.org/10.3390/jpm13020334
[xi] Espin E et al. Cellular and molecular biomarkers of long COVID: a scoping review. eBioMedicine 2023;91: 104552
[xii] Lai YJ et al. Biomarkers in long COVID-19: A systematic review. Front. Med. 10:1085988, 20 January 2023
[xiii] The SF-36 (36-Item Short Form Survey) is a set of easily self-administered quality-of-life measures used to evaluate the dimensions of activity level, improvement of their condition, the ability to work, have social activities, their pain level as well as their mood and general health status perception. Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.

Study Endpoints (cont'd)	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-C[xiv]), 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)[xv], 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 ≥25%, ≥50% or ≥75% improvement in the DALCI Score©[xvi] at Weeks 4, 8 and 12. *See Section 10.7 for details.* 9. Efficacy: Change from baseline in the EQ-5D-5L[xvii] score at Weeks 4, 8 and 12. 10. Efficacy: Proportion of subjects with relief of at least one core[xviii] 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. 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 (ie, 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.

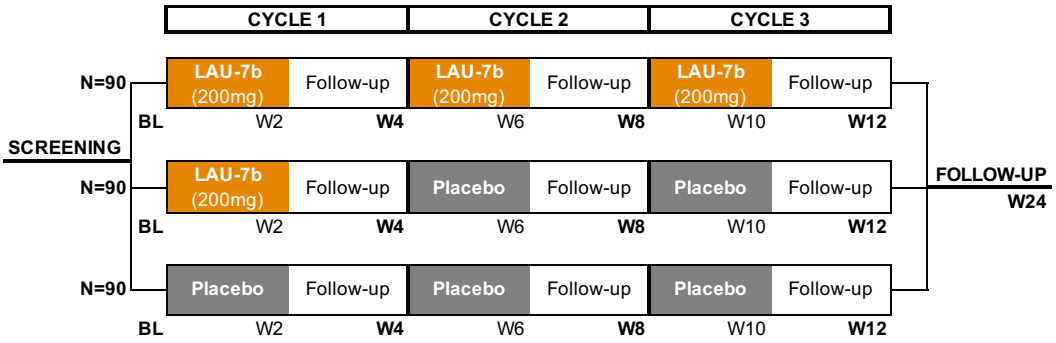
[xiv] The PGI-C is a single item questionnaire that asks: "Overall, how would you rate the change in your ability to perform usual daily activities since you started the study?". These are the 7-point scale options: 1) "very much better", 2) "much better", 3) "minimally better", 4) "no change", 5) "minimally worse", 6) "much worse", or 7) "very much worse". Higher scores indicate a change for the worse and lower scores indicate a change for the better.

[xv] This specialized instrument was developed to characterize and evaluate the debilitation caused by a physical exertion, whether a usual daily activity or a leisure activity.

[xvi] The DALCI Score© is a novel proposed score that measures the impact of core LONG COVID symptoms on the ability of a subject to perform daily activities, in order to evaluate the overall burden of LONG COVID on the subject's life.

[xvii] EQ-5D-5L is a validated Quality-of-Life short questionnaire by EuroQol Research Foundation.

[xviii] Core (most common) LONG COVID symptoms: fatigue, post-exertional malaise, trouble sleeping, shortness of breath, general pain and discomfort, cognitive problems (most commonly known as brain fog or memory fog) and mental health symptoms. *See Section 10.7 for details.*

Study Endpoints (cont'd)	**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.
Study Design Overview	ESSOR is a randomized, double-blind, placebo-controlled study of the oral antiviral and inflammation-controlling LAU-7b for the treatment of symptomatic non-hospitalized adults with LONG COVID. This design is appropriate for this phase of development as it targets symptomatic individuals with persistent, interfering symptoms subsequent to an episode of SARS-CoV-2 infection. It builds on the known efficacy and safety profile of LAU-7b in hospitalized adults with COVID-19, as well as on the preclinical evidence of LAU-7b as a host-directed antiviral with inflammation-controlling effects in several preclinical models of respiratory and neurological inflammation - two of the most frequently affected organs in LONG COVID. In the Phase 2 portion of the ESSOR study, a total of up to 270 subjects with LONG COVID will be randomized. Subjects will be 18 years and older, of both genders, diagnosed with LONG COVID and exhibiting a LONG COVID symptomatology including a minimum of one moderate to severe core LONG COVID symptom. There is a minimum 12 weeks between the start (test positivity or symptom onset) of the causative COVID-19 infection and screening for this study, to ensure the symptoms are those of LONG COVID. Each study arm will consist of three (3) cycles of 14 days of treatment intake each spaced by a drug-free period of 14 days. 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. Below is a schematic of the study structure for the Phase 2 portion:  All subjects will self-administer the study treatment at home, orally, once a day, along with the largest meal of the day, if possible, for a period of 14 days per cycle or until early termination, on top of stable (must have reached maximum effect prior to screening or minimum 2 weeks prior to screening, whichever is longest) Standard of Care (SOC) symptomatic relief medication, where applicable. According to the visit strategy, the Week

Study Design Overview (cont'd)	4 and 8 visits should be carried out as telehealth contacts while the Week 2, 10 and 12 visits will be in-person. The last follow-up will be on Week 12 relative to randomization. A longer-term telehealth contact is planned on Week 24 to evaluate LONG COVID symptoms, general health, significant cardiovascular events and survival, but is not part of the core study analyses. The end of participation 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 subjects will continue to undergo the SOC and planned study assessment, whenever possible. The study will be overseen by an independent Data and Safety Monitoring Board (DSMB). Based on the results of the Phase 2 portion, the most promising treatment regimen will be evaluated in a distinct Phase 3 portion, in a 1:1 randomization against placebo, and the sample size of this distinct and self-sufficient study portion will be estimated (see Section 7.2.1 of the protocol for details). The biomarker sampling sub-study is described in detail in Appendix 2. Overall, it consists of contributing blood samples 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. First introduced on a voluntary basis in Protocol Version 1.3, the biomarker sampling sub-study will be integrated in the subject's participation under this Protocol Version 1.4 and will involve all ESSOR clinical sites (up to 6 sites). Up to 100 subjects in total will participate in the sub-study which will only be conducted during the Phase 2 portion of the ESSOR study.
Study Population	**Study Inclusion Criteria:** • Subjects must be 18 years and older, of either gender, and able to give informed consent; • Subjects diagnosed with LONG COVID and exhibiting persisting, relapsing or new LONG COVID symptom(s) at least 12 weeks beyond the start (test positivity or symptom onset) of the causative COVID-19 infection; • At least one of the LONG COVID symptoms must be from the core list of LONG COVID symptoms, and be present for a minimum of 2 weeks prior to screening and of moderate or severe intensity as per the 4-level Likert severity scale (0 to 3; 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms); • If female, must be either post-menopausal (one year or greater without menses), surgically sterile, or, for female subjects of child-bearing potential who are capable of conception, must be: practicing a highly effective method of birth control (acceptable methods include intrauterine device, complete abstinence, spermicide + barrier, male partner surgical sterilization, or hormonal contraception) during the study treatment intake and through 30 days after the last dose of the study medication. Periodical abstinence is not classified as an effective method of birth control. A pregnancy test for female subjects of child-bearing potential must be negative at the Screening Visit; • Subjects deemed capable of adequate compliance including attending scheduled follow-up calls/visits for the duration of the study, have internet access and able

Study Population (cont'd)	to read and answer questionnaires on electronic Patient Reported Outcomes platform (ePRO) or paper; • Screening laboratory test and vital signs results within ranges compatible with the subject's health condition, as per investigator's judgement. See also the last exclusion for certain liver function tests; • Subjects deemed capable of swallowing the study treatment capsules. **Study Exclusion Criteria:** • Subject is currently hospitalized (any reason); • Pregnancy or breastfeeding; • Any COVID vaccination within 4 weeks of screening or planned during study participation; • Presence of any health condition judged by the investigator to be directly causing one or more of the most common LONG COVID symptoms; • Health condition deemed to possibly interfere with the study endpoints and/or the safety of the subjects. For example, the following conditions should be considered contraindicated for participation in the study. In case of doubt, the Investigator should consult with the Sponsor's medical representative: o Febrile neutropenia; o Fibromyalgia deemed to interfere with generalized pain disorder measurements; o Presence of end-stage cancer (palliative care). • Presence or suspicion of drug or alcohol abuse, as judged by the Investigator; • Known history of a severe allergy or sensitivity to retinoids, or with known allergies to excipients in the oral capsule formulation proposed to be used in the study; • Participation in another interventional drug, alimentary supplement, psychological or device...etc. clinical trial within 30 days (or a minimum of 5 elimination half-lives for drugs) prior to screening, except ongoing participation in non-interventional studies; • Presence of total bilirubin >1.5 x ULN (in the absence of demonstrated Gilbert's syndrome), ALT and/or AST > 2.5 x ULN.
Dose and Mode of Administration	**Dose rationale in non-hospitalized subjects with LONG COVID** According to the randomization, a daily dose of 200 mg (2 x 100 mg capsules) or placebo (2 x placebo capsules) will be administered orally once-a-day for 14 consecutive days per cycle, along with the largest meal of the day, if possible. The capsules should not be broken down or opened to facilitate intake. Study treatment will be administered on top of stable (must have reached maximum effect prior to screening or minimum 2 weeks prior to screening, whichever is longest) SOC symptomatic relief medication, where applicable. On the exposure standpoint, the LAU-7b 200 mg/day 14-day regimens should achieve, within days of starting a cycle, an average fenretinide circulating level of circa 2-3 µM, which correspond to concentrations eliciting both the antiviral and inflammation-controlling effects. Furthermore, tissue distribution studies have shown that fenretinide elicits higher lung and brain tissue concentrations relative to blood; it is therefore

Dose and Mode of Administration (cont'd)	unnecessary to use the 3 days x 300 mg loading dose, albeit safe, used in the RESOLUTION Phase 2/3 study in hospitalized subjects, where the disease is in a viremic phase and more at risk of acutely aggravating in certain patients. Furthermore, given the lack of understanding of LONG COVID pathogenesis and the preservation of LAU-7b's effect over time, the Phase 2 portion of the study aims to evaluate two dosing regimens in order to determine if repeating treatment cycles has an impact on the outcome. The most promising treatment regimen will be further evaluated in the Phase 3 confirmatory portion of the study, after regulatory approval. **Randomization** For the Phase 2 portion of the study, eligible subjects will be randomized in a 1:1:1 double-blinded fashion to either LAU-7b (active) arms (2) or placebo (control) group (1), after stratification for the severity (mild/moderate versus severe) of the COVID-19 infection linked to the LONG COVID condition. In the Phase 3 portion, a 1:1 randomization will be used versus placebo, and could use a similar stratification factor or others.
Disallowed medications and precautions	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: cyclosporine A; verapamil; tamoxifen; ketoconazole, chlorpromazine and thioridazine; RU486 (mifepristone); indomethacin; or sulfinpyrazone are prohibited during the entire study treatment period (84 days).
Statistical Analysis	**Sample size considerations:** This is an adaptive Phase 2/3 study which consists in a regimen-finding Phase 2 portion that is hypothesis generating, followed by a confirmatory Phase 3 portion. Given the exploratory nature of the Phase 2 portion, no formal sample size calculation or statistical power estimation have been done for that portion. The proposed arm size of 90 subjects /arm, for a total of up to 270 subjects (a multiple of 6, since there is one stratification factor) is considered to be sufficient to observe trends, and will have greater than 80% power to detect a 10-point difference in the PCS between a treatment group and the placebo group at 5% two-sided significance level, assuming that the common standard deviation is 20. Once the results are available, a formal consultation with regulatory agencies and experts will be conducted, to determine the proper endpoint strategy for the confirmatory portion of the study protocol. The selection of endpoints will benefit from this Phase 2 part of the study, and the sample size will be estimated in order to have at least 90% power with a two-tailed test to make the results of the Phase 3 portion confirmatory. There is limited knowledge on the impact of drug interventions on LONG COVID at this time and the ESSOR study will provide a wealth of information on the effect size, the amplitude and rate of recovery from LONG COVID symptoms. **Primary Efficacy Endpoint Analysis:** The primary efficacy endpoint is based on testing the treatment effect on functional health status between LAU-7b study arms for the PCS [redacted] of the SF-36 questionnaire, a parametric variable ranging from 0-100, compared to baseline, between the LAU-7b arms and the placebo arm. The analysis will include all determinations up to Week 12, including after early treatment discontinuation. Appropriate imputation methods for addressing the missing data not related to intercurrent events will be used for the primary analysis, and a sensitivity analysis that adopts a different imputation approach will be conducted. Missing data handling related to intercurrent events will be detailed in the SAP.

Statistical Analysis (cont'd)	The null hypothesis is that the average PCS of subjects is the same between a pool of the LAU-7b study arms and the placebo arm and the working hypothesis is that there is a difference in favor of a pool of the LAU-7b study arms and the placebo arm. An alpha of 0.05 (two-tailed) will be used. The model will include the absolute change from baseline PCS as 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, COVID vaccination status (vaccinated, unvaccinated), COVID-19 infection severity. Other prognostic factors at baseline may be considered in exploratory analysis. Independently of the MMRM outcome, each LAU-7b study arm will be compared with the placebo arm and both LAU-7b study arms will be compared to each other, The statistical analyses for the other study parameters are summarized in Section 12.5.2 of the protocol and will be detailed in the SAP).

2 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.

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3 GLOSSARY OF TERMS AND ABBREVIATIONS

AA: Arachidonic Acid
AE: Adverse Event
ALT: Alanine Aminotransferase
ANCOVA: analysis of covariance
AST: Aspartate Aminotransferase
ATRA: All-Trans Retinoic Acid
AUC: Area Under the Curve
BBB: blood-brain-barrier
BID: *Bis In Die* (Latin), twice daily
BMI: Body Mass Index
BW: Body Weight
C_{avss}: Average Concentration at Steady-State
CD40L: CD40 ligand, CD154
CF: Cystic Fibrosis
CFTR: Cystic Fibrosis Transmembrane Conductance Regulator
C_{min} : Minimal Concentration in Matrix (plasma, blood….etc)
C_{max}: Maximal Concentration in Matrix (plasma, blood…etc)
COVID-19: Coronavirus Disease 2019
CRF: Case Report Form
CRO: Contract Research Organization
CTCAE: Common Terminology Criteria for Adverse Events
CXCL10: Interferon gamma-induced protein 10 (IP-10)
DHA: Docosahexaenoic Acid
DLT: Dose Limiting Toxicity
DSMB: Data and Safety Monitoring Board
EC: Ethics Committee
ECG: Electrocardiogram
ERK1/2: Extracellular Signal-Regulated Kinase 1/2
FRD: Fenretinide, 4-HPR
GCP: Good Clinical Practice
CRP: C-Reactive Protein
ICF: Informed Consent Form
IFNγ: Interferon gamma
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
IRB: Institutional Review Board
IRCM: Institut de Recherches Cliniques de Montréal

ITT : Intent-to-Treat
IV : Intravenous
IWRS: Interactive Web Response System
KO : Knock-Out
MedDRA: Medical Dictionary for Regulatory Activities
MTD: Maximally Tolerated Dose
NCE: New Chemical Entity
NF-κB: Nuclear Factor-kappaB
NSAID: Non-steroidal anti-inflammatory drug
PCS: Physical Component Score
PD: Pharmacodynamic
PI: Principal Investigator
PK: Pharmacokinetic
PO: *per os* (Latin), by mouth, orally
PP: Per Protocol
PPAR: Peroxisome Proliferator Activating Receptor
ppFEV$_1$: Forced Expiratory Volume in one second percent predicted
QD: *Quaque Die* (Latin), every day/daily
QoL: Quality of Life
RAR: Retinoic Acid Receptor
RBC: Red Blood Cells, erythrocytes
RBP: Retinol Binding Protein
RXR: Retinoid-X-Receptor
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SD: Standard Deviation
SOC: Standard of Care
SUSAR: Suspected Unexpected Serious Adverse Reactions
TEAE: Treatment Emergent Adverse Event
TESAE: Treatment Emergent Serious Adverse Event
TID: *Ter In Die* (Latin), three times daily
TMF: Trial Master File
TNF-α: Tissue Necrosis Factor Alpha

4 STUDY PERSONNEL

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5 INTRODUCTION

5.1 Investigational product

LAU-7b is a novel solid amorphous dispersion of fenretinide (100 mg per capsule) formulated for oral administration as an orange opaque, size 00, hard gelatin capsule. The active product ingredient is N-(4-hydroxyphenyl)retinamide, also referred to as fenretinide, 4-HPR or FRD, is a synthetic amide of all-trans retinoic acid with a molecular formula $C_{26}H_{33}NO_2$. Fenretinide is an investigational drug (new chemical entity, NCE) with well-documented history of safety in non-clinical and clinical studies ([redacted] US National Cancer Institute (NCI) since 1992).

LAU-7b was investigated in two Phase 1 clinical studies (elderly and non-elderly healthy subjects and adult patients with cystic fibrosis (CF)), and two Phase 2 clinical studies: one study in adults with CF, and one study in hospitalized adults with moderate-to-critical COVID-19. LAU-7b is currently being evaluated in a Phase 3 study in hospitalized adults with moderate-to-severe COVID-19.

Fenretinide was also extensively tested in clinical studies (Phases 1 to 3), involving more than 3,000 patients (mostly in oncologic indications), and was proven to be safe and relatively well tolerated for long term use [1]. Fenretinide has not yet been commercialized in any country and remains a NCE.

The investigational product formulation of LAU-7b contains the following non-medicinal ingredients: [redacted]

An orange opaque, size 00 hard gelatin capsule without active substance will be used as a control and matching placebo for blinding purposes and contains the same non-medicinal ingredients.

5.1.1 Purpose for LAU-7b, a novel and improved oral formulation of fenretinide

Fenretinide is poorly absorbed following oral administration, and it suffers from a wide inter-subject variation in bioavailability when delivered orally in an oily vehicle, such as the softgel capsules used in most oncology trials, containing fenretinide suspended in corn oil. The poor bioavailability and the large size of the softgel capsules was a limiting factor in the clinical studies conducted with these, particularly in the pediatric population.

There was thus a need for new pharmaceutical dosage form of fenretinide, especially for oral administration, capable of overcoming the poor oral bioavailability of the previous corn-oil based oral formulation and the fair patient compliance.

Laurent Pharmaceuticals has purposedly developed a novel oral dosage form of fenretinide with increased oral bioavailability and formulated as a powder that can be encapsulated or compressed in various sizes, thus with expected better compliance for both adult and pediatric patient populations, more specifically by reducing the size/number of unit dosage forms to ingest. The Laurent Pharmaceuticals' formulation (LAU-7b) [redacted] was successfully tested by Laurent in a Phase 1b study in adults with CF)[2]. [redacted]

5.2 COVID-19 and LONG COVID Overview

SARS-CoV-2 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. COVID-19 manifests as a wide range of illnesses, from asymptomatic infection to severe pneumonia, ARDS, and death.

While most patients with COVID-19 are thought to have a favorable prognosis, older patients and those with chronic underlying conditions may have worse outcomes with rapid progression to acute respiratory distress syndrome (ARDS) and requirement for invasive mechanical ventilation, thus creating an unsustainable burden for the health care system and a rapidly escalating crisis[3].

Furthermore, and in parallel, there is an accumulating body of knowledge confirming that a sizeable proportion (10-30%) of patients infected with SARS-CoV-2 have relapsing, persistent (or develop) longer term signs and debilitating symptoms interfering with their daily activities [4], and the scale of newly disabled individuals is contributing to labour shortages [5]. This is named LONG COVID (also named Post COVID-19 condition, Post-Acute Covid Syndrome (PACS), Post-Acute Sequelae of COVID/SARS-CoV-2 (PASC)). There is a significant burden of LONG COVID symptoms on patients and a very significant unmet medical need. There are likely multiple, potentially overlapping, causes of LONG COVID, including damage from original infection, lingering reservoirs of virus in the body causing organ injury, immune-dysregulation with or without reactivation of underlying pathogens, including herpesviruses such as Epstein‑Barr virus (EBV) and human herpesvirus 6 (HHV-6), among others [6, 7], or a dysregulated immune-inflammatory response damaging small blood vessels or nerves [4].

There is still no unanimous definition of what constitutes LONG COVID symptoms since it is heterogeneous, composed of numerous symptoms and conditions with variable and potentially overlapping etiologies. However, there is a notion of timing/presence of symptoms after 4 weeks post-infection [8], and/or presence of symptoms for 12 weeks or more post-infection [9], and not explained by an alternative etiology including a COVID re-infection. The sequelae of SARS-CoV-2 infection can involve multiple organ systems and are often grouped together as "LONG COVID" or PASC [10]. The terms themselves are nebulous, the clinical presentations extremely variable, and the prognosis uncertain [11, 12]. The absence of evidence-based treatments further fuels the frustration of affected patients and their clinicians. Add to these problems a fragile and fragmented healthcare system and the result is disarray in the clinical approach to this complex and multifaceted disorder.

Generally, LONG COVID signs and symptoms include shortness of breath, fatigue with or without exertion, myalgia, glucose intolerance, multisystem inflammatory syndrome, postural orthostatic tachycardia, peripheral neuropathy and others, reflective of a multi–organ-system involvement. Although this categorization is helpful for research and tracking of electronic health records, it does little to help clinicians or affected people make their way through a maze of difficulties from diagnosis to treatment.

A lack of understanding of LONG COVID inevitably also complicates care. LONG COVID clinics have been established to provide multidisciplinary care, although most affected patients are also followed by primary care providers or seen by various specialists, depending on the duration and severity of their dominant symptoms. Educational programs for patients and clinicians are lacking. Referrals to subspecialists such as cardiologists, pulmonologists, and neurologists are common but often lead to more delays, fragmentation of care, and frustration at all levels.

There is unfortunately a stigmatization affecting these patients because of perceived simulation or psychosomatization of symptoms. Most people with LONG COVID do not feel empowered to take control

of their care and are grappling with difficulty expressing how deeply their life is affected, when most of the objective tests do not highlight a physical problem.

5.3 Treatment of LONG COVID

While a number of therapeutic tools were progressively discovered and adopted for the prevention or treatment of COVID-19, consisting of vaccines, virus-directed antivirals and neutralizing antibodies, there is no approved disease-modifying medication for the prevention or treatment of LONG COVID. Treatment of these patients is limited to currently available symptomatic therapies. Such impressive effort at coping with the COVID-19 infection is all the more striking in contrast to the void in patient care for LONG COVID, a syndrome that may affect 10% or more of infected people [13].

There is a significant unmet medical need for either preventing the long-lasting symptoms of LONG COVID or treating them. There is only a limited number of prophylactic or therapeutic modalities, even less drug candidates, being tested for this multifaceted and multisystemic condition. A number of these interventions only focus on specific symptoms of LONG COVID. The severity of each symptom, the number of these symptoms and their interference with the patient's daily usual activities (the burden) generally determine if the patient will seek care.

Beyond caring for the symptoms there is an overarching need for taking care of the patient's ability to return to pre-infection activity level. It is well and good if a treatment is addressing one of the burdensome symptoms but the patient may still be unable to return to their usual daily activities, whether physical due to lingering fatigue or dyspnea, or CNS-based such as brain fog or insomnia. This is where a treatment tackling various facets of the condition, a general disease-modifying effect, could impact significantly the individual and the society.

5.4 Study Rationale

LAU-7b is developed as a next generation, broadly effective oral COVID-19 therapeutic with dual antiviral and inflammation-controlling activity. LAU-7b is currently being evaluated in hospitalized subjects with moderate-to-severe COVID-19 in a Phase 3 confirmatory study on the basis of a positive efficacy signal in the pilot Phase 2 portion of the study. Results from the Phase 2 portion showed 100% reduction in the risk of progression to mechanical ventilation and death by Day 60 in LAU-7b-treated hospitalized moderate-to-severe COVID-19 subjects, relative to placebo. Subjects on LAU-7b tended to recover more rapidly and leave hospital faster. LAU-7b was well-tolerated, with safety comparable to placebo. Due to its unique host-directed mechanism of action and convenient once daily oral administration, LAU-7b holds the promise of a next-generation COVID-19 and LONG COVID therapeutic.

<u>LAU-7b lipid modulation as host-directed antiviral</u>

LAU-7b works by modulating host cell membrane lipids composition and fluidity, and de-novo cell lipogenesis. SARS-CoV-2 must reprogram host cellular lipid metabolism to favor its entry and replication, a mechanism shared by all lipid-enveloped viruses [14]. Because it acts on the host rather than the virus by inhibiting delta-4 and delta-9 desaturases[15, 16], LAU-7b has potential for broad-spectrum antiviral activity regardless of mutations, as already demonstrated in vitro on multiple SARS-CoV-2 variants (including Delta and Gamma) and the MERS-CoV [17]. Broader antiviral potential of fenretinide was demonstrated in preclinical testing against Dengue fever [18], Zika virus [19], respiratory syncytial virus [20], and HIV [21], via a mechanism also involving lipid modulation.

LAU-7b pro-resolving effects on inflammation

Fenretinide, the active pharmaceutical ingredient in LAU-7b, was also shown to trigger certain membrane phospholipid metabolic pathways involved in the resolution phase of inflammation, a natural mechanism that keeps the inflammatory response under control without inducing immune-suppression (a "pro-resolving" effect).

LAU-7b was evaluated in a Phase 2 clinical trial in adults with CF aiming to treat the exaggerated inflammatory response that leads to irreversible lung damage. Earlier Phase 1b clinical data from adults with CF, with LAU-7b escalating doses of up to 300 mg administrated orally, once-a-day, showed that LAU-7b was safe and well tolerated, and able to maintain the balance between arachidonic acid (AA) and docosahexaenoic acid (DHA) pathways, with a favourable effect on certain biomarkers of inflammation (interleukins IL-6, IL-8, IL-10, and neutrophils count) at the onset of a pulmonary exacerbation episode, suggestive of a protective effect on the lungs.

Fenretinide's lipid modulating properties and resulting pro-resolving effect on inflammation at low doses were demonstrated in multiple preclinical models of acute and chronic inflammation, including a mice model of septic shock and cytokine storm induced by *Streptococcus suis* [22], CF mice model of inflammation and infection induced by *Pseudomonas aeruginosa* [23], and mice model of allergic asthma [24].

Even more relevant for its potential benefit against LONG COVID neurological symptoms, fenretinide has shown ability to cross the blood-brain barrier (tissue distribution study in rats) and exert inflammation-controlling effect in multiple preclinical models of neuro-inflammation: A mouse model of spinal cord injury [25], two animal models of ALS [26, 27], and a mouse model of depression and blood-brain-barrier (BBB) dysfunction [28]. Furthermore, fenretinide demonstrated in several in vitro studies an effect on abrogation of macrophage polarization to M1 phenotype that produces pro-inflammatory cytokines and promoting M2 phenotype producing anti-inflammatory cytokines, as well as reducing microglial activation [29, 30]. Finally, fenretinide is used clinically to treat children and adults with glioblastomas and astrocytoma, at high doses, indicative of adequate brain penetration [31, 32].

Treatment goal and expected clinical benefits

Due to its antiviral properties, its good blood-brain barrier penetration and its pro-resolving effects on inflammation, LAU-7b is being proposed to reduce or abate LONG COVID symptom severity, promote a return to pre-infection usual activity level, by maintaining a balanced immune-inflammatory status.

As it is postulated that LONG COVID may be associated with residual pockets of SARS-CoV-2 viral particles, a host-directed antiviral such as LAU-7b is expected to be useful against multiple variants. Furthermore, the timely resolution of inflammation is as important as its initiation phase and a good balance between pro-inflammatory and pro-resolving mediators is key to maintaining an efficient and harmless inflammatory response. Incomplete resolution leads to chronic inflammation and fibrosis, and ultimately to organ impairment [33, 34].

The treatment goal is to sufficiently reduce the LONG COVID symptom burden to return the individual to its pre-infection usual activity level, inasmuch as possible. The expected clinical benefit can take the form of individual symptom severity reduction or elimination, a lowered level of burden to the individual and to the care team, a lower reliance on symptomatic relief Standard of Care (SOC) and a less fragmented care.

This study (ESSOR) aims to investigate the potential benefit and safety of LAU-7b against LONG COVID in non-hospitalized subjects with some moderate-to-severe symptoms. This is considered a logical extension of investigating the potential benefit LAU-7b may have against various phases of COVID-19. The LAU-7b antiviral properties and its ability to cross the BBB, doubled by the evidence of inflammation-controlling

activity in multiple animal models of lung and brain injury, which are two of the most affected organs by post-COVID syndrome, warrants the evaluation of LAU-7b against LONG COVID.

5.4.1 Proposed Mechanism of Action in LONG COVID

LAU-7b was shown to be a master regulator of key membrane lipids (essential fatty acids and sphingolipids) in conjunction with the inhibition of certain inflammation signaling pathways (MAPK/ERK1/2, NF-kB, cPLA2), which are believed to play an essential role in 1) the resolution of inflammation and prevention of an over-reactive response; and 2) the coronavirus cellular entry, replication and avoidance of the host defense.

Therefore, LAU-7b is proposed as a therapy for LONG COVID symptoms and its associated burden, for its antiviral properties and the potential to maintain a balanced inflammatory response including the control of neuroinflammation, which may help with neurological/psychiatric symptoms, common in LONG COVID.

Although being a derivative of a vitamin A, fenretinide behaves as an atypical retinoid with both retinoid acid receptor-dependent and independent activities, showing a different pharmacological behavior compared to retinoic acid [35]. Fenretinide is a potent transactivator of retinoid acid receptor (RAR)γ and a moderate activator of RARβ, but is not an activator of RARα and retinoid-X-receptor (RXR)α [36]. At low doses [redacted] fenretinide was shown to have modulating activity on certain bioactive membrane lipids (phospholipids and sphingolipids) that play central roles in the activation/resolution of the inflammation process, as well as in the host defense against pathogens. In the case of LONG COVID, such a host-directed effect would help in reducing the stimulation of immune response triggered by hidden reservoirs of SARS-CoV-2 viral particles, which may be responsible for some burdensome symptoms.

Although the complete mechanism of action in LONG COVID is not fully elucidated, fenretinide is hypothesized to work in this multifaceted condition by modulating cell membrane lipids fluidity and reducing *de-novo* lipogenesis via inhibiting certain fatty acids desaturases (delta-4-desaturase, delta-9-desaturase) [37, 38]. Recent publications have cited MAPK/ERK, NF-κB and cPLA2 as important factors for coronavirus entry and replication in the host cells [39, 14, 40, 41]. Fenretinide was also shown to increase phospholipids linked to the resolution phase of inflammation, a process that mimics body's own inflammation-controlling mechanism and less likely to induce immune-suppression.

It was shown in animal models and in humans that fenretinide was able to control inflammation by modulating the ratio between the pro-inflammatory AA and the anti-inflammatory DHA in phospholipids in the cell membrane. The inflammation-controlling effect promoted by fenretinide involves a number of signaling pathway, such as inhibition of macrophage inflammatory mediators via the ERK 1/2 pathway [42], inhibition of the activation of the pro-inflammatory transcriptional NF-κB [43], as well as inhibition of the downregulation of Peroxisome Proliferator Activating Receptor (PPARγ), which is known to have a role in lipid metabolism [44]. More recently, it was demonstrated that fenretinide has the ability to also inhibit the activity of calcium-dependent cytosolic phospholipase A2 (cPLA2), which was previously described as a factor for the abnormal high levels of pro-inflammatory AA present in the cell membrane of CF patients. Recent evidence demonstrated fenretinide's ability to modulate membrane sphingolipids biosynthesis [45] and to increase the function of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) surface protein through its activity on the lipid microdomains (rafts) in the cell membrane.

Of particular relevance for LONG COVID is the ability to cross the blood brain barrier and act on similar pathways in the brain. This is exemplified by the mice model of spinal cord injury whereby oral fenretinide treatment after spinal cord contusion injury in mice reduced inflammation and tissue damage in the spinal cord and improved locomotor recovery [25]. Fenretinide led to a significant decrease in AA and an increase in

DHA levels in plasma and injured spinal cord tissue, reduced the expression of pro-inflammatory genes and the levels of oxidative stress markers.

Additionally, fenretinide attenuated oxidative stress and blunted inflammation in hippocampus of LPS-challenged mice. Fenretinide treatment markedly improved Nrf2 (nuclear factor erythroid-2 related factor 2) expression and nuclear translocation in mouse brain endothelial cells and promoted Nrf2-antioxidant responsive element (ARE) transcription activity, as well as its down-streaming signals leading to improved anti-oxidant enzymes. These findings are suggesting a neuroprotective potential of fenretinide to attenuate depressive-like behavior [28].

5.4.1.1 Fenretinide Nonclinical Toxicity

[redacted] conducted toxicity studies of fenretinide via per-os (PO), intra-peritoneal (IP), or intravenous (IV) routes of administration in mice, rats, rabbits, and dogs, and many of the studies carried out were published [46, 47, 48, 49]. Doses of up to 7000 mg/kg were given in acute studies, while in multiple-dose studies doses of up to 1800 mg/kg/day were administered. No mortality was observed in acute studies. Clinical observations following administration of high oral doses consisted primarily of diarrhea, loose stools, unkempt appearance, and reduced spontaneous activity. In multiple dose toxicity studies, up to one-year duration, mortality in fenretinide-treated animals was rare and occurred in less than 5% of animals tested. [redacted]

Reproductive Toxicity Studies. Doses ranging from 20 to 800 mg/kg/day (120 - 4800 mg/m^2) had no effect on the fertility and general reproductive performance of female or male rats; however, the complete inhibition of uterine implantation has been reported in mice receiving 100 mg/kg/day of fenretinide. Studies in rats and rabbits indicated that 800 mg/kg/day dose of fenretinide was teratogenic. The key role of retinoic acid in embryonic development mediates the high teratogenicity of retinoid pharmaceuticals, such as isotretinoin used for treatment of cancer and acne. Oral megadoses of pre-formed vitamin A (retinyl palmitate), and retinoic acid itself, also have teratogenic potential by this same mechanism. A screen of retinoids for developmental toxicity following single-dose PO administration to hamsters on Day 8 of gestation suggested

that fenretinide was less teratogenic than ATRA [51, 52]. Late gestation, parturition and pup survival were unaffected in a peri-postnatal toxicity study.

Genetic Toxicity Studies. In a variety of in vitro and in vivo test systems, fenretinide did not induce any genotoxic effects [53]. Its major metabolite, 4-MPR, was also negative in the mammalian cell mutation assay.

Metabolism and Excretion. Animal and human studies indicate that fenretinide undergoes significant phase 1 and phase 2 biotransformation *in-vivo*. The most abundant metabolite produced in human, dogs and rodents in *in-vivo* is N-(4-methoxyphenyl)retinamide (4-MPR) [54, 55], whereas additional metabolites, 4-oxo-N-(4 hydroxyphenyl)retinamide (4-oxo-fenretinide) and 4-hydroxy-N-(4 hydroxyphenyl)retinamide (4-OH-fenretinide), have been subsequently reported [56]. In contrast to rodents, 4-oxo-fenretinide is present at lower concentrations in humans. Although 4-MPR is now generally considered to be inactive [57, 58], 4-oxo fenretinide was found to be an active metabolite that inhibits cell proliferation [56, 59].

The enzymes responsible for production of 4-MPR (phase 2, methylation reaction) were not clearly determined, however they include microsomal amine-N-methyltransferases, that are known to be involved in the metabolism of many drugs and carcinogens [60]. The oxidative metabolism of fenretinide (phase1) is carried out by multiple cytochromes P450 (CYP)s, 3A4, 2C8, 2C9, 2C19, 2D6 and 2B6. This has been confirmed very recently by in-vitro metabolic stability experiments in human liver microsomes and hepatocytes (unpublished data) showing that based on its intrinsic clearance, fenretinide was identified as a low hepatic clearance compound. Fenretinide is likely cleared by human hepatocytes via a high-capacity low affinity pathway (unpublished data). Glucuronidation was shown to not playing a major role in the metabolism and clearance of fenretinide and its metabolites at clinically relevant levels [61].

Recently performed in-vitro drug metabolism studies with fenretinide over the concentration range of 0.5 – 20 μM produced an inhibition (IC_{50} < 0.5 μM) of CYP3A4, CYP2C9 and CYP2B6, produced a slight inhibition of CYP1A2 (0.5% – 31.2%; IC_{50} > 20 μM) and did not inhibit CYP2D6, CYP2C8 and 2C19 (IC_{50} > 20 μM). Based on this data, fenretinide can be considered a potent inhibitor of CYP3A4, CYP2C9, and CYP2B6 when incubated with midazolam, diclofenac and bupropion in the presence of human liver microsomes. Fenretinide was metabolized by several isoenzymes including CYP3A4, CYP 2C8, CYP2C9, CYP2D6 and CYP2B6. Comparison of the in vitro results of the CYP450 profiling experiments with the CYP450 inhibition experiments for fenretinide indicates that fenretinide is metabolized by and can inhibit CYP3A4, CYP2C9 and CYP2B6. Furthermore, in agreement with the literature, these recent experiments also showed that the propensity of fenretinide to use either uptake (OATP1B1 and OATP1B3) or P-GP efflux transporters appears to be low. The in vitro metabolic profile combined with safety data from a multitude of clinical studies in human indicate that fenretinide has a moderate to low potential for drug-drug interactions.

5.4.2 Direct and Supportive Clinical Evidences

5.4.2.1 Safety and Efficacy Results from the RESOLUTION Phase 2/3 study in hospitalized adults with COVID-19

At the time of the generation of this ESSOR protocol, the RESOLUTION Phase 2/3 study has successfully achieved its randomization objective for the Phase 2 pilot portion, with 240 subjects screened and 232 randomized and is just short of midway in the recruitment objective for the confirmatory Phase 3 portion.

In the Phase 2 pilot portion performed at 14 clinical sites in US and Canada, the rate of screen failure was lower than expected with most subjects being consented, screened and randomized within hours of first contact by the site staff. The randomization stratified by site resulted in a balanced active/placebo sample per site. All subjects were enrolled between 18 August 2020 and 15 May 2021.

The enrollment in the Phase 3 extension [redacted] at 19 clinical sites in Canada and US. [redacted]

Study demographics for the Phase 2 pilot portion: Out of the total 232 subjects with moderate, severe or critical COVID-19 (WHO Health Status score of 3, 4 and 5 respectively, 148 subjects had moderate-to-severe disease (not requiring oxygen or requiring low-flow oxygen supplementation) and 84 were critically ill subjects requiring high-flow oxygen supplementation but not mechanical ventilation (Table 1).

Table 1: RESOLUTION Subject demographics

Baseline Characteristics	LAU-7b (n=117)	Placebo (n=115)
Age (years)		
Mean	57.5 ± 13.5	56.7 ± 12.4
Sex, n (%)		
Female	46 (39.3%)	45 (39.1%)
Male	71 (60.7%)	70 (60.9%)
BMI (kg/m2)		
Mean	33.95 ± 7.95	35.06 ± 7.80
Race, n (%)		
White	92 (78.6%)	86 (74.8%)
Black, Asian, and other ethnic groups	25 (21.3%)	29 (25.2%)
Score on ordinal scale, n (%)		
3. Hospitalized, not requiring supplemental oxygen	17 (14.5%)	12 (10.4%)
4. Hospitalized, requiring supplemental oxygen at low flow cannula	59 (50.4%)	60 (52.2%)
5. Hospitalized, non-invasive ventilation or high-flow oxygen devices	41 (35.0%)	43 (37.4%)

Overall, the two treatment arms were very well balanced and no bias due to an odd distribution of baseline characteristics was noted. The subject demographics were similar among the two treatment arms and more than 60 % of subjects had at least 3 co-morbidities. The Health Status 3 and 4 subgroups (moderate to severe COVID-19) together represented 64.9 and 62.6 % of all randomized subjects (LAU-7b and placebo, respectively). Finally, both treatment arms were well balanced in terms of use of most COVID SOC concomitant medications, such as remdesivir and systemic corticosteroids.

Safety summary for the Phase 2 pilot portion: In the safety population (all randomized subjects who took a minimum of one dose of study medication, n=232), a total of 798 adverse events (AEs) were experienced by 191 out of 232 subjects (Table 2). The same safety information is presented in (Table 3) for the moderate-to-severe subgroup of 148 subjects.

Table 2: RESOLUTION Safety summary in overall safety population (n=232)

	LAU-7b		Placebo	
	Subjects (n=117)	Events (n=377)	Subjects (n=115)	Events (n=421)
Any Treatment Emergent Adverse Events (TEAEs), n (%)	97 (82.9%)	374 (99.2%)	94 (81.7%)	418 (99.3%)
Relationship to study treatment, n (%) *				
Not related	31 (26.5%)		38 (33.0%)	
Unlikely related	30 (25.6%)		27 (23.5%)	
Possibly related	31 (26.5%)		24 (20.9%)	
Related	5 (4.3%)		5 (4.3%)	
Severity, n (%)				
Mild	39 (33.3%)		38 (33.0%)	
Moderate	27 (23.1%)		32 (27.8%)	
Severe	19 (16.2%)		11 (9.6%)	
Life Threatening	12 (10.3%)		13 (11.3%)	
Serious Treatment Emergent Adverse Events, n (%)	23 (19.7%)	31 (8.2%)	22 (19.1%)	30 (7.1%)
TEAEs leading to study treatment discontinuation	22 (18.8%)	22 (5.8%)	18 (15.7%)	20 (4.8%)
TEAEs with a fatal outcome, n (%)	13 (11.1%)	13 (3.4%)	11 (9.6%)	11 (2.6%)

* The relationship to study treatment is investigator-determined

Table 3: RESOLUTION Safety summary in moderate-to-severe subgroup (n=148)

	LAU-7b		Placebo	
	Subjects (n=76)	Events (n=206)	Subjects (n=72)	Events (n=263)
Any Treatment Emergent Adverse Events (TEAEs), n (%)	59 (77.6%)	206 (100 %)	57 (79.2 %)	262 (99.6 %)
Relationship to study treatment, n (%)				
Not related	21 (27.6 %)		19 (26.4 %)	
Unlikely related	20 (26.3 %) *		15 (20.8 %)	
Possibly related	17 (22.3 %) *		21 (29.2 %)	
Related	1 (1.3 %) *		2 (2.8 %)	
Severity, n (%)				
Mild	28 (36.8 %)		28 (38.9 %)	
Moderate	22 (28.9 %)		18 (25 %)	
Severe	9 (11.8 %)		5 (6.9 %)	
Life Threatening	0 (0 %)		6 (8.3 %)	
Serious Treatment Emergent Adverse Events, n (%)	7 (9.2 %)	9 (4.4 %)	10 (13.9 %)	14 (5.3%)
TEAEs leading to study treatment discontinuation	6 (7.9 %)	6 (2.9%)	9 (12.5 %)	11 (4.2 %)
TEAEs with a fatal outcome, n (%)	0 (0%)	0 (0%)	4 (5.6 %)	4 (1.5 %)

In the overall safety population, almost all AEs were treatment emergent (TEAEs) in both treatment arms. The majority of the subjects (52 to 55%) in both treatment arms experienced "not related or unlikely related" events to the study treatment, 20 to 26% experienced "possibly related" events, a minority (4.3%)

experienced "related" events and 17-18.5% of subjects did not report adverse events. The majority of the subjects (56 to 60%) experienced mild to moderate events while 10 to 16% of the subjects had severe adverse events and a minority (10-11%) had life-threatening events, mostly worsening of COVID-19 respiratory failure. A total of 24 treatment-emergent fatalities occurred in the study, spread similarly between the two arms of the study; none of the fatalities were deemed to be related to the study treatment.

In the moderate-to-severe subgroups pooled together (Health Score 3+4), both treatment arms showed comparable distribution of causality relationship and severity. However, considering the LAU-7b treatment prevented some life-threatening complications or death, when compared to placebo, this is reflected in the uneven distribution of life-threatening events, fatalities and events causing discontinuation, more frequent in the placebo arm.

Across most body systems in the overall safety population, the incidence of TEAEs was comparable between the LAU-7b arm and the placebo arm, supporting the conclusion that LAU-7b has a good safety profile in COVID-19 patients, even for body systems known to be typical of fenretinide AEs, such as gastrointestinal, eye disorders and even skin disorders despite a slightly higher incidence in the LAU-7b arm, mostly mild dry skin events. The vast majority of treatment-emergent SAEs (TESAE) were related to the COVID-19 condition and no SUSAR was reported to Health Authorities. As in the overall safety population, the incidence of TEAEs in the 3 and 4 subgroup was comparable between the LAU-7b arm and the placebo arm across most body systems, with a higher incidence in the LAU-7b arm in the musculoskeletal and connective tissue disorders body system (7.3% versus 2.3%), and all deemed unrelated or unlikely related (back pain, arthralgia, joint effusion, myalgia, pain in extremity, wrist deformity, synovial cyst…etc.).

The independent study DSMB reviewed twice in a blinded and unblinded manner the safety information from the Phase 2 pilot portion and recommended to continue the study unchanged until its conclusion. [redacted] in the Phase 3 extension, the DSMB met twice and recommended to continue the study unchanged.

Efficacy Summary for the Phase 2 pilot portion: The primary analysis of efficacy is performed on the intent-to-treat (ITT) population (moderate-to-critical subjects who randomized and took a minimum of one dose of study medication, n=232). Along with full safety evaluation, a number of efficacy variables were pre-identified as topline results. These are the primary efficacy endpoint (the proportion of subjects alive and free of respiratory failure on Day 29, heath statuses 1-4 inclusively, ITT and PP), and the following secondary endpoints: Rate of all causes death by Days 29 and 60, Rate of transfer to mechanical ventilation by Day 60, Time to recovery (return back home) and finally the duration of hospitalization (including any re-hospitalization).

In the overall moderate-to-critical ITT population, no statistically significant differences between LAU-7b and Placebo were found for the primary endpoint of improving the proportion of subjects alive and free of respiratory failure on Day 29 (LAU-7b: 81/117 subjects, 69.2% versus Placebo: 83/115 subjects, 72.2%; p=0.74).

A clinically meaningful positive efficacy signal was achieved in the pre-specified subgroup moderate-to-severe COVID-19 subjects (n=148, representing 64% of the overall study population), with LAU-7b plus SOC demonstrating a 100% reduction in the risk of all-causes death and the risk of progressing to mechanical ventilation by Day 60, when compared to placebo plus SOC. (Table 4).

Table 4: RESOLUTION Efficacy summary in moderate-to-severe ITT subgroup (n=148)

(3+4) Moderate-to-Severe COVID (ITT population)	LAU-7b (n=76)	Placebo (n=72)	Relative reduction	p-value
Proportion of patients alive and free of respiratory failure at Day 29*	60/60	54/58	6.9% improvement	0.0553
Death from all causes by Day 60	0/76 (0%)	4/72 (5.6%)	100%	0.0536
Escalation to Invasive Mechanical Ventilation by Day 60	0/76 (0%)	5/72 (6.9%)	100%	0.0253**
Time to Recovery - Kaplan Meier estimate of 75% Chance of Recovery (days)	8 days	10 days	20%	0.3567
Duration of Hospitalization in Days (SD)	6.33 (8.39)	6.50 (5.78)	2.6%	0.0974

** Assumes patients lost-to-follow-up or who withdrew consent prior to Day 29 are alive and free from respiratory failure, but are not included in the total counts.*
*** Statistically significant*

More specifically, none of the 76 moderately to severely ill COVID-19 subjects treated with LAU-7b died or progressed to mechanical ventilation, while 4 subjects died (4/72, 5.6%, p=0.0536) and 5 progressed to mechanical ventilation (5/72, 6.9%, p=0.0253) in the placebo arm. The study also showed an improvement of 6.9% relative to placebo (p=0.0553) in the proportion of subjects alive and free of respiratory failure at Day 29, when treated with LAU-7b, as well as a faster recovery and a marginally shorter hospitalization.

This positive signal, in particular the total prevention of the need for mechanical ventilation or mortality in subgroups 3 and 4, was recognized by clinicians as being clinically relevant and worthy of clinical confirmation for this particularly underserved hospitalized population. Avoiding at all costs the progression toward respiratory failure and the need for ICU and invasive mechanical ventilation is a high priority.

The subgroup analysis of critically ill COVID-19 subjects didn't show an improvement in the LAU-7b arm over placebo, suggesting that subjects already in respiratory failure at baseline may be too severely affected by the disease to benefit from LAU-7b treatment.

Based on the results of the Phase 2 pilot portion, the study was extended to perform a confirmatory Phase 3 portion only focusing on hospitalized moderate-to-severe adults with COVID-19 (Health Status 3 and 4) and the primary endpoint was changed to "Proportion of patients requiring mechanical ventilation and/or death by Day 60".

Summary and conclusion: Subjects that were not in respiratory failure at baseline (moderate-to-severe COVID, Health Status 3 and 4) responded positively to treatment with LAU-7b, supporting the confirmatory evaluation in this hospitalized patient population (ongoing). The safety profile was found to be favorable in the overall safety population and particularly in the moderate-to-severe adults with COVID-19.

This safety profile observed so far in COVID-19 subjects is supportive of this proposed ESSOR study in subjects diagnosed with LONG COVID, due to the common cause of the condition and the overlap of COVID symptomatology and severity.

5.4.2.2 Phase Ib with LAU-7b in Adult CF Patients

Laurent Pharmaceuticals in collaboration with The Research Institute of the McGill University Health Centre completed a Phase Ib, First-In-CF-Patients study with LAU-7b [2]. It was a single-site, double-blind, placebo-controlled escalating multiple oral dose study in 15 adults with CF and a forced expiratory volume in one second percent predicted ($ppFEV_1$) of 40% and above. They were randomized 3:1 (active:placebo) to receive each dose level in a sequential fashion, for cycles of 21 days each, spaced by drug-free periods of a minimum

of 7 days. The study drug or matching placebo was to be taken once a day, orally, along with the largest meal of the day, if possible, in addition to current SOC therapies. Three (3) ascending dose levels of LAU-7b were administered (100 mg, 200 mg and 300 mg/day).

The three main objectives of the study were:

- To establish the safety and tolerability of LAU-7b in adult CF patients;
- To evaluate the single- and multiple-dose PK profile of LAU-7b at three dose levels;
- To recommend doses of LAU-7b to be used in future Phase II CF trials;

Results and conclusions of the study

Safety: The vast majority of adverse events (AEs) were mild, reversible with no sequelae, and without any action needed. Interestingly, the number of AEs in the active group decreased with the increase in LAU-7b dosing. The incidence of ophthalmological events was not different from previous fenretinide studies carried out in the cancer patient population. Biochemical and hematological safety parameters were not affected by LAU-7b at all dose levels. LAU-7b was shown to be safe at the doses studied (100 to 300 mg QD for 21 consecutive days), in adults with CF.

Pharmacokinetics and efficacy: Following single and multiple doses of LAU-7b, plasma exposure (C_{max} and AUC) increased with dose, and this increase was judged dose proportional (p-value > 0.05). The plasma concentration profile indicated first-order elimination kinetics and multiple dosing resulted in moderate accumulation. Mean $t_{1/2}$ values at PK steady-state ranged from 8.25 h to 16.65 h. Exposure and disposition kinetics in adult CF subjects are comparable to what was observed in non-CF adults.

There was a LAU-7b dose-related increase in the DHA levels, a decrease in the AA/DHA ratio in plasma phospholipids and a decrease in the markers of oxidative stress that may be indicative of a reduced peroxidation and better protection of DHA, especially during episodes of increased inflammation such as pulmonary exacerbations. While the changes were not significant statistically, the expected rise in certain inflammatory markers during PEx seemed blunted in participants while on LAU-7b, and the rise in IL-8 during the course of the study was numerically less when on LAU-7b. The highest dosing regimen tested (300 mg/day for 21 consecutive days) was recommended as an optimal dose for the subsequent Phase II CF trial described below, since it was deemed safe and showed positive activity.

5.4.2.3 Phase I (RELATIVITY) food-effect, age-effect and pharmacodynamic study with LAU-7b

The RELATIVITY[62] study was to assess the PK of LAU-7b in healthy subjects, following single and multiple dose administration of LAU-7b. Since food intake has been shown to increase the exposure to fenretinide, the majority of prior clinical studies with fenretinide were conducted administering the study drug with meals. Laurent also followed the same path and LAU-7b was tested under fed condition in both CF and COVID-19 trials.

Food effect and dose proportionality assessment: LAU-7b was administered in the study Part A under various food conditions: high-fat meal and fasting conditions, both compared to a normo-caloric meal. The use of a normo-caloric meal as a reference was based on the need to understand the effects of food on LAU-7b PK when administered with a typical meal, not necessarily a high-fat meal which may be less well tolerated or advised. The high-fat meal was also tested as the greatest food effect condition. In this study, the subjects received the study drug under the three fasting and fed conditions with the assigned meal type, as a single dose administration, separated by a 7-day washout period. The study also aimed to compare the PK of

the 300 mg and the 200 mg doses under the normo-caloric fed condition, since used in CF and COVID-19 trials.

Age effect: The study Part B assessed the effect of age on the PK of LAU-7b to satisfy the requirements of the FDA Guidance for Industry *E7 Studies in Support of Special Populations: Geriatrics Questions and Answers*, for drugs that are developed to be used in geriatric patients. This study therefore included a group of elderly subjects in order to address the lack of information on LAU-7b absorption, distribution, metabolism, and excretion in this population.

Pharmacodynamic-pharmacokinetic: The study Part C investigated the effect of [redacted] supplement on the levels of retinol and RBP when co-administered with LAU-7b for 7 days. This part also allowed to confirm the degree of accumulation of LAU-7b and metabolites upon multiple dosing, compared to adults with CF.

RESULTS:

Food effect and dose proportionality assessment: For all analytes (fenretinide and two metabolites), the intake of food, either as a normo-caloric or high fat meal, increased the absorption of fenretinide and plasma exposure to 4-oxo-fenretinide, and 4-MPR when compared to the administration under fasting conditions. The increase in absorption tended to be slightly lower when administered with a high-fat meal compared to the normo-caloric meal. Both fed states resulted in similar increases in overall bioavailability of the parent drug as well as its metabolites, with their PK profiles generally impacted similarly. The elimination half-life of all 3 analytes remained unaffected by the fed condition. Comparative analyses showed that PK profiles for fenretinide and metabolites were mostly dose-proportional between single doses of 200 and 300 mg.

Age effect: Generally, a slightly higher overall plasma exposure was observed for LAU-7b in elderly subjects compared to matched non-elderly subjects. This increased bioavailability was around 30%, and both metabolites showed modest increases of only up to 15%.

Pharmacodynamic-pharmacokinetic: The co-administration of [redacted] supplementation did not affect the PK profiles of LAU-7b. Accordingly, 4-oxo-fenretinide and 4-MPR plasma exposure remained mostly unchanged compared to the administration of LAU-7b alone. Independent of [redacted] supplementation, repeated daily administrations of LAU-7b resulted in mean plasma exposure and peak concentrations for fenretinide and 4-oxo-fenretinide were 30% to 65% higher following multiple daily doses (Day 6) when compared to a single dose (Day 1). For 4-MPR, an inactive metabolite, the exposure was around expectedly 2.5-fold following multiple administration, owing to its longer elimination half-life.

Safety: Overall, single and multiple administrations of LAU-7b either under fast or fed conditions, were well tolerated in healthy participants (elderly and non-elderly), with no safety concerns.

Inter-study comparison between people with CF (Phase Ib) and healthy subjects from the RELATIVITY study: A comparison was done between the single-dose pharmacokinetics in adults with CF from the Phase 1b study[2], where three dose levels were tested (100, 200 and 300 mg) versus the corresponding 200 and 300 mg doses in non-elderly subjects from the RELATIVITY study (Figure 1). From the exposure standpoint (Area Under the Curve, AUC), subjects with CF showed a slightly lower extent of absorption (80%) relative to healthy subjects at the 300 mg dose and a comparable extent of absorption with the 200 mg dose. The maximal plasma concentration (C_{max}) was lower for both doses (77 and 72% for 300 and 200 mg, respectively), relative to healthy subjects. The elimination half-life was comparable between healthy subjects and subjects with CF, with a tad lower mean value in the latter case (7 hours). This data provides confidence that while having an impaired lipid absorption and receiving pancreatic enzyme supplements, people with CF have comparable LAU-7b exposure versus healthy subjects, and the slight difference may be partially explained by the slightly shorter elimination half-life.

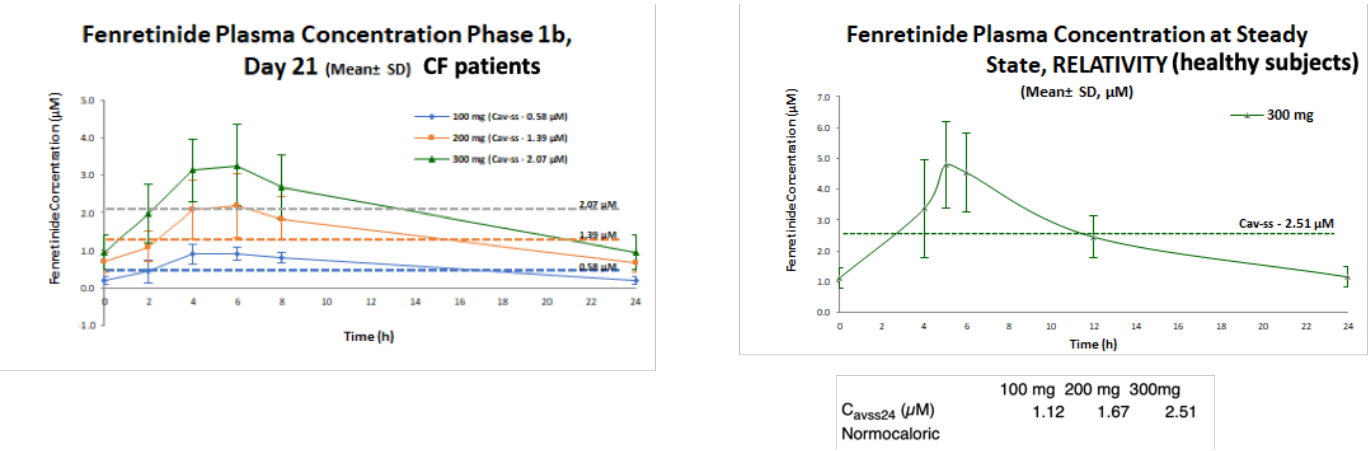

Figure 1: LAU-7b pharmacokinetic profiles in adults with CF and healthy subjects from the RELATIVITY study

In adults with CF, the average plasma concentration of fenretinide over the dosing interval at pharmacokinetic steady-state (C_{avss}) is above 1 µM with the dose of 200 mg and slightly above 2 µM with the 300 mg dose, and is only 0.58 µM with the 100 mg dose. In healthy subjects (RELATIVITY), the plasma concentrations are slightly higher compared to adults with CF, which is consistent with the fact that people with CF usually show a decreased gastrointestinal absorption. Indeed, the calculated C_{avss} in healthy subjects, based on the data for the 300 mg dose administered with a normocaloric meal on Day 7, and modeled to derive the C_{avss} for the 100 and 200 mg doses, showed that LAU-7b is slightly better absorbed from healthy subjects compared to subjects with CF, reaching a C_{avss} of 1 µM with the 100 mg dose and 2.51 µM with the 300 mg dose.

5.4.2.4 APPLAUD, an International Phase 2 with LAU-7b in Adult CF Patients

Laurent Pharmaceuticals conducted APPLAUD[63], a randomized, double-blind, placebo-controlled Phase II study in adults with CF across 39 clinical sites located in Canada, the United States of America and Australia.

To be eligible for the study, subjects diagnosed with CF must have undergone at least one IV or oral antibiotic-treated PEx in the year prior, have a $ppFEV_1$ of 40% and above and meet all other study inclusion/exclusion criteria prior to randomization, which was LAU-7b:placebo (1:1 allocation), after stratification for screening ppFEV1 (<70% vs. ≥70%), the number of PEx in prior year (≤3 vs. >3), and the co-administration or not of a commercially available CFTR modulator. All subjects continued their CF SOC during the intervention period of 24 weeks, which consisted of taking LAU-7b 300 mg/day dose, or matching placebo orally once daily, in the fed state with the first meal of the day, for 6 cycles of 21 days, each spaced by 7-day drug-free pauses.

A total of 166 adults randomized to either LAU-7b or placebo (83 in each arm, ITT/safety population). A total of 122 subjects completed a minimum of 5 cycles of study treatment (per-protocol population, PP) for secondary analyses). The main demographics and baseline characteristics are presented in Table 5 below.

Table 5: APPLAUD Subject demographics

Characteristics ITT/Safety population	LAU-7b (N=83)	Placebo (N=83)
Mean Age, years (SD)	31.5 (10.7)	33.9 (13.0)
Female, n (%)	50 (60.2)	49 (59.0)
Mean Height, cm (SD)	165.1 (9.6)	165.6 (8.4)
Mean Weight, kg (SD)	63.9 (12.2)	64.5 (14.3)
Mean Body Mass Index kg/m^2 (SD)	23.34 (3.35)	23.39 (4.10)
Mean PEx count in prior year (SD)	2.3 (1.8)	2.1 (1.5)
Rate of prior year PEx hospitalization (%)	62.7%	56.6%
Mean CFQ-R respiratory domain (SD)	67.2 (18.5)	71.0 (16.0)
Mean study treatment exposure, days (SD)	138.3 (69.0)	150.2 (39.1)
Mean study treatment compliance (SD)	94.4 (12.8)	98.3 (4.1)
Mean (SD) ppFEV1 at baseline, ITT	63.18 (16.77)	62.29 (15.13)
Mean (SD) ppFEV1 at baseline, PP	62.67 (16.26)	62.13 (14.67)

Percentages based on the number of randomized subjects; ppFEV1 = Percent Predicted Forced Expiratory Volume in 1 second; PEx = Pulmonary Exacerbation; CFQ-R = Cystic Fibrosis Questionnaire-Revised; **ITT** population: all subjects randomized to a treatment group who received at least one dose of study treatment; **PP** population: all subjects randomized to a treatment group with at least 5 cycles of study treatment administered in accordance with the protocol (defined as at least 80% compliance).

The study was independently monitored for safety by an independent Data Monitoring Committee from the CF Foundation Therapeutic Development Network. A total of five (5) meetings occurred and on all five occasions, the Committee recommended to continue the study unchanged owing to no safety concerns.

RESULTS:

Primary Efficacy Endpoint: Treatment with LAU-7b reduced the loss of lung function by 40% (0.8 $ppFEV_1$; p=0.345) in the ITT population, and by 49% (0.95 $ppFEV_1$; p=0.263) in the PP population, compared to placebo, at 24 weeks. In the PP population for the primary efficacy variable through 24 weeks, results achieved statistical significance, in favor of LAU-7b (1.23 $ppFEV_1$; p=0.0486).

The planned analysis according to stratification factors showed that subjects with $ppFEV_1$ of 70% or greater at baseline responded better, showing a 65% reduction in loss of lung function loss at 24 weeks (2.66 $ppFEV_1$; p=0.069). Similar positive trends were observed in subjects stabilized on CFTR modulators (1.39 $ppFEV_1$; p=0.236, representing a 81% reduction), including the highly effective CFTR modulator Trikafta® (1.13 $ppFEV_1$, p=0.532, representing a 60% reduction in this smaller sample).

Key secondary endpoints: The incidence of PEx (either combined IV- or oral-treated or IV-treated alone) in the ITT population was very low in both study arms with less than 20% of subjects having on-study IV-treated PEx and less than 35%, any type of PEx, the latter being about a third of the prior yearly rate of PEx (Table 5). The relative risk (95% confidence interval) of a LAU-7b subject to experience any type of PEx was comparable to placebo (1.16, 0.75 to 1.79), and was slightly higher but comparable to placebo for the IV antibiotics-treated PEx (1.34, 0.68 to 2.64), both not statistically significant. In the combined IV- or oral-treated PEx analysis, there were no apparent differences between treatment arms for the number of PEx-related antibiotic treatments (0.86 versus 0.81 treatment/subject for LAU-7b and placebo, respectively) and for the number of days of PEx-related antibiotic treatments (7.71 versus 8.34 days of antibiotic treatment/subject for LAU-7b and placebo, respectively. There were no significant changes in body weight and Body Mass Index (BMI) during the study, in both study arms.

Effect on inflammation: The most robust LAU-7b-related effects were favorable and observed for the C-reactive protein (CRP) and for calprotectin, and replicated with the PP population for which statistical significance was reached. The levels of CRP and calprotectin increased in the study in the placebo arm but remained close to baseline in the LAU-7b arm. Favorable LAU-7b relative changes from baseline were also

observed for neutrophils, leucocytes, serum amyloid A and oxidative marker nitrotyrosine (NT3), however these changes didn't reach statistical significance. Further investigation of these trends in the subgroup of subjects receiving Trikafta®, also showed a favorable effect of LAU-7b on several inflammation biomarkers in these subjects, albeit not significant due to the small sample size.

Safety: Almost all participants experienced TEAEs, in both study arms. There were slightly more TEAEs in the LAU-7b group than in the placebo group, and the difference mainly consists in a higher number of reported mild to moderate transient eye disorders (delay in dark adaptation or glare), expected based on the known reversible and transient effect of this drug on circulating vitamin A levels with chronic administration.

The vast majority of TEAEs were non-serious (95% on LAU-7b vs. 96% on placebo). The highest reported TEAE severity was mild in 26.5% and 32.5% of the subjects, moderate in 54.2% and 51.8% of the subjects, severe in 15.7% and 8.4% of the subjects for the LAU-7b and placebo groups, respectively, with no life-threatening events, no reported deaths and no SUSAR reported to health authorities.

Ophthalmological events, mostly subject-reported (through questionnaires) mild dark or light adaptation difficulties, were more frequent in the LAU-7b treatment group, consistent with the expected decrease in circulating retinol (vitamin A) levels. Noteworthy, there were subjects on placebo showing similar dips in low light vision but they were less frequent and it should be added that in the RESOLUTION study in COVID-19 subjects given a 14-day treatment, there were no reports of perceived reduction of vision in dark environment.

In total, 20 (24.1%) and 15 (18.1%) subjects experienced at least one serious TEAE in the LAU-7b and placebo groups, respectively. Thirty-four of these serious TEAEs were CF related PEx that reached the seriousness criteria due to the need of hospitalization for administering IV antibiotics (14 in placebo group and 20 in LAU-7b group). The distribution of serious TEAEs was deemed to be comparable among study groups. Other safety assessments were unaffected during the study, in both study groups (laboratory tests, vital signs, physical examinations, and ECG). The safety of LAU-7b therapy was confirmed with no unexpected findings, a comparable incidence of serious TEAEs with placebo, in majority CF-related PEx.

Summary and conclusion: LAU-7b showed an acceptable safety profile and evidence of efficacy in reducing the loss of lung function relative to placebo in adults with CF, on top of SOC including CFTR modulators, providing support for further development of LAU-7b as a potential treatment complementary to CFTR modulators.

5.4.2.5 Additional Supportive clinical experience with fenretinide

Fenretinide has been extensively studied in humans, mostly for the prevention and treatment of cancer. There is a large body of safety data existing for fenretinide from previous low-dose/long-term clinical studies (1-2μM plasma concentration) and mid/high-dose clinical studies (2-14.5 μM plasma concentrations) using oral administration of fenretinide, as well as very high doses (up to 28 μM plasma concentration) with IV administration. These Phase I to Phase III studies have been carried out in more than 3,000 subjects, including both adults and pediatric patient populations, some for as long as 5 years of treatment (with the low doses). Most recent clinical studies have been carried out by the US National Cancer Institute (NCI) using the original corn-oil based softgels formulation. [redacted]

Fenretinide was originally explored in adult patients primarily as a chemopreventive agent, and in that setting it was used at low doses to avoid side effects. Numerous clinical studies employing chronic oral doses of 200 to 800 mg fenretinide/day (≤ 3 μM plasma levels) using the corn-oil based formulation, have been well

tolerated in previous trials, with the 200 mg/day dose tolerated for as long as five years in the case of chemoprevention trials [64, 65, 66, 67]. Most of these studies utilized a once daily administration, some with a 3-day drug-free rest period every 4 weeks to prevent potential symptoms of nyctalopia.

Low-dose / long-term clinical trials

Intolerance of oral chronic doses achieving 1-2 µM plasma levels of fenretinide in chemoprevention clinical trials has been minimal and reversible [64, 65, 68].

Fenretinide has been safely administered in chemoprevention trials up to dose of 300 mg per day (1-1.5 µM plasma levels) for prolonged periods of time from 6 months to 5 years in large cancer populations with no significant toxicity[31, 64, 67, 68, 69, 70, 32]. Mild grade of nyctalopia and dermatologic disorders (dry skin, pruritus) were the most common side-effects of fenretinide treatment; rate of occurrence of both types of events tended to decrease with time or to recover spontaneously during the treatment period or shortly after cessation of dosing. Fenretinide plasma concentration (12 h post dose) at steady state was estimated to be ~1µM at 200 mg dose and ~1.5µM at 300 mg dose. Adverse effects typical of other retinoids, such as decreased bone density, ligament calcification, and skeletal hyperostosis were not observed in these studies. Even after five years of therapy, abnormalities in night vision improved significantly after 7 days off therapy, and completely resolved one month after stopping fenretinide; plasma retinol concentrations returned to normal within one month following discontinuation of fenretinide [69, 70].

Single and repeat daily dose PK studies with fenretinide softgel formulation in healthy subjects and patient population indicate that fenretinide plasma exposure (C_{max}, AUC) also increased upon repeat daily dosing to reach a steady state level at 4-5 days [71, 65, 72]. Presence of food increased significantly the plasma levels of the drug and has been used since as standard recommendation for fenretinide dosing [65]. The increase in exposure was dose proportional up to 800 mg. Plasma exposure on Day 21 with 300 mg/day dose of LAU-7b formulation in adult CF subjects was approximately equivalent to the exposure at the dose of 800 mg on Day 28 in healthy adults with the softgel formulation, indicating an increase in fenretinide bioavailability by a factor of >2 with LAU-7b.

High-dose clinical trials

Phase I trials of high-dose (up to 14.5 µM plasma levels) oral fenretinide in pediatric solid tumors have been conducted with the corn-oil softgel formulation [66, 31,].

In two Phase I studies in children with neuroblastoma, fenretinide was given up to the dose of 4000 mg/m^2/day over 28 days (3-6 patients/dose level), followed by a 7-day interruption, for a period of 6-25 courses without dose-limiting (DLT) intolerance [66, 32]. Fenretinide pharmacokinetics was linear in the dose range 100–1,700 mg/m^2. Steady state peak plasma concentrations between 1.3 µM at 100 mg/m^2 and 14.5 µM at 4000 mg/m^2 were observed in the first course of treatment on Day 28. Similar to what has been observed in adult patients, cutaneous intolerance (dry skin and lips) and nyctalopia (Grade 1-2) were the most common adverse effects observed at most dose levels which rapidly reversed during the 7-day drug-free intervals and did not appear to be dose related. Grade 2 toxicities included skin xerosis (6 cases), hepatic toxicity (1 case), diarrhea (1 case), nyctalopia (3 cases), and headache (1 case). Nyctalopia of grade 3 occurred in one patient with the 1000 mg/m^2 dose. None of the patients discontinued the drug because of intolerance. The maximum tolerated dose was not reached in these studies; however, they were terminated due to difficulties with patient compliance in consuming the required number of corn-oil based softgel capsules.

In a study in 54 children (2-20 years old) with high-risk solid tumors conducted by the Children's Cancer Group “CCG”, a maximum tolerated dose (MTD) of oral fenretinide, divided BID - TID, given for 7 days,

every 3 weeks, was defined as 2475 mg/m^2/day, which achieved fenretinide peak plasma levels of 9.9 ± 5 µM with minimal systemic intolerance [31]. Increased steady-state fenretinide levels were seen by Day 7 of therapy. Plasma retinol levels were decreased on Day 1 at all levels, and further decreased to an average of 33% of baseline by Day 7, with recovery to 55-106% of baseline by Day 21 (start of next course).

In all these high-dose pediatric studies, a wide range of peak plasma concentrations were observed at a given dose. It is possible that the differences of tolerability observed in these two studies (MTD achieved vs. no DLT observed) was dose-schedule dependent (i.e., TID vs. QD).

5.4.2.6 Conclusion

The results from both adult (Phases I-III) and pediatric Phase I trials of high-dose oral fenretinide suggest that peak plasma levels exceeding 10 µM can be achieved with good tolerability.

Prolonged periods of fenretinide treatment (up to 5 years) in the cancer prevention studies were associated with fenretinide steady-state peak plasma concentrations of 1-2 µM at daily doses of 200 to 400 mg and no significant intolerance/safety concerns. In the cancer treatment studies in children the peak plasma concentrations reached 14.5 µM with relatively mild adverse effects. In general, no significant intolerance was observed in children with peak plasma levels below 3µM. The incidence and severity of the most commonly observed toxicities related to fenretinide treatment such as nyctalopia, headache, dry eye, cutaneous, ungual, or mucosal toxicities observed in patients with 3–10 µM peak levels increased at peak levels >10 µM. The adverse events were resolved after dose reduction or after discontinuation of the treatment. Maximum tolerated dose was not reached in children with neuroblastoma at daily doses of 4000 mg/m^2 and fenretinide plasma peak levels of 14.5 µM.

Fenretinide reduces plasma retinol and retinol binding protein levels potentially leading to development of symptoms of nyctalopia in some patients. This effect was rarely dose limiting, and quickly reversible following dose reduction or discontinuation of treatment. Moreover, this effect does not seem to be proportional to the dose. In previous fenretinide clinical studies a drug free period of 3-7 days following a 28-day oral exposure was proven to help prevent or alleviate nyctalopia and was integrated in all clinical studies.

[redacted]

The RELATIVITY PK study confirmed that food increases the absorption of LAU-7b and that high-fat meals do not procure any supplemental advantage over normo-caloric meals in this regard. The study confirmed in non-CF adults the good dose proportionality of exposure within the range of doses of LAU-7b used in CF and COVID-19 trials. It showed that elderly subjects have about 30-35 % more exposure than matching non-elderly adults. The elimination half-lives of fenretinide and metabolites continue to support the once-a-day administration. An excellent safety was observed in the RELATIVITY study with healthy subjects of two age groups and in the case of the repeated dose part, two sequences of dosing with LAU-7b at 300 mg/day, a higher dose than the planned daily dose in the ESSOR trial.

The completed APPLAUD Phase 2 clinical trial also has a safety profile compatible with the severe nature of CF disease, and does not reveal a concerning safety signal, as evidenced by the favorable decisions rendered by the independent Data Monitoring Committee on five occasions. The repeated cyclic administration used in the APPLAUD trial is similar to what is proposed in the ESSOR trial but the daily dose is lower, the number of cycles is lower (1-3) and the drug-free pauses are longer in the ESSOR trial.

Of particular relevance to the ESSOR trial is the excellent safety observed in the RESOLUTION trial in the 117 subjects who received LAU-7b therapy [redacted], and most favorable in the 76-subject subset of subjects with moderate and severe COVID-19, similar to the profile of LONG COVID non-hospitalized patients targeted by the ESSOR trial.

All of the above trials contribute a reassuring and predictable safety profile.

Furthermore, the positive efficacy signal seen across several endpoints in the moderate-to-severe subgroups of the RESOLUTION trial contributes in part to the justification for the objective of the ESSOR trial to reduce the severity of LONG COVID symptoms and favor a return to pre-infection usual daily activities through reducing the overall burden of these symptoms. There is a very significant individual and societal need for addressing LONG COVID.

These collective results are supporting the relevance and the safety of the proposed treatment cycles of two weeks on/two weeks off with 200 mg/day of LAU-7b, and the testing of 1 or 3 cycles through a regimen finding exercise, versus placebo on top of symptomatic relief SOC.

5.4.3 Specific Rationales for the ESSOR Phase 2/3 study and its Biomarker sampling Sub-Study

5.4.3.1 Design/Structure and Dosing Regimen

This ESSOR adaptive Phase 2/3 study aims at investigating the potential benefit and safety of LAU-7b against LONG COVID in non-hospitalized subjects with at least one moderate-to-severe core LONG COVID symptom. This is considered a logical extension of investigating the potential benefit LAU-7b may have against various phases of COVID-19. The LAU-7b antiviral properties and its ability to cross the BBB, doubled by the evidence of inflammation-controlling activity in multiple animal models of lung and brain injury, which are two of the most affected organs by post-COVID syndrome, warrants the evaluation of LAU-7b against LONG COVID.

This design is building on the positive impact afforded by LAU-7b in the pilot Phase 2 portion of the RESOLUTION study, where hospitalized subjects with a baseline Health Status of 3 or 4 (not in respiratory failure) equivalent to moderate-to-severe disease, showed a clear benefit. It is also capitalizing on the positive impact on lung function in the large APPLAUD trial in adults with CF, through its effect on controlling inflammation. These justify expanding the reach to LONG COVID patients with sufficiently burdensome symptoms that interfere with their usual daily activities.

While biomarkers for LONG COVID are not yet fully established [73, 74] and considering that there is no known disease-modifying treatment for LONG COVID yet, it is appropriate and desirable to monitor an array of biomarkers susceptible to change upon administration of LAU-7b, earmarked as a potential disease-modifying LONG COVID treatment [75]. A biomarker sampling sub-study was first introduced in Protocol Version 1.3 on a voluntary basis. In this Protocol Version 1.4, biomarkers will be sampled from all new randomized subjects at all (up to 6 sites) participating clinical sites (the biomarker sampling sub-study is described in details in Appendix 2).

Furthermore, the ESSOR trial enrollment will be stratified according the severity (mild/moderate or severe, two categories) of the COVID-19 infection causing the LONG COVID. It will be easier to discriminate the impact these two categories may have on LAU-7b efficacy because the randomization will allocate the subjects in each category to each treatment arm in a balanced manner.

Despite the fact that COVID-19 infection rates are currently decreasing, time is of the essence to identify useful treatments for patients affected by LONG COVID as these continue to interfere with the lives of these

patients long after the causal infection. The study is of a simple design, with its primary objective being to evaluate the efficacy of two LAU-7b dosing regimens versus placebo at treating the LONG COVID condition.

This study is randomized and placebo-controlled to reinforce its conclusiveness and the robustness of its outcomes. There will be no active control treatment but subjects will be permitted to be on stable symptomatic relief SOC for LONG COVID while participating. A randomized, double-blind study design will avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment. A parallel design is most appropriate for this type of indication. Moreover, since it is not known if LAU-7b has long lasting effects on LONG COVID, thus a potential for some carryover effect in a crossover design, making such design not suitable.

Once the results of the Phase 2 portion are available, a formal consultation with regulatory agencies and experts will be conducted, to determine the proper endpoint strategy for the confirmatory portion of the study protocol. The selection of endpoints will benefit from the Phase 2 part of the study, and the sample size will be estimated in order to have at least 90% power with a two-tailed test to make the results of the Phase 3 portion confirmatory.

5.4.3.2 Rationale for dose selection:

Based on the Phase Ib study in adults with CF and on the RELATIVITY study in healthy subjects, the doses of 200 mg and 300 mg/day elicit target plasma concentrations in the [redacted] µM range derived from pre-clinical pharmacology experiments conducted *in vitro* and *in vivo*, required for both antiviral and inflammation-controlling activities, and these peak concentrations are generally achieved and plateau after 3 daily doses. Furthermore, tissue distribution studies have shown that fenretinide elicits higher brain and lung tissue concentrations relative to blood; it is therefore justified to avoid the 300 mg/day loading dose used for the first 3 days in the RESOLUTION Phase 2/3 study in hospitalized subjects at risk of complications, where the disease is more advanced in a high portion of the subjects.

The duration of the intervention (up to 3 treatment cycles of 14 days each) in ESSOR is justified by the long-lasting nature of the LONG COVID symptoms and the likelihood that a repeated treatment exposure, including a multi-cycle dosing regimen, could be required to improve the functional health status, abate the symptomatology and progress the subjects toward recovering their daily usual activities. It is also justified to evaluate if a single cycle of study treatment could suffice to improve the functional health status, as a minimally effective regimen. Furthermore, it is well known that when a patient feels better, there is a high propensity to discontinue treatment, in particular if there are still several days of treatment remaining. To circumvent this predicament, subjects will be assessed at each treatment cycle and encouragements will be provided to favor treatment adherence.

The 200 mg/day dose chosen for this study and the evaluation of one or three treatment cycles of 14 days is supported by the good safety profile observed for 6-treatment cycles of 21 days with the 300 mg/day dose in the APPLAUD Phase 2 trial in adults with CF. Also relevant for the ESSOR trial, is the safety data of the 117 COVID-19 subjects from the Phase 2 pilot portion of RESOLUTION (plus about half of the 110 randomized subjects in the Phase 3 extension) who received the target 14-day regimen consisting of a loading dose of 300 mg/day for the first 3 days and a maintenance dose of 200 mg/day for the remaining 11 days.

5.4.3.3 Rationale for Study Assessments

The study targets the enrolment of LONG COVID patients that are not hospitalized but have sufficiently severe LONG COVID symptoms to interfere with their usual daily activities. The current SOC for such patients diagnosed with LONG COVID generally consists of addressing each symptom with symptomatic relief tailored to each patient's spectrum of symptoms.

The main study objective is to evaluate LAU-7b at treating LONG COVID in a disease modifying manner, as depicted by symptoms measurements, impact on daily activities as well as any changes in relevant biomarkers. Despite the nature of the assessments, and because LAU-7b is an experimental drug not having been commercialized, there is a need for establishing the baseline health status of the potential participants before handing out the study treatment, hence the need for an in-person screening visit at the clinical sites. Once deemed eligible, the subjects will receive the study treatment assigned to them by the randomization scheme. To minimize the burden of the study visits, some visits will be carried out by telehealth methods since the study assessments after screening consist of questionnaires, LONG COVID symptom verification, health-related questions and biomarker sampling on two post-dose occasions. The subjects will self-administer the study treatment at home and the clinical site will do the scheduled follow-up contacts by phone/telehealth or in person as specified in the Schedule of Events, Section 2. The clinical site will also document any need for hospitalization/re-hospitalization and COVID unplanned care visits without hospitalization, during the core study period of 12 weeks /84 days, as well as at the long-term follow-up of Week 24.

SF-36 (36-Item Short Form Survey): The Physical Component [redacted] (PCS) of the SF-36 questionnaire is the primary efficacy endpoint of the study. The other domains of the SF-36 will be evaluated as a secondary endpoint. The SF-36 is an established and widely used (including LONG COVID interventional trials) health-related quality of life measure developed by RAND Corporation as part of a multi-year, multi-site study to explain variations in patient outcomes. The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures that rely upon patient self-reporting. Scores are weighted and transformed into a scale ranging from 0 (greatest possible health restrictions, i.e., severe disability) to 100 (no health restrictions). In the case of the ESSOR study, the subjects will be asked to fill the complete SF-36 questionnaire at screening and at Weeks 4, 8 and 12. This is expected to further understand the dimensions of activity level, improvement of their condition, the ability to work, have social activities, their pain level as well as their mood and general health status perception.

PGI-C (Patient Global Impression of Change) score: This self-report form is widely used in clinical trials to assess a change from the beginning of an intervention and consists of a 7-point scale. In the case of LONG COVID in the ESSOR study, the subjects will be asked to rate the change in their ability to perform usual daily activities since they started the study. This is a key secondary efficacy variable of the study and it will serve to calculate the proportion of subjects who declare a marked improvement (at least "much better"), from baseline to Weeks 4, 8 and 12.

Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function. It was developed in the mid-1990's to meet a growing demand for more precise evaluation of fatigue associated with anemia in cancer patients. Subsequent to its development, it has been employed in over 150 published studies including over 40,000 people. In all cases, the FACIT-Fatigue has been found to be reliable and valid. It is a subset of the longer (47-items) Functional Assessment of Cancer Therapy – Anemia (FACT-An). The recall period is 7 days and the response scale employs a 5-point Likert-type scale.

DePaul Post-Exertional Malaise Questionnaire (DPEMQ): This specialized instrument was developed to characterize and evaluate the debilitation caused by a physical, cognitive, or emotional exertion, that would not have caused a problem before illness, highly relevant to LONG COVID [76].

DALCI Score©: This is a novel score that measures the impact of core LONG COVID symptoms on the ability of a subject to perform daily activities, in order to evaluate the overall burden of LONG COVID on the subject's life. It uses a number of common (core) symptoms in adults, such as: fatigue, post-exertional malaise, trouble sleeping, cognitive problems (memory loss, difficulty thinking or concentrating), mental health symptoms (anxiety, depression), shortness of breath, general pain and discomfort. The symptoms will

each be graded for their severity/impact on daily activities, using a standard LIKERT, and their overall impact on daily activities will be categorized as "Burdensome" (symptom of moderate or severe severity) or "Non-burdensome" (symptom of mild severity). The treatment effect will be evaluated based on comparing between the study arms the proportion of subjects experiencing a given percent change from baseline in the total DALCI Score©.

EQ-5D-5L Quality of Life questionnaire: This questionnaire is a well-documented scoring system that have been widely used and validated as a Quality of Life (QoL) assessment tool for this type of population and is also used in the RESOLUTION trial. It will be administered at screening and at Weeks 4, 8 and 12. This is relevant for outcomes since subjects with varying degrees of functionality will represent a variable pharmacoeconomic weight.

Pre-study hematology, serum chemistry and urine pregnancy test: Hematology and serum chemistry laboratory tests aim at establishing the health condition of the potential participant as part of the determination of eligibility and to have a reference should similar tests be performed during participation, as a consequence of LONG COVID, another health condition as well as any adverse events, whether or not deemed related to the study treatment. The urine pregnancy test is mandatory for any women of child-bearing potential, to ensure only non-pregnant women are enrolled, due to the known teratogenicity of vitamin A and derivatives such as fenretinide.

Biomarker sampling sub-study: Please refer to Appendix 2 for specific procedures and rationales for the sub-study.

6 STUDY OBJECTIVES

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)).

Secondary objectives:
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.

Rationale for the selection of objectives:

The primary objective of this study is simple and clinically relevant by focusing on the improvement in the overall disease burden impacting daily activities, rather than a specific symptom. LONG COVID is a multifaceted condition affecting in an individualized manner each patient. Many patients experience fatigue-related symptoms, malaise after exertion, others have CNS-based symptoms such as brain fog and difficulty concentrating and many experience several symptoms. The commonality among these diverse symptoms appears when they interfere with the person's ability to carry on the usual daily activities, he/she were able to do prior to the COVID-19 infection. The primary objective is centered around evaluating two regimens of LAU-7b for their effectiveness at treating the LONG COVID condition in a general sense (improve the

functioning), therefore reducing or abating symptoms through a disease-modifying effect by controlling inflammation and exerting host-directed antiviral activity. The primary objective is aligned with the primary efficacy endpoint and a number of secondary endpoints by evaluating the impact of the disease burden on the functional health status of the subjects and the restoration of their life. Such impact can be important, both from an individual standpoint as well as from the societal point of view. Patients with sufficiently burdensome LONG COVID symptoms are prevented from working, enjoying life and contributing in a productive manner to the society. They pull care resources, whether in specialized multidisciplinary LONG COVID clinics or from separate, fragmented care providers. In both cases, there is a significant pharmacoeconomic impact, even if the patient does not end up requiring hospitalization.

The secondary efficacy objectives 2-5 aim to be supportive of the primary objective, in terms of individual restoration of daily activity level, quality of life, symptom intensity and relief and burden of LONG COVID care visits, requiring hospitalization or not.

The secondary efficacy objective 6 is specifically centered around reducing the known higher incidence of cardiovascular events in COVID-19 infected individuals, in particular those who had a more severe COVID-19 infection episode, one requiring hospitalization.

The 7th secondary efficacy objective is specific to the biomarker sampling sub-study and aims at characterizing the impact of LAU-7b treatment on a number of selected systemic biomarkers, by comparing their change from baseline between the study arms.

This will help guiding further development of LAU-7b in the treatment of LONG COVID, including a possible Phase 3 confirmatory extension or other studies.

7 STUDY DESIGN

[redacted]

7.1.1 Primary Efficacy Endpoint

The overall functional health status evaluated with the physical component [redacted] (PCS) of the SF-36[xix] questionnaire at Week 12 compared to baseline (screening), with covariate adjustments for baseline PCS, gender, age group, COVID vaccination status (vaccinated, unvaccinated), COVID-19 infection severity. Other prognostic factors may be considered in exploratory analysis. This will be analyzed with a repeated measure analysis of variance (MMRM).

Justification for the Primary Efficacy Endpoint

LAU-7b is proposed to exert inflammation-controlling and antiviral activity against LONG COVID. This condition affects individuals at different degrees and at different locations in the body. In this multifaceted setting, what is most important is for an intervention to take care of the most burdensome symptoms, those that interfere substantially with the patient's ability to perform the usual daily activities he/she was carrying out prior to the COVID-19 infection. Because of the diversity of the most frequent symptoms, their frequent combination in a given individual, the fact that for most, there is no objective physical measurement and the hypothesis that LAU-7b could possibly tackle diverse dimensions of the LONG COVID condition through a disease-modifying effect, there is need for the primary efficacy variable to be representative of the subject's

[xix] The SF-36 (36-Item Short Form Survey) is a set of easily self-administered quality-of-life measures used to evaluate the dimensions of activity level, improvement of their condition, the ability to work, have social activities, their pain level as well as their mood and general health status perception. Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.

functional health status. The Physical Component [redacted] (PCS) of the SF-36 questionnaire is well suited for this purpose and easy to interpret.

The primary efficacy endpoint is based on result from the PCS [redacted] of the SF-36 questionnaire. It is hypothesized that the combined effects of one of the regimens of LAU-7b + SOC will ameliorate the LONG COVID symptoms to the point of improving the overall functional health status score relative to baseline, compared to placebo + SOC alone. The use of the PCS to assess the change from baseline to Week 12, compared between study arms, using a repeated measure analysis of variance (all assessments timepoints in the analysis) with covariate adjustments for baseline PCS, causative COVID-19 infection severity, gender, and other prognostic factors susceptible of have an incidence on the outcome, is ideally suited for establishing the overall benefit of LAU-7b on the subject ability to function and explore the relationship between the duration of LAU-7b exposure (regimens) and the benefit. The other domains of the SF-36, the specialized questionnaires and scales constituting several secondary endpoints will help define more precisely the effect on the core dimensions of LONG COVID.

7.1.2 Secondary and Exploratory Endpoints

1. Safety: Incidence of AEs, SAEs as well as AEs leading to study medication discontinuation, from randomization through Week 12 (see specific reporting instructions in Protocol Section 11.1.1).
2. Efficacy: Proportion of subjects achieving a marked improvement (very much better or much better) as measured with the Patient Global Impression of Change (PGI-C)[xx], from baseline to Weeks 4, 8 and 12.
3. Efficacy: Change from baseline in the FACIT-Fatigue scale (13-item)[xxi], from baseline to Weeks 4, 8 and 12.
4. Efficacy: Change from baseline in the DePaul Post-Exertional Malaise Questionnaire (DPEMQ)[xxii], 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 ≥25%, ≥50% or ≥75% improvement in the DALCI Score© at Weeks 4, 8 and 12. *See Section 10.7 for details.*
9. Efficacy: Change from baseline in the EQ-5D-5L[xxiii] score at Weeks 4, 8 and 12.

[xx] The PGI-C is a single item questionnaire that asks: "Overall, how would you rate the change in your ability to perform usual daily activities since you started the study?". These are the 7-point scale options: 1) "very much better", 2) "much better", 3) "minimally better", 4) "no change", 5) "minimally worse", 6) "much worse", or 7) "very much worse". Higher scores indicate a change for the worse and lower scores indicate a change for the better.

[xxi] This specialized instrument was developed to characterize fatigue, in cancer and used successfully in a multitude of other conditions with a phenotype of fatigue. It is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function. The recall period is 7 days and the response scale employs a 5-point Likert-type scale.

[xxii] This specialized instrument was developed to characterize and evaluate the debilitation caused by a physical exertion, whether a usual daily activity or a leisure activity.

[xxiii] EQ-5D-5L is a validated Quality-of-Life short questionnaire by EuroQol Research Foundation.

10. Efficacy: Proportion of subjects with relief of at least one core[xxiv] 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.
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 (ie, 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 6 months, 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.

7.2 Study Overview

7.2.1 Description

ESSOR is a randomized, double-blind (subjects, investigators and blinded study staff), placebo-controlled adaptive Phase 2/3 study of the oral antiviral and inflammation-controlling LAU-7b for the treatment of symptomatic non-hospitalized adults with LONG COVID. This design is appropriate for this phase of development as it targets symptomatic individuals with persistent, interfering symptoms subsequent to an episode of SARS-CoV-2 infection. It builds on the known efficacy and safety profile of LAU-7b in hospitalized adults with COVID-19, as well as on the preclinical evidence of LAU-7b as a host-directed antiviral effect (*in-vitro*), and inflammation-controlling effects in several animal models of respiratory and neurological inflammation, lung and brain being two of the most frequently affected organs in LONG COVID.

To be eligible for the ESSOR study, subjects must be diagnosed with LONG COVID and exhibiting a LONG COVID symptomatology including a minimum of one moderate to severe core LONG COVID symptom, be aged 18 years and above, and meet all other study inclusion and none of the exclusion criteria at screening. There is a minimum 12 weeks between the presumed or confirmed causative COVID-19 infection and screening for this study, to ensure the symptoms are those of LONG COVID.

[xxiv] Core (most common) LONG COVID symptoms: fatigue, trouble sleeping, shortness of breath, general pain and discomfort, cognitive problems (most commonly known as brain fog or memory fog) and mental health symptoms. *See Section 10.7 for details.*

The Phase 2 portion of the ESSOR study aims at comparing 2 different regimens of LAU-7b versus placebo, the study has therefore 3 arms. Each study arm will consist of three (3) cycles of 14 days of treatment intake each spaced by a drug-free period of 14 days. Eligible subjects will be randomized (1:1:1) to receive in a blinded fashion, after stratification for the severity (mild/moderate versus severe[xxv]) of the COVID-19 infection linked to the LONG COVID condition, either:

ARM 1: Cycles 1, 2 and 3: LAU-7b 200 mg per day once a day (2 capsules of 100 mg each) 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.

In the Phase 2 portion of the study, a total of up to 270 subjects with LONG COVID will be randomized. Subjects will be enrolled at up to 10 centers in Canada. Based on the results of the Phase 2 portion, the most promising treatment regimen will be evaluated in a distinct Phase 3 portion, in a 1:1 randomization against placebo, and the sample size of this distinct and self-sufficient study portion will be estimated.

All subjects will self-administer the study treatment at home, orally, once a day, along with the largest meal of the day, if possible, for a period of 14 days per cycle or until early termination, on top of stable SOC symptomatic relief medication, where applicable. To reduce the study burden to subjects, the Weeks 4 and 8 visits will be carried out as telehealth contacts.

The last follow-up will be in person, on Week 12 relative to randomization. A long-term telehealth contact is planned on Week 24 to evaluate LONG COVID symptoms, cardiovascular events, health and survival, but is not part of the core study analysis. The end of participation 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 subjects will continue to undergo the SOC and planned study assessment, whenever possible.

This design is appropriate for this phase of development and will ensure that the highest quality of data is collected with minimal bias and the subject's safety and wellbeing are preserved. An independent Data and Safety Monitoring Board (DSMB) is monitoring this study.

Assuming positive results of the Phase 2 portion, one of the LAU-7b regimen (Arm 1 or 2) will be selected for a confirmatory Phase 3 comparison with placebo, which will be the outcome of formal discussions with regulators and be submitted for regulatory approval. The number of subjects per arm will be set according to the effect size observed in the primary efficacy endpoint of the Phase 2 portion or according to one of the secondary endpoints showing the greatest benefit of LAU-7b compared to placebo. The indicative study structure for the confirmatory Phase 3 extension is also presented below.

The overall ESSOR study structure is presented in Figure 2.

[xxv] Definition of severity for causative COVID-19 episode: **Mild**: mildly symptomatic and stayed at home, did not require hospitalization. **Moderate**: was sufficiently sick and at risk of complications that hospitalization was required, even if saturating properly under room air (no use of cannulas to supply oxygen). **Severe**: Required hospitalization and received supplemental oxygen via a nasal cannula up to 4 L/ min (low flow); **higher flows and more invasive oxygenation makes the patient Critical COVID-19 and non-eligible for this study**.

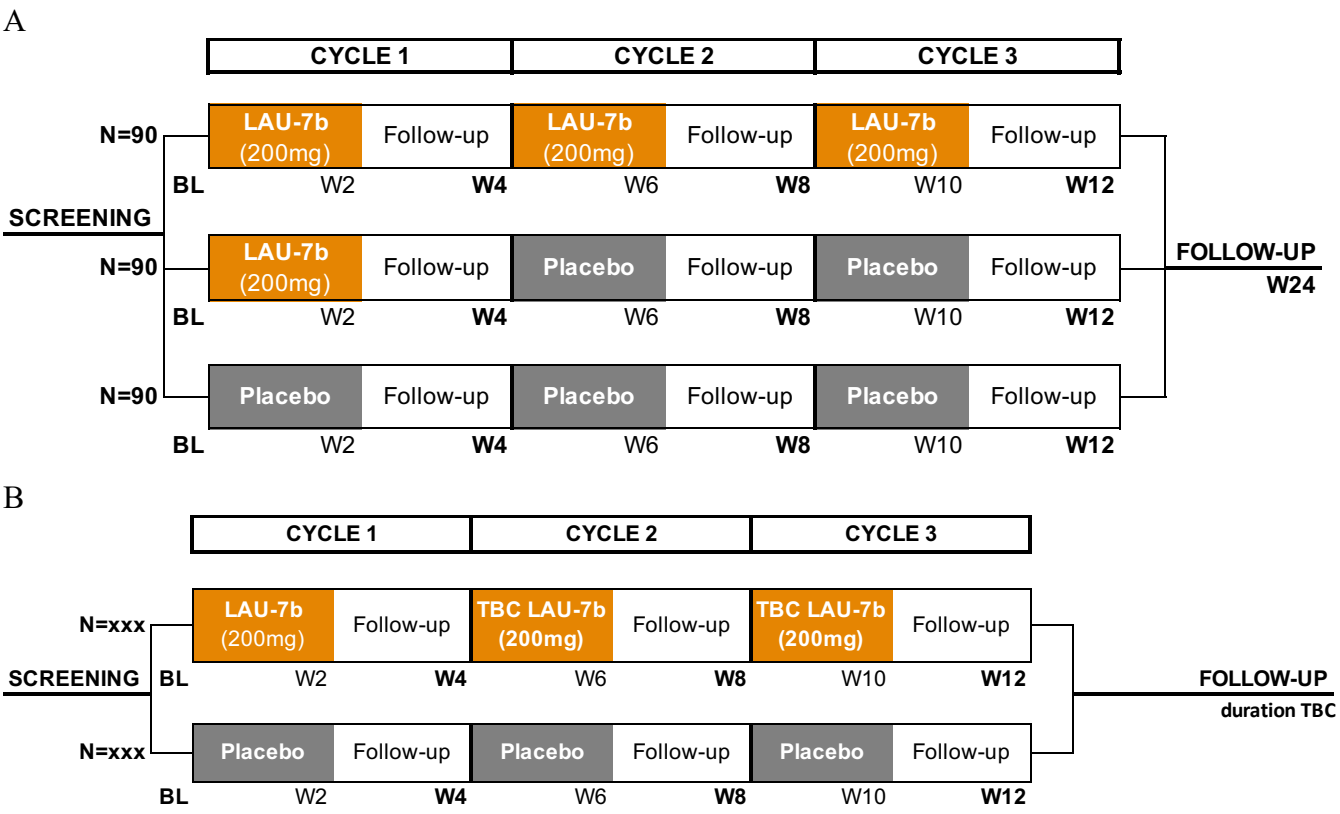

Figure 2: Overall structure of the ESSOR Phase 2/3 study (A: Phase 2 portion, B: Phase 3 portion, indicative)

The biomarker sampling sub-study is described in detail in Appendix 2. Overall, it consists of contributing blood samples 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 observe the time course of the levels of biomarkers and any treatment effect they depict. 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. First introduced on a voluntary basis in Protocol Version 1.3, the biomarker sampling sub-study will be integrated in the subject's under this Protocol Version 1.4 and will involve all ESSOR clinical sites (up to 6 sites). Up to 100 subjects in total will participate in the sub-study which will only be conducted during the Phase 2 portion of the ESSOR study.

7.2.2 DSMB

Throughout the study, the DSMB monitors blinded and unblinded safety measures, subject demographics and overall study quality at regular intervals as specified in the DSMB charter, or as requested by the DSMB chair. The DSMB will receive reports of adverse events by organ class, with emphasis on SAE's, clinically significant adverse events with a high causality potential to the study treatment. Members of the DSMB are not directly involved in the conduct of the study and cannot serve as Investigators in this study.

The DSMB is composed of:

- Three physicians, all involved in the care of COVID-19 patients, experienced in clinical research, independent of Laurent Pharmaceuticals and not involved as an Investigator on the study.
- One study biostatistician that can be unblinded with regards to subject randomization, meaning that he/she is not involved in the statistical design, analysis and reporting of the study.

- Ad-Hoc members recruited to provide specific expertise and meet the Board's mandate.

Each DSMB member signed a Conflict-of-Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and / or associated with commercial interests pertinent to study objectives.

Data will continue to be presented in a blinded manner during the open sessions of the DSMB unless noted otherwise below. At DSMB meetings data and discussion are confidential. Participant identities will not be known to the DSMB members.

Mandate of the DSMB (defined in greater detail in the DSMB Charter):

- Review safety information emerging from the study (and any other study of fenretinide). The DSMB will have access to the randomization code, if justified;
- Make recommendations about study continuation, with or without protocol amendment;
- Recommend early study termination if judged necessary in light of available safety data;
- Meet at specific times of the study to review the safety data cumulated to date. The following specific times have been selected a priori:
    - When a minimum of 40% of the initially planned 204 subjects have completed their LAU-7b (or placebo) treatment and Week 8 contact and corresponding safety information is available;
    - Independently of the above, every 6 months during the active randomization period; and
    - Anytime as needed for review of clinically significant safety information brought to the attention of the DSMB.

7.2.3 Study Stopping Rule Guideline

The following should serve as a general guide for the DSMB to recommend stopping the enrolment, stopping an arm of the study, and/or further drug administration in the study or a given arm of the study for safety reasons. Other considerations may be used to arrive at such decisions, which must involve Laurent Pharmaceuticals Executive Management. Taking in consideration the low odds of this patient population to develop severe complications, including death from LONG COVID:

- Occurrence of any case of death that is attributable to LAU-7b (in such a case, the blind will have to be broken and allocated treatment identified);
- Occurrence of an increased number, relative to placebo, of unexpected SAEs that could be attributable to the drug (at least *possibly related* causality relationship) that raise the DSMB/Investigators concerns about subjects' safety.

7.3 Blinding and Randomization

Given the potential for bias in the interpretation of the study endpoints, the ESSOR study must be placebo-controlled, double-blind, and randomized in order to obtain sufficiently robust data and provide key information in the design of subsequent well controlled clinical trials of LAU-7b in the treatment of non-hospitalized patients with LONG COVID.

7.3.1 Rationale for Placebo Control

It is appropriate that this study be placebo-controlled since there is no current disease-modifying treatment for LONG COVID, the majority of the endpoints rely on the subject's self-perception of change and well-being, and as such, the mere participation in a clinical trial can bear significant placebo effect. Considering the diversity of the symptoms, the current SOC is to address each of them in a symptomatic relief manner. This results in fragmented care and reliance on diverse care providers, even if part of a multidisciplinary specialized LONG COVID clinic. Symptomatic relief can take the form of medications, the use of biomedical devices, dietary modifications and psychological support. All are appropriate but are not necessarily successful for all patients. In this evolving circumstance where search for efficacious and flexible treatment options for LONG COVID is most indicated, participation in this study will not exclude co-administration with new SOC treatments, as they become available, as long as the subject is already stabilized on the said SOC treatment prior to screening and it is not added during participation in ESSOR. This will be evaluated on a case-by-case basis. However, co-enrolment in other interventional studies of unproven LONG COVID treatments is not permitted. A placebo control is suitable and will permit to have unbiased assessment of the study variables. It is essential to maintain the subjects on their SOC for other health conditions, assuming this meets all inclusion/exclusion criteria.

7.3.2 Blinding and Breaking the Blind

This is a double-blind study. Subjects, Investigators and Site Staff, sponsor and data managers will be kept blinded to treatment assignments until the end of the study, except for emergency unblinding as described below.

Only the Clinical Trial Material manufacturer's and Packaging/Distribution provider's unblinded personnel as well as the staff coordinating the interactive web response system (IWRS) will be knowledgeable of individual treatment assignments. As well, in the case of emergency unblinding as described below, some additional people will become aware of treatment assignment for specific subject(s).

The study blind may be broken for an individual subject or several subjects in the event of an emergency in which knowledge of the treatment assignment is needed for the safety of the subject(s) and/or for medical decision-making or as required by local regulatory authority. Unless the event for which the blind needs breaking is life threatening, the investigator should first contact the Sponsor's medical monitor (or designee) prior to breaking the blind.

The investigator will obtain unblinding information by accessing the IWRS system. The reason and justification for breaking the blind must be fully documented in the source documentation. The Investigator that unblinds a subject, will inform the Sponsor as soon as possible after the unblinding is done in IWRS.

7.3.3 Randomization Scheme and Stratification

Computer-generated randomization sequences will be programmed into the IWRS. At the time of Randomization. The IWRS will assign a Subject number (Randomization Number) to each subject who will be randomized (1:1:1 for the Phase 2 portion, 1:1 for the confirmatory Phase 3 portion) to receive one of the allocated study treatments in a blinded fashion, after stratification for the severity (mild/moderate versus severe, see definitions below[xxvi]) of the COVID-19 infection linked to the LONG COVID condition.

[xxvi] Definition of severity for causative COVID-19 episode: **Mild**: mildly symptomatic and stayed at home, did not require hospitalization. **Moderate**: was sufficiently sick and at risk of complications that hospitalization was required, even if saturating properly under room air (no use of cannulas to supply oxygen). **Severe**: Required hospitalization and received supplemental oxygen via a nasal cannula up to 4 L/ min (low flow); **higher flows and more invasive oxygenation makes the patient Critical COVID-19 and non-eligible for this study**

8 SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Screening Inclusion Criteria

Subjects may be randomized to the study only if they meet all of the following criteria at screening:

1- Subjects must be 18 years and older, of either gender, and able to give informed consent;

2- Subjects diagnosed with LONG COVID and exhibiting persisting, relapsing or new LONG COVID symptom(s) at least 12 weeks beyond the start (test positivity or symptom onset) of the causative COVID-19 infection;

3- At least one of the LONG COVID symptoms must be from the core list of LONG COVID symptoms, and be present for a minimum of 2 weeks prior to screening and of moderate or severe intensity as per the 4-level Likert severity scale (0 to 3; 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms);

4- If female, must be either post-menopausal (one year or greater without menses), surgically sterile, or, for female subjects of child-bearing potential who are capable of conception, must be: practicing a highly effective method of birth control (acceptable methods include intrauterine device, complete abstinence, spermicide + barrier, male partner surgical sterilization, or hormonal contraception) during the study treatment intake and through 30 days after the last dose of the study medication. Periodical abstinence is not classified as an effective method of birth control. A pregnancy test for female subjects of child-bearing potential must be negative at the Screening Visit;

5- Subjects deemed capable of adequate compliance including attending scheduled follow-up calls/visits for the duration of the study, have internet access and able to read and answer questionnaires on electronic Patient Reported Outcomes platform (ePRO) or paper;

6- Screening laboratory test and vital signs results within ranges compatible with the subject's health condition, as per investigator's judgement. See also the last exclusion for certain liver function tests;

7- Subjects deemed capable of swallowing the study treatment capsules.

8.2 Screening Exclusion Criteria

Subjects are to be excluded from the study for *any* of the following reasons:

1. Subject is currently hospitalized (any reason);
2. Pregnancy or breastfeeding;
3. Any COVID vaccination within 4 weeks of screening or planned during study participation;
4. Presence of any health condition judged by the investigator to be directly causing one or more of the most common LONG COVID symptoms;
5. Health condition deemed to possibly interfere with the study endpoints and/or the safety of the subjects. For example, the following conditions should be considered contraindicated for participation in the study. In case of doubt, the Investigator should consult with the Sponsor's medical representative:
    - Febrile neutropenia;
    - Fibromyalgia deemed to interfere with generalized pain disorder measurements;
    - Presence of end-stage cancer (palliative care).

6. Presence or suspicion of drug or alcohol abuse, as judged by the Investigator;
7. Known history of a severe allergy or sensitivity to retinoids, or with known allergies to excipients in the oral capsule formulation proposed to be used in the study;
8. Participation in another interventional drug, alimentary supplement, psychological or device...etc. clinical trial within 30 days (or a minimum of 5 elimination half-lives for drugs) prior to screening, except ongoing participation in non-interventional studies;
9. Presence of total bilirubin >1.5 x ULN (in the absence of demonstrated Gilbert's syndrome), ALT and/or AST > 2.5 x ULN.

8.3 Study Drug Discontinuation and Withdrawal of Subjects

Subjects should discontinue permanently the study drug intake (and any further biomarker sampling, where applicable) in the event of any of the following (Since a low LAU-7b dose is used in this study, no dose reductions are allowed):

1. If a subject is intubated, thus preventing the administration of the study medication intact;
2. Occurrence of a serious and/or life-threatening adverse event deemed related to the study drug by the investigator;
3. If the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue treatment;
4. If a subject is serially and persistently noncompliant with study procedures and/or assessments, the Investigator or the Sponsor may withdraw the subject from further treatment;
5. A subject's treatment is unblinded by the Investigator;
6. If a female subject has a confirmed pregnancy during the study treatment intake and up to 30 days after the last dose of the study treatment, this should be immediately reported to the Medical Monitor and Sponsor (within 24 hours of awareness) and the subject shall discontinue the study drug if still applicable. Such pregnancy should be followed up until conclusion, with an assessment of child health at birth.

The subject has the right to withdraw from the study at any time. Subjects withdrawn from further treatment but agreeable to provide outcome information should continue to undergo the safety and efficacy assessments as per protocol, whenever possible, up to Week 12 (end of core study follow-up). In all cases, the reason for study drug discontinuation will be noted in the case report form (CRF). This is in the view of maximizing the number of subjects with actual follow-up information and minimizing subjects lost to follow-up.

Subjects should be withdrawn from the study in the event of any of the following:

1. If the subject withdraws consent to participate in the study as a whole;
2. If the subject is lost to follow-up.

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

The monitoring of hospitalization/re-hospitalization, significant cardiovascular events and survival status up to Week 24 are necessary for the long-term objective.

In the event a subject is hospitalized, study intervention may continue to be administered, as feasible, and based on medical judgement of the investigator and the treating physician.

8.4 Replacement of Subjects

Subjects who withdraw their consent or are screen-failed prior to randomization, will be replaced to ensure that up to 270 subjects enroll in the study. Subjects who withdraw (study or further treatment) after randomization will not be replaced.

9 STUDY CONDUCT

9.1 Study Visits and Procedures

9.1.1 Screening and Eligibility Assessments (Visit 1, in person, within 7 days of randomization):

Prior to randomization, potentially eligible and interested subjects will undergo the following:

1. Verification of identity and age;
2. Prior to any study specific screening activities, all potential subjects will sign the Study Informed Consent Form (ICF). The consent forms will comply with all applicable regulations governing the protection of human subjects. An ICF, approved by the Sponsor and the site's institutional review board (Can be central) (IRB or REB, as applicable), must be used. At this point, the subject's initials (actual or de-identified) are used for identification purposes for screening activities up to the time of randomization in the IWRS (next visit);
3. Obtain demographic information and recent & relevant medical history (typically the previous 6 months history and ongoing health conditions), including the grading of the severity (mild/moderate vs severe) of the COVID-19 infection causative of LONG COVID, for the purpose of stratification (if unknown, assume mild/moderate, see definition in Section 7.2.1);
4. Perform the initial LONG COVID symptom inventory, as well as the onset and severity of the core LONG COVID symptoms, graded with the DALCI© score;
5. Verification of the prior medications (typically the previous 3 months) including the assessment of COVID vaccination, and concomitant medications;
6. Body weight, height (measured if possible but self-reporting is accepted), BMI will be calculated automatically in the eCRF;
7. Obtain vital signs including sitting blood pressure, heart rate, respiratory rate, and body temperature;
8. For women, assess the childbearing potential, and if applicable, the pregnancy status and the contraception method;
9. Eligibility laboratory tests consisting of hematology and serum chemistry (required laboratory testing can be found in Section 11.2);
10. For women of childbearing potential (in case of doubt, consider the subject to be of childbearing potential), perform a urine pregnancy test. The pregnancy test result must be negative to pursue participation in the study. If positive, this is a screen failure;
11. Review of all inclusion and exclusion criteria and scheduling, where possible, of the randomization visit within 7 days of the screening visit.

9.1.1.1 Repeat performance of screening assessment(s)

Repeat of individual screening assessment(s) that did not meet eligibility criteria is not permitted unless there is clear and documented evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction. If the repeat values of the individual assessment(s) are within the eligibility criteria and completed before randomization, then the subject is eligible for the study.

9.1.1.2 Rescreening

Not applicable.

9.1.2 Randomization and First Dosing (Visit 2, in-person, Day 1)

It is expected, unless the pre-study laboratory test results are available rapidly to complete the eligibility determination, that randomization will be a distinct in-person visit, no more than 7 days from screening, once the laboratory test results are obtained. Once all screening procedures are complete and eligibility is confirmed, the subject will transition to randomization. The following should be performed during the visit.

1. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© score;
2. Verification of the concomitant medications;
3. For women if applicable, confirm the pregnancy status and the contraception method;
4. For women of childbearing potential, perform a urine pregnancy test. The pregnancy test result must be negative to randomize the subject in the study. If positive, this is a screen failure. Randomized women of childbearing potential will also be handed pregnancy test kits with instructions for at-home performance of pregnancy tests prior to starting Cycles 2 and 3;
5. Collect blood samples for biomarker sub-study as described in Appendix 2;
6. Administer[xxvii] the SF-36 questionnaire, the FACIT-Fatigue scale, the DePaul Post-Exertional Malaise Questionnaire and the EQ-5D-5L questionnaire;
7. Verification of all inclusion and exclusion criteria;
8. Randomization on the IWRS platform and the 3 assigned treatment bottles will be retrieved from the pharmacy, clearly identified by treatment cycle (1, 2 or 3) and handed to the subject along with a dosing calendar and/or access to an ePRO-based dosing diary for recording the study treatment intake (or paper diary in case ePRO is not used by a given subject). The IWRS will issue the Subject Number (Randomization Number); it will be used from that point forward for the entire study participation, to identify the subject. It is permitted for the subject to be dosed/self-dose at the clinical site as long as the study treatment is taken with food and in such instance, there is no mandatory observation period;
9. Adverse event verification and follow-up on ongoing adverse events.

If the subject elects to take the first dose of the study treatment at home, the subject should do it on the same day with a meal and instructed to enter the intake in his ePRO dosing diary (or paper diary in case ePRO is not used by a given subject).

9.1.3 Contacts and Visits

For this study in non-hospitalized subjects with diagnosed LONG COVID, it is planned that the subjects will not visit in person for certain follow-up visits. However, should there be a need for an unplanned care visit or hospitalization, these are study endpoints and therefore must be properly documented at the time of a given in-person visit or Telehealth contact or at any time the subjects inform the clinical site or the site becomes aware of the event (reason for care; duration of hospitalization; interventions performed). The

[xxvii] For this ESSOR study, an ePRO web application (electronic Patient-Reported Outcomes) will be used, as part of the study's EDC. Subjects with a suitable personal device such as a smartphone, a tablet or a personal computer and/or access to internet, will be granted an access which will enable filling the health questionnaires while at the site or back home just prior or during the planned visits/contacts. In the unlikely cases of subjects without access to internet or ePRO malfunction, the paper version of the questionnaire will be used in-person or phone interviews will be performed. The ePRO platform will also have a diary for recording the study drug intake.

overall scheme of contacts (up to Week 12) and the longer-term (up to Week 24) can be found in the Schedule of Event on page 13. Details by planned contacts or visits are presented below.

1. **Day 15 +/- 2 days (Visit 3, In-Person):**
    a. Concomitant medication verification;
    b. For women if applicable, confirm the pregnancy status and the contraception method;
    c. Enquire if COVID-related unplanned care visits or hospitalization were required since the last contact and if any significant cardiovascular events occurred;
    d. Collect blood samples for biomarker sub-study as described in Appendix 2;
    e. Study treatment compliance check by review of dosing diary information available via ePRO;
    f. Adverse event verification and follow-up on ongoing adverse events.

2. **Day 28 +/- 3 days (Week 4, Visit 4, Telehealth):**
    The following activities are planned for this telehealth visit:
    a. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© score;
    b. Concomitant medication verification;
    c. For women if applicable, obtain the result of the pregnancy test done at home for this visit to confirm the pregnancy status and verify the contraception method. A positive result to the pregnancy test will prevent any further study treatment administration but subject will continue the follow-up contacts and visits as planned;
    d. Administer the SF-36, the FACIT-Fatigue scale and the EQ-5D-5L questionnaires (see details of administration in Section 9.1.2);
    e. Perform the PGI-C single item question (administration along questionnaires, see method in Section 9.1.2);
    f. Query the return to pre-infection usual daily activity level;
    g. Enquire if COVID-related unplanned care visits or hospitalization were required since the last contact;
    h. Study treatment compliance by review of dosing diary information available via ePRO;
    i. Ensure subject starts Cycle 2 of study treatment and use the right bottle to do so;
    j. Adverse event verification and follow-up on ongoing adverse events.

3. **Day 56 +/- 3 days (Week 8, Visit 5, Telehealth):**
    The following activities are planned for this telehealth visit:
    a. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© score;
    b. Concomitant medication verification;
    c. For women if applicable, obtain the result of the pregnancy test done at home for this visit to confirm the pregnancy status and verify the contraception method. A positive result to the pregnancy test will prevent any further study treatment administration but subject will continue the follow-up contacts and visits as planned;
    d. Administer the SF-36, the FACIT-Fatigue scale and the EQ-5D-5L questionnaires (see details of administration in Section 9.1.2);
    e. Perform the PGI-C single item question (administration along questionnaires, see method in Section 9.1.2);
    f. Query the return to pre-infection usual daily activity level;

g. Enquire if COVID-related unplanned care visits or hospitalization were required since the last contact;
h. Study treatment compliance by review of dosing diary information available via ePRO;
i. Ensure subject starts Cycle 3 of study treatment and use the right bottle to do so;
j. Adverse event verification and follow-up on ongoing adverse events.

4. Day 70 +/- 2 days (Week 10, In-Person biomarker sampling Visit):

Collect blood samples for biomarker sub-study as described in Appendix 2.

5. Day 84 +/- 7 days (Week 12, Visit 6, In-Person visit):

The following activities are planned for this key In Person visit, the last one that is part of the study core:

a. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© score;
b. Concomitant medication verification;
c. Body weight;
d. Obtain vital signs including sitting blood pressure, heart rate, respiratory rate, and body temperature;
e. For women if applicable, confirm the pregnancy status and the contraception method;
f. Administer the SF-36, the FACIT-Fatigue scale and the EQ-5D-5L questionnaires (see details of administration in Section 9.1.2);
g. Perform the PGI-C single item question (administration along questionnaires, see method in Section 9.1.2);
h. Administer the DePaul Post-Exertional Malaise Questionnaire (see details of administration in Section 9.1.2);
i. Query the return to pre-infection usual daily activity level;
j. Enquire if COVID-related unplanned care visits or hospitalization were required since the last contact;
k. Study treatment compliance by review of dosing diary information available via ePRO;
l. Collect all study treatment bottles, with or without leftovers, and if forgotten by subject, provide a prepaid return envelope for returning the bottles;
m. Adverse event verification and follow-up on ongoing adverse events.

Telehealth longer-term follow-up (Week 24, Visit 7, Telehealth):

The following activities are planned for this telehealth visit, a visit that is not part of the study core:

a. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© scale;
b. Enquire if COVID-related unplanned care or visits or hospitalization were required since the last contact and there were any significant cardiovascular events.

Early-Termination Visit (not a specific visit number):

The following activities are planned for this visit, which can be preferably in person or by telehealth. This visit should be arranged at the earliest convenience if the subject stops early the study treatment, withdraws consent or is withdrawn:

a. Refresh the LONG COVID symptom inventory and grade the severity of the core symptoms with the DALCI© score;
b. Concomitant medication verification;
c. Body weight if in person;

d. Obtain vital signs including sitting blood pressure, heart rate, respiratory rate, and body temperature, if in person;
e. For women if applicable, confirm the pregnancy status and the contraception method;
f. Administer the SF-36, the FACIT-Fatigue scale and the EQ-5D-5L questionnaires (see details of administration in Section 9.1.2);
g. Perform the PGI-C single item question (administration along questionnaires, see method in Section 9.1.2);
h. Administer the DePaul Post-Exertional Malaise Questionnaire (see details of administration in Section 9.1.2);
i. Query the return to pre-infection usual daily activity level;
j. Enquire if COVID-related unplanned care visits or hospitalization were required since the last contact;
k. Study treatment compliance by review of dosing diary information available via ePRO;
l. Collect all study treatment bottles, with or without leftovers, and if forgotten by subject (or visit is telehealth-based), provide/send a prepaid return envelope for returning the bottles;
m. Adverse event verification and follow-up on ongoing adverse events.

9.2 Study Drug Treatment

For the Phase 2 portion, the study is a regimen-finding study and there will be 3 study arms. The total duration of study treatment is up to 3 consecutive cycles of 14 days of either LAU-7b or placebo, each followed by 14 days without study drug intake.

All randomized subjects who confirm having taken the first dose of their treatment will be monitored through Week 12 for the core of the study and up to Week 24 for the longer-term follow-up, or until early termination. The last day of study drug treatment will be approximately Day 70, earlier in case of premature treatment discontinuation, procedure preventing oral intake of study medication such as intubation, death, or later if some doses were missed and taken on subsequent days; variations in time of intake up to 12 hours from target are allowed. If beyond 12 hours delay, that day's dose is deemed missed and dosing continue as usual on subsequent days. Double-dosing on a given day is not permitted to replace a missed dose on the prior day.

Specifically, subjects undergoing intubation preventing oral intake of study medication will not receive the drug by other means such as through a feeding tube. Subjects will continue their study participation as planned except for procedures that cannot be performed due to disease aggravation.

In all cases, the study treatment will be administered on top of current, approved, stable SOC symptomatic treatments for LONG COVID as long as the SOC treatment must have reached maximum effect prior to screening or minimum 2 weeks prior to screening, whichever is longest).

Based on the results of the Phase 2 portion, the most promising treatment regimen will be evaluated in the confirmatory Phase 3 portion, in a 1:1 randomization against placebo, for a number of cycles to be defined based on the Phase 2 portion.

9.2.1 LAU-7b (fenretinide)

It consists of an orange opaque, size 00, hard gelatin capsule containing 100 mg of fenretinide. The formulation contains the following non-medicinal ingredients: [redacted]

The capsules are dispensed in HDPE bottles containing 28 capsules, sufficient for a cycle of treatment and clearly identified by treatment cycle (1, 2 or 3) by the site pharmacy. Study medication will be handled as follows:

- Shipped frozen (-25 to -15°C) to the clinical site pharmacy;
- Stored frozen (-25 to -15°C) in the clinical site pharmacy;
- Stored refrigerated (2 to 8°C, 36-46°F) at the subject's home.

9.2.2 Placebo

A matching orange opaque, size 00 hard gelatin capsule without fenretinide will be used as a placebo for blinding purposes and will contain the same non-medicinal ingredients.

The capsules are dispensed in HDPE bottles containing 28 capsules, sufficient for a cycle of treatment and clearly identified by treatment cycle (1, 2 or 3) by the site pharmacy. Study medication will be handled as follows:

- Shipped frozen (-25 to -15°C) to the clinical site pharmacy;
- Stored frozen (-25 to -15°C) in the clinical site pharmacy;
- Stored refrigerated (2 to 8°C, 36-46°F) at the subject's home.

9.2.3 Packaging, Labeling, and Shipping

Study treatment will be provided in appropriately-sized HDPE bottles containing enough medication for one cycle of 14 days (28 capsules). Study drug bottles will be specifically identified by treatment cycle (1, 2 or 3) and bear instructions to ensure proper intake. The details will be described in the Pharmacy Manual.

Shipments will be done using a Sponsor-defined courier, under frozen temperature (target -25 to -15°C), a temperature data logger may accompany the shipment to ensure an adequate cold chain of custody.

9.2.4 Storage, Dispensing and Compliance Verification of Study Drug

Upon receipt of the study drug shipper container, the investigator should record the receipt, date, time, and temperature of the product based on inspection or on the temperature logger reading, where applicable. Any study drug that arrives in improper storage conditions or is damaged in any way must be reported to the Laurent designee, as instructed in the Pharmacy Manual, as soon as possible and shall be quarantined until instructed otherwise.

At the clinical sites, the study drug bottles will be stored in a suitable freezer (-25 to -15°C) in a secure location with limited access. Most preferably, the storage freezer will be continually monitored and alarmed in order to document any excursion outside the desired temperature range. Alternatively, the use of a calibrated min-max thermometer in the storage freezer is acceptable as long as the thermometer readings are taken daily during weekdays, at a minimum.

Upon instructions from the IWRS, the pharmacy/site staff will, at the time of each dispensing, formally identify and remove the assigned treatment bottles for each treatment cycle from the secure freezer, check the expiry date on the labels and identify each by treatment cycle (1, 2 or 3) by either affixing an over-label number or by writing down the cycle number. The necessary treatment bottles will be dispensed to the subject by the site staff, in person for the randomization visit. The subject will be handed a subject-specific dosing calendar and/or a dosing diary (ePRO-based or paper-based) to fill on each day of treatment intake. Other means of ensuring proper bottle usage and correct timing of treatment intake may be used.

To avoid incorrect subject dosing, the instructions/paperwork/bottles must bear clearly the "subject number" and site staff **must be trained** to **correlate each treatment bottle with the target subject and the target cycle (1, 2 or 3)**, since there may be multiple subjects active on the study medication at any point in time.

The study drug may only be used as directed in this ESSOR protocol. It is against regulations to use investigational products for other purposes.

9.2.5 Administration of Study Drug Treatment

On each of the 14 days of study treatment portion of each cycle, the subject will self-administer once-a-day two capsules to ingest with the main meal of the day (if possible). The capsules should not be broken down to facilitate their ingestion or to administer their content through a feeding tube if the subject is intubated and cannot ingest anymore the capsules intact. On each of the 14 days of study treatment pause of each cycle, the subject will not take any study treatment.

9.2.6 Study Drug Reconciliation and Destruction

Investigators must maintain accurate records regarding the receipt, dispensing, and where applicable, return or destruction of study drug for each subject in the study. At each follow-up call, the subjects will be reminded to bring back all the used and unused containers with or without leftovers to the clinical site at the Week 12 in person visit. If they forget to bring the bottles back, the subject will be given a pre-labeled+paid return envelope and will be instructed to return all the study treatment bottles, with or without leftovers, in the provided envelope. At the site, any used study treatment containers, as well as any unused containers or unused portions of containers, must be maintained until accounted for by the monitor. After accountability by the monitor and approval, the study treatment and containers should be destroyed per the site's SOP for destruction of biological waste or returned to the Sponsor or Sponsor designee for disposition.

9.3 Treatment and Protocol Compliance

Subjects are expected to receive oral daily doses based on the protocol schedule and have all contacts done within the allowable time windows (outlined in the Schedule of Events, page 13 and further detailed in Study Visits and Procedures).

Regardless of allowable visit windows, each cycle of study drug treatment should target a total of 14 days. In the event a subject misses a dose, he/she should not double-dose on the next dosing day; instead, he/she should continue as planned and record this omission in the dosing diary for review at the next contact by the clinical site.

In the event a subject misses a scheduled visit, this should be rescheduled for the earliest possible date. Subjects who are persistently noncompliant may be withdrawn from the study at the Investigator's or the Sponsor's discretion.

9.4 Allowed and Disallowed Concomitant Medications

The SOC for patients with LONG COVID is currently fragmented and adapted to each patient's phenotype, with symptomatic relief interventions, whether with drugs or else. It may evolve during the performance of the ESSOR study. Considering the relatively short study treatment duration (up to 70 days, with one, two or three cycles of 14 days of LAU-7b or placebo) and the lack of clinically proven drug interactions for fenretinide, there is only a limited number of disallowed medications for this study. The LONG COVID SOC is permitted as long as stable prior to screening and not added during participation, alongside other medications the subjects may take for chronic conditions. Co-enrolment in other interventional studies of

unproven LONG COVID treatments (drugs, biomedical devices, dietary modifications, psychological interventions...etc.) is not permitted.

9.4.1 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: cyclosporine A or analogue; verapamil; tamoxifen or analogue; ketoconazole, chlorpromazine and thioridazine; RU486 (mifepristone); indomethacin; or sulfinpyrazone is prohibited.

After consulting the Study Reference Manual, in case of doubt about a subject's concomitant medication, study personnel should consult with the Sponsor's representative before enrolling/pursue participation of a subject on study.

10 EFFICACY ASSESSMENTS

10.1 SF-36 Questionnaire

A portion of the SF-36 questionnaire serves to obtain the primary efficacy endpoint of the study, the PCS [redacted], characterizing the overall functional health status of the subject. The SF-36 is a 36-Item Survey (APPENDIX 1, Figure 3 and Figure 4), a part of the Medical Outcomes Study (MOS), a multi-year, multi-site study to explain variations in patient outcomes, RAND Corporation developed the SF-36 in 1992. SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and have been widely used. This is expected to further understand the dimensions of activity level, improvement of their condition, the ability to work, have social activities, their pain level as well as their mood and general health status perception. It is planned that this will be completed using an ePRO web application at all timepoints and the fallback will be the paper version.

10.2 Patient Global Impression of Change (PGI-C)

The PGI-C[77] is a key secondary efficacy variable of the study (APPENDIX 1,

Figure 5 and Figure 6). It is is widely used in clinical trials to assess a change from the beginning of an intervention and consists of a 7-point scale used in the ESSOR study to determine the proportion of subjects experiencing a marked improvement (at least "much better") in their ability to perform daily usual activities, from baseline to Weeks 4, 8 and 12. Since this is a descriptor of change, it will be assessed only post-randomization as listed in the Schedule of Events, page 13. It is planned that this will be completed using an ePRO web application at all timepoints and the fallback will be the paper version.

The PGI-C is a single item questionnaire that asks: "Overall, how would you rate the change in your ability to perform daily usual activities since you started the study?". These are the 7-point scale options: 1) "very much better", 2) "much better", 3) "minimally better", 4) "no change", 5) "minimally worse", 6) "much worse", or 7) "very much worse". Higher scores indicate a change for the worse.

10.3 FACIT-Fatigue Scale

This specialized instrument was developed to characterize fatigue, in cancer and used successfully in a multitude of other conditions with a phenotype of fatigue. It is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function (APPENDIX 1, Figure 7 and Figure 8). It was developed in the mid-1990's to meet a growing demand for more precise evaluation of fatigue associated with anemia in cancer patients. Subsequent to its development, it has been employed in over 150 published studies including over 40,000 people. In all cases, the FACIT-Fatigue has been found to be reliable and valid. The recall period is 7 days and the response scale employs a 5-point Likert-type scale. It is planned that this will be completed using an ePRO web application at all timepoints and the fallback will be the paper version.

10.4 DePaul Post-Exertional Malaise Questionnaire (DSQ-PEM)

This specialized instrument was developed to characterize and evaluate the debilitation caused by a physical exertion, whether a usual daily activity or a leisure activity. This scale developed by Cotler *et al.* [78] consists of the following five DSQ items which measure PEM items: "A dead, heavy feeling after exercise", "Muscle weakness even after resting", "Next day soreness after everyday activities", "Mentally tired after the slightest effort", and "Physically drained after mild activity". Frequency and severity of PEM over a determined timeframe is assessed using 5-point Likert scales (APPENDIX 1, Figure 9 and Figure 10). Five additional PEM items within the DSQ examine duration of symptom exacerbation after activity, how quickly they would recover and whether participant is not exercising because it makes their symptoms worse. It is planned that this will be completed using an ePRO web application at all timepoints and the fallback will be the paper version.

10.5 EQ-5D-5L Questionnaire

This questionnaire is a well-documented scoring system that have been widely used and validated as QoL assessment tool for this type of population and is also used in the RESOLUTION trial (APPENDIX 1, Figure 11 and Figure 12). It will be administered at screening and at Weeks 4, 8 and 12. This is relevant for outcomes since subjects with varying degrees of functionality will represent a variable pharmacoeconomic weight. It is planned that this will be completed using an ePRO web application at all timepoints and the fallback will be the paper version.

10.6 Body height, weight, with BMI calculated

Height (screening only) and weight will be measured (can also be self-reported) with shoes off at screening. The BMI will be calculated by the eCRF platform.

10.7 Daily Activity LONG COVID Impact Score (DALCI© score)

The DALCI Score© is a novel proposed score that measures the impact of core LONG COVID symptoms on the ability of a subject to perform daily activities, in order to evaluate the overall burden of LONG COVID on the subject's life.

LONG COVID affects individuals differently, and there have been reports of over 100 symptoms. The most common symptoms[xxviii] in adults are listed in the below table. The core LONG COVID symptoms must have persisted or started since the index infection and at least one of them be moderate or severe, for a minimum of 2 weeks prior to screening. Symptom(s) cannot be explained by an alternative etiology including a COVID re-infection.

The core LONG COVID symptoms will be assessed at screening and each study visit according to the schedule of events. The symptoms will each be graded for their severity/impact on daily activities, using a standard LIKERT scale shown below:

1- No symptom
2- Mild symptom (no interference with daily activities)
3- Moderate symptom (interfere and may limit daily activities)
4- Severe symptom (strong interference preventing daily activities

Table 6: DALCI© score template

Core LONG COVID Symptoms	**Severity and impact on daily activities**			
	0 **No symptom**	**1 (Mild)** **No interference with daily activities**	**2 (Moderate)** **Interfere and may limit daily activities**	**3 (Severe)** **Strong interference preventing daily activities**
Fatigue				
Post-exertional malaise				
Trouble sleeping				
Cognitive problems: memory loss, difficulty thinking or concentrating				
Mental health symptoms: anxiety, depression				
Shortness of breath				
General pain and discomfort				
IMPACT ON LIFE INTERPRETATION	**NON-BURDENSOME**		**BURDENSOME**	

With regards to their overall impact on daily activities, mild symptoms are considered "Non-burdensome", and moderate and severe symptoms are considered "Burdensome". These two encompassing categories, in

[xxviii] https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms/post-covid-19-condition.html#s

particular the "Burdensome" category, are descriptors of the impact of the core LONG COVID symptoms on daily activities.

For each core LONG COVID symptom, the corresponding Likert severity score will be entered in the corresponding column. A total score for each impact on life category (Non-burdensome and Burdensome) will be calculated, as well as an overall total visit's severity score encompassing both categories.

The treatment effect will be evaluated using the change relative to baseline for the "Burdensome" category score, expressed as a percentage of the baseline "Burdensome" total category score, and the proportion of subjects experiencing a specific level of improvement will be calculated for each study arm. For example, the proportion of subjects experiencing ≥25%, ≥50% and ≥75% improvement will be a secondary endpoint.

10.8 Evaluation of the Return to Pre-Index Infection daily usual activity level

This is one of the secondary endpoints of the study. It is used to determine the proportion of subjects who judge to have regained their daily usual activity level of pre-index-infection, from randomization to Weeks 4, 8 and 12. Since this is a descriptor of change, it will be assessed only post-randomization as listed in the Schedule of Events, page 13.

This is a single, standalone question distinct from the questionnaires, with either yes or no as answer: "Do you judge that you have regained the daily usual activity level you had prior to being infected by COVID-19 back in Month xxxx? By daily usual activity we mean work, leisure, physical exercise...etc."

11 SAFETY ASSESSMENTS

Safety evaluation consists of the reporting of Adverse Events (AEs).

11.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines.

11.1.1 Documentation of Adverse Events

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. 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 unfavorable and unintended sign (including an abnormal laboratory finding, for example), 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.

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 non-core) will only be entered in the LONG COVID symptom log even if they appear or worsen after the initial inventory at baseline, 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[xxix] and/or exceeds in severity the normal LONG COVID evolution, then the said LONG COVID symptom shall also be entered on the AE log.

[xxix] LONG COVID symptoms should not be considered as unexpected safety findings unless they are significantly different in severity, duration or frequency compared to the natural course of LONG COVID.

Planned surgical procedures for an illness or disease that existed before the subject was screened in the study are **not** to be considered AEs.

Abnormal results of diagnostic procedures, including laboratory test abnormalities, are considered AEs if they result in any one of the following:

- Discontinuation of study treatment;
- Require treatment or any other therapeutic intervention;
- The necessity for further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality);
- Association with clinical signs or symptoms that may have a significant clinical impact, as determined by the Investigator.

Subjects are encouraged to report AEs spontaneously or in response to general, non-directed questioning. All AEs are to be followed until resolution or until a stable clinical endpoint is reached. The investigator should question subjects about AEs and changes in pre-existing illnesses since their last visit and must record the information in the subjects' medical records. The onset and end dates, severity, relationship to study agent, action taken, and outcome must be recorded for each AE. All AEs are to be recorded on the appropriate CRF and in detail on the source documents.

While in respect of the special reporting instructions above, 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 treatment emergent (TEAE) and must be recorded in the CRF and, if an SAE, reported immediately to the Sponsor. Adverse events that are ongoing at the end of the follow-up period should be marked as ongoing. However, it is the responsibility of the Investigator to follow up on these events until resolution, where possible, according to standard medical care.

Any AE or SAE that the investigator becomes aware of outside of the reporting period (after Week 12) of a subject that has or is believed to have a causal relationship to the study drug should be reported to Laurent Pharmaceuticals via telephone. Subjects who experience such AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator.

All AEs and clinically significant laboratory abnormalities encountered during the study should be followed until resolution or stabilization of the event(s). Any action taken and follow-up results must be recorded in the subject's medical record. Follow-up laboratory results should be filed with the subject's source documentation and CRF. For all AEs that require the subject to discontinue treatment, relevant clinical assessments and laboratory tests should be performed until final resolution or stabilization of the event(s).

All AEs for randomized subjects will be recorded in the CRF and the subject's source documents. AEs for subjects who are screened but not subsequently randomized in the study will be recorded in the subject's source documents and in the CRF. The following data should be documented for each AE:

- Description of the event;
- Classification of "serious" or "not serious";
- Date of first occurrence and date of resolution (if applicable);
- Severity;
- Causal relationship to study drug(s);

- Action taken;
- Outcome;
- Concomitant medication or other treatment given

An independent DSMB will assess AEs that are reported from study sites. The DSMB will meet at regular intervals throughout the duration of the study or will meet as determined by the DSMB chair, and may recommend early termination of the study for safety reasons (see Sections 7.2.2 and 7.2.3)

11.1.1.1 Adverse Event Severity

The Investigator must determine and record the severity of all serious and non-serious AEs. The Common Terminology Criteria for Adverse Events (CTCAE), Version 6.0, (Cancer Therapy Evaluation Program website; available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm ; accessed 22 August 2023) should be used for grading the severity of AEs. AEs of CTCAE Grades 4 and 5 should be documented as "life-threatening."

The severity of an AE that does not appear in the CTCAE scale should be determined according to the definitions below. Clinically significant laboratory tests should be recorded as AEs in the subject's source documents and e-CRF.

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death

11.1.1.2 Adverse Event Causality

Every effort should be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be classified using the following criteria:

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event re-appeared on re-exposure to the investigational study drug.

Possibly Related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely Related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not Related	Does not have a temporal relationship. Or, The event is related to an etiology other than the investigational study drug (the alternative etiology must be documented in the study subject's medical record).

ICH guidelines (March, 1995) clarify "reasonable causal relationship" to mean "that there are facts [evidence] or arguments to suggest a causal relationship."

The causality assessment must be made by the Investigator based on information available at the time that the AE/SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available. Possibly Related and Related will be considered related and Not Related and Unlikely Related will be considered not related, for summary purposes.

For all TESAEs, when causality is assessed as being 'related' or 'possibly related', a detailed written rationale must be provided by the investigator. A rationale must also be provided for all non-serious TEAEs assessed as related and/or leading to study drug discontinuation.

11.1.1.3 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken should be classified according to the categories shown below:

Classification	**Definition**
Dose Not Changed	Study drug dose not changed in response to an AE;
Dose Interrupted	Study drug administration interrupted in response to an AE;
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE;
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

11.1.1.4 Adverse Event Outcome

An AE should be followed until the investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown below:

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms;
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms;
Not Recovered/Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing;
Fatal	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE;
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up).

11.1.1.5 Treatment Administered

The Investigator will ensure adequate medical care is provided to subjects for any AEs, including clinically significant laboratory abnormalities. The Investigator will describe whether any treatment was administered for the AE. "Yes" is used if any treatment was administered in response to an AE and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

11.1.2 Serious Adverse Events

SAEs are generally any AEs that result in one or more of the following:

- Fatal (death, regardless of cause, that occurs up to Week 12, or occurs after Week 12 but within 30 days and is suspected of being a delayed toxicity due to administration of the study drug);
- Is immediately life threatening (i.e., presents an immediate risk of death at the time of the AE, not an AE that hypothetically might have caused death if it were more severe);
- Requires or prolongs inpatient hospitalization;
- Causes persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE.

Definition of Life-Threatening Adverse Experience:
An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Definition of Disabling/Incapacitating Experience:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

Medical Monitor:
Andrea (Andie) Herrera-Gayol, MD, MSc, PhD
[redacted]

11.1.2.1 Serious Adverse Event Reporting

Any SAE that occurs during this study, including death from any cause, must be reported to the designated contact for SAE reporting within 24 hours from time of awareness via the creation of an adverse event in the Electronic Data Capture (EDC) tool, telephone, fax, or email, whether or not related to the study agents. An initial SAE report form must also be sent by email to the designated contacts. If initially reported via telephone or short email notification, this must be followed up by an EDC entry as well as filled initial SAE report form submitted by email within 24 hours of the occurrence of the SAE. A written SAE follow-up report must be submitted by email whenever there is sufficient and relevant information to support a proper medical review and assessment (this follow-up report should at least include the proposed causality relationship to study drug, subject evolution notes, laboratory test results, new concomitant medications, new relevant diagnostic tests including autopsy for deaths (when performed), or any relevant medical information. It is imperative that the safety desk be informed within 24 hours of an SAE so that reporting to the health authority can be met, if applicable, within the required time frame. Subsequent SAE follow-up reports can also be submitted by email (using the paper SAE report) ONLY when there is a new or a significant change in the subject health status (worsening of the initial event, death, or when the SAE has resolved completely).

For the SAE report: All concomitant medications used to manage the SAE, including dosing adjustments should be summarized in the concomitant medication section of the SAE report for a thorough review of the event by the Sponsor and the medical monitor.

Because of the need to report to health authorities all Suspected Unexpected Serious Adverse Reactions (SUSAR) in a timely manner, it is vitally important that an Investigator report immediately any adverse experiences which would be considered serious, even if the Investigator does not consider the adverse experience to be clinically significant or drug related. Should the Investigator become aware of an SAE (regardless of relationship to study drug) that occurs until the last core study follow-up, at 12 weeks, or until early termination or death, whichever occurs first, the SAE must be reported in accordance with the procedures specified in this protocol.

All SAEs that are not resolved by the end of the study, or that were not resolved upon discontinuation of the subject's participation in the study, are to be followed until the AE resolves, the AE stabilizes, the AE returns to baseline values (if a baseline value is available), or it is shown that the AE is not attributable to the study drug or study conduct. If a subject becomes pregnant during the dosing portion of the study (from Day 1 to Day 70, and in any instances, 30 days after the last dose of study treatment), the subject will not be receiving further study medication, if applicable. Follow-up regarding the outcome of the pregnancy and any postnatal sequelae in the infant is required. Such pregnancies are considered immediately reportable AEs (within 24 hours of awareness) and are to be documented in the e-CRF.

11.1.2.2 Suspected Unexpected Serious Adverse Reactions (SUSAR)

SUSARs are SAEs that are possibly related or related to the study drug and are unexpected (i.e., not listed in the investigator brochure). SUSARs will be collected and reported expeditiously to competent authorities

and independent ethics committees (REBs)/institutional review boards (IRBs) according to regulations. Medical and scientific judgment is to be exercised in deciding whether expedited reporting is appropriate in other situations, such as for important medical events that are not immediately life threatening or do not result in death or hospitalization, but jeopardize the subject or the subject population.

The investigator should consult with the medical monitor if there is any doubt regarding classification of an SAE.

11.2 Clinical Laboratory Assessments

Blood samples will be collected at screening according to the Schedule of Events (page 13) and analyzed locally. Screening laboratory results must be available and reviewed by the Investigator before randomization. The required tests are indicated below:

Table 7: Laboratory Tests Panels

Serum Chemistry	Hematology
Creatinine	Hematocrit
Potassium	Hemoglobin
Sodium	Platelet count
Calcium	Leucocytes
Alkaline phosphatase	Neutrophils
ALT	Lymphocytes
AST	RBC (erythrocytes)
Total bilirubin	
Glucose	

Local laboratory normal ranges and accreditations should be current and filed in the Investigator Site File and in the study's Trial Master File.

In addition, according to the Schedule of Events, a screening urinary pregnancy test (β-human chorionic gonadotropin) for females of childbearing potential will be performed at the clinic or by the subject at home, and must be negative at screening, before randomization and prior to the start of treatment Cycles 2 and 3.

11.3 Vital Signs

Vital signs at screening include sitting blood pressure performed per site's standards, temperature (oral or tympanic), pulse rate and respiratory rate.

12 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will provide details of the methods of analysis to address all study objectives. The SAP will be finalized before the cutoff date for any analysis, interim or final.

Data summaries by treatment group will be presented. For categorical data such as the PGI-C, the LIKERT symptom severity gradings and the DALCI© bothersome category, data will be tabulated in frequency tables to display the number and proportion of subjects for each category by treatment group. For continuous variables, data will be summarized with the number of subjects, mean, standard deviation, median, and minimum and maximum values by treatment group. Baseline assessments for each outcome variable will be defined as the screening measurement unless a repeat value was obtained, see restrictions in Section 9.1.1.1, before the first dose of study treatment. Statistical significance will be set at the 5% level (two-sided) with no adjustments for multiplicity, owing to the hypothesis-generating nature of the Phase 2 portion. Consideration will be given for adjusting for pre-specified prognostic baseline factors such as age, the strata of the subject and other risk factors, where applicable and as specified below and the SAP.

Diligent efforts will be made to prevent missing data in the study. For example, subjects who discontinue the study treatment early should still be followed for all regularly scheduled visits for safety and relevant efficacy assessments, until the primary Week 12 follow-up, and if possible, until the Week 24 long term follow-up. A clear distinction should be made between treatment discontinuation and study withdrawal. Efficacy assessments occurring after early treatment discontinuation should not be included in the per-protocol analysis.

12.1 Sample Size Considerations

The primary measure of efficacy is the absolute change in the PCS [redacted] of the SF-36 questionnaire from baseline to Week 12, LAU-7b compared to placebo-treated patients. This is an adaptive Phase 2/3 study which consists in a regimen-finding Phase 2 portion that is hypothesis generating, followed by a confirmatory Phase 3 portion. 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 proposed arm size of 90 subjects/arm, the study will have greater than 80% 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 domain 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;

Once the results of the Phase 2 portion are available, a formal consultation with regulatory agencies and experts will be conducted, to determine the proper endpoint strategy for the confirmatory portion of the study protocol. The selection of endpoints will benefit from this Phase 2 part of the study, and the sample size will be estimated in order to have at least 90% power with a two-tailed test to make the results of the Phase 3 portion confirmatory.

There is limited knowledge on the impact of drug interventions on LONG COVID at this point and the ESSOR study will provide a wealth of information on the effect size, the amplitude and rate of recovery from LONG COVID symptoms.

12.2 Analysis Populations

- **The intent-to-treat (ITT) population** will include all subjects 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 the specific populations described below. The subjects will be kept in their randomized treatment arm for the analyses.
- **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 protocol deviations as pre-identified prior to the database lock). The PP population will serve as the basis for secondary analyses of all study endpoints. The subjects will be kept in the treatment arm that they actually received for the analyses.
- **The safety population** will include all subjects 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 subjects will be kept in the treatment arm that they actually received for the analyses.
- **The biomarker population** will include all subjects randomized to a treatment group who consent for the biomarker sampling sub-study and contribute the baseline biomarker samples and samples from at least one of the two on-study biomarker sampling time points.

12.3 Subject Disposition and Discontinuations

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

- 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.

12.4 Baseline and Demographic Characteristics including Protocol Deviations

Demographic and baseline data will be summarized by treatment group using descriptive statistics. Demographics will include, among others, age, gender, ethnicity, weight, height, body mass index. Protocol deviations/violations will be provided as a subject data listing only. Major protocol deviations/ violations will be identified and their impact rated for analysis purposes.

The demographics and baseline characteristics summary will be presented for the ITT and the PP populations to allow review of the characteristics of those included in the efficacy analyses, which will be based on these analysis sets.

12.4.1 Prior and Concomitant Medications

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 up to the Week 12 follow-up or earlier if early-terminated.
- Post-treatment medication: not applicable.

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. Prior medications and concomitant medications will be summarized descriptively based on the ITT population.

12.4.2 Study Drug Exposure

The duration of study drug exposure is defined as follows: Last dose date minus first dose date plus 1 day, regardless of any interruptions in dosing, for each cycle of study treatment, and summed for the 3 cycles. If the last dose date of study treatment is missing for the study participation as a whole, the subject's discontinuation or completion date will be used for analysis purpose. Duration of study drug exposure will be summarized descriptively as a continuous variable (number, mean, SD, median, minimum, and maximum), by study group, using the safety/ITT population.

12.4.3 Study Drug Compliance

Study drug compliance will be performed on the Safety population. Study drug compliance will be assessed by calculating as follows: 100 × (1 − [total number of days of study drug interruption]/(total duration of study drug exposure)). The total number of days of study drug interruption is defined as the sum of (number of days of each study drug interruption), where number of days of each study drug interruption is defined as the interruption end date minus the corresponding interruption start date plus 1 day. Treatment compliance percentages will be summarized descriptively as continuous variables (number, mean, SD, median, minimum, and maximum). The percentage of subjects whose compliance is <80% or ≥80% will be summarized, by study group.

12.5 Efficacy Analysis

12.5.1 Analysis of Primary Endpoint

Values for the PCS [redacted] of the SF-36 questionnaire as well as their change relative to baseline will be tabulated by time point and descriptive statistics will be used. In the analysis for the primary efficacy endpoint, absolute changes from baseline in PCS, including all measurements up to Week 12, and including treatment discontinuations will be analyzed based on a mixed-effect repeated-measure model (MMRM). Appropriate imputation methods for addressing the missing data not related to intercurrent events will be used for the primary analysis, and a sensitivity analysis that adopts a different imputation approach will be conducted. Missing data handling related to intercurrent events will be detailed in the SAP.

The planned model will include the absolute change from baseline in PCS as 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, COVID vaccination status (vaccinated, unvaccinated), and COVID-19 severity. Other prognostic factors at baseline may be considered in exploratory analysis.

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.

Additional post-hoc analyses may be performed in an exploratory manner depending on the frequency of other phenotypes or concomitant drugs/treatments.

12.5.2 Analysis of Secondary Efficacy Endpoints

Pre-defined Clinical Parameters:

- Frequency analyses: The proportions of subjects for a number of secondary endpoints will be analyzed using a Fisher exact test. Logistic regression including treatment group, the randomization stratification factor, COVID vaccination status (vaccinated/unvaccinated), comorbidities and other prognostic factors at baseline will also be performed. A similar approach will be used for the analysis of the long-term follow-up data, which consist of proportions of subjects surviving, subjects with LONG COVID symptoms, but will be reported separately from the core analyses.
- Time to event data variables: The time to relief of the first core LONG COVID symptom will be tabulated by treatment group and compared using a Cox proportional hazards model. If the proportional hazards assumption is violated, a stratified analysis will be conducted using stratified Cox regression. Additionally, Kaplan-Meier methods will be used to produce graphical presentations of the time to relief of the first core LONG COVID symptom.
- Other continuous variables: The FACIT-Fatigue scale, the DePaul Post-Exertional Malaise Questionnaire, the EQ-5D-5L Quality-of-life and the data from the other domains of the SF-36 questionnaire will be derived from the questionnaire according to the corresponding scoring manual and will be summarized by treatment group. The LONG COVID symptom counts are also analyzed as a continuous variable. Data will be summarized by treatment group using descriptive statistics. Analysis of the absolute change from baseline for the FACIT-Fatigue scale, the EQ-5D-5L or the DePaul Post-Exertional Malaise Questionnaire questionnaires will be performed using an ANCOVA with treatment as fixed effect and either the FACIT-Fatigue, the EQ-5D-5L or the DePaul Post-Exertional Malaise Questionnaire score at baseline as a covariate. For the other SF-36 domains, these will be performed similar to the primary efficacy variable, by using a MMRM model. For the LONG COVID symptom counts, an ANOVA will be used to compare treatments.

12.5.3 Analysis of Exploratory Biomarker Endpoints

The ESSOR study statistical analysis plan (SAP) will provide details of any method of analysis to address the sub-study objectives.

Data summaries for continuous variables data like the biomarker results will be presented by ESSOR treatment group with the number of subjects, mean, standard deviation, median, and minimum and maximum values. Baseline assessments for each outcome variable will be defined as the randomization (Day 1) measurement, before the first dose of study treatment.

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.

Values for biomarkers measured in plasma, serum or blood, as well as their change relative to baseline, will be tabulated by time point and descriptive statistics will be used.

An analysis of variance for repeated measures, where applicable, will be used to compare treatments assuming datasets meet standard pre-requisites for such analysis (normal or log-normal distribution and homogeneity of variance). Factors of interest will be incorporated in the statistical model as effects, including for example the stratification group at entry, the age group, the gender and others, as applicable, and defined in the SAP. Alternative methods will be used if necessary.

12.6 Safety Analyses

The safety analyses will be performed at least three times, 1- when a minimum half of the planned enrolled subjects have completed their LAU-7b (or placebo) treatment and Week 12 contact and corresponding safety information is available, 2- at the time of final analysis of the Week 12 of the study, and 3- at the time of final analysis of the long-term follow-up (Week 24) of the study.

Safety analyses will be performed on the safety population (those subjects who receive at least one dose of study treatment). Blinded safety data will be assessed by the DSMB at regular meetings. The DSMB may request unblinding of subjects for safety concerns in addition to receiving the unblinded interim analyses results.

Safety and tolerability will be assessed by the following:

- Adverse events described and categorized according to the MedDRA, version 26 or more recent.

12.6.1 Adverse Events

Adverse events will be tabulated with reported incidences by treatment, number of subjects that presented adverse events by treatment group, serious adverse events by treatment group, number of adverse events by body system and by treatment group. Summaries will be presented by MedDRA system organ class and preferred term.

For the purpose of analyses and tabulations, AEs will be classified as pretreatment AEs, TEAEs or post-treatment AEs. More specifically: Pretreatment 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 on the Week 12 follow-up, or earlier if early terminated. Post-treatment AEs are those that increased in severity or that appeared after the last core study follow-up, planned for 2 weeks after the last dose of study drug (Week 12). 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.

AE summary tables will be presented for TEAE only and will include the following: All TEAEs, TEAEs by relationship, TEAEs by maximal severity, TEAEs leading to treatment discontinuation, Serious TEAEs and fatal TEAEs. All AEs, including pre-treatment AEs, will be presented in individual subject data listings.

The number and percentage of subjects with at least one AE, as classified by preferred term and system organ class, will be summarized for each treatment group. The 95% confidence intervals alongside each reported AE occurrence percentage will be presented as a measure of precision to facilitate interpretation. For these summaries, subjects 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 must be listed. In addition, detailed listings will be provided for subjects who die, experience a SAE, or discontinue the study treatment because of an AE. These listings will include treatment, subject's age, duration of follow-up, amount of fenretinide received, and time since last intake.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

All subject data generated by the study will be recorded in each subject's CRFs. Data reported on the CRFs that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. CRFs will be considered complete when all missing and/or incorrect data have been resolved and all safety data have been recorded.

The Investigator, or designated representative, should complete the CRF as soon as possible after information is collected. CRFs must be completed only by persons designated by the Investigator. The completed CRF will be reviewed by Laurent Pharmaceuticals or its agents on a routine basis.

The Investigator must approve formally all the information in the CRFs for the subjects for whom he/she is responsible. The United States Food and Drug Administration (FDA) or Health Canada may inspect all records related to the study.

13.1.1 Source Documentation

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator and designees agree to maintain accurate e-CRFs and source documentation as part of the case histories. Source documents are the originals of any documents used by the Investigator, sub-Investigator, or clinical site that will allow verification of the existence of the subject and substantiate the integrity of the data collected during the trial. All data entered into the CRF also must be available in the source documents. The Investigator will allow designated representatives of Laurent Pharmaceuticals, IRB/REB and regulatory bodies, including the FDA and Health Canada to have direct access to the source documents to verify the data reported in the CRFs. Personally identifiable source documentation shall not be copied or removed from the Investigator site, and to the extent permitted by law and/or regulations, will not be made publicly available. All representatives of Laurent Pharmaceuticals, IRB/REB and regulatory bodies must respect confidentiality.

13.1.2 Record Retention

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, or 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region, whichever is the longest time period.

14 MONITORING

In accordance with current applicable regulations, Good Clinical Practice (GCP), and Laurent Pharmaceuticals procedures, monitors will contact the site before the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Laurent Pharmaceuticals requirements. When reviewing procedures for data collection, the discussion will include identification, agreement, and documentation of data items which will be recorded in each subject's CRF.

The study will be monitored to ensure the following:

- Data are authentic, accurate, and complete;
- The safety and rights of subjects are being protected;
- The study is being conducted in accordance with the currently approved protocol, any other study agreements, GCP, and all applicable regulatory requirements.

The Investigator and the head of the clinical site agree to allow the monitor direct access to all relevant documents.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to Laurent Pharmaceuticals lies with the principal or qualified Investigator generating the data.

Laurent Pharmaceuticals or its designated representative will conduct in-person or remote study site visits to verify the qualifications of the principal Investigator and sub-Investigators, may inspect clinical site facilities as needed, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study data will be enacted in the CRF and documented in an audit trail, which will be maintained within the clinical database.

16 COMPLIANCE, PROTOCOL AMENDMENT AND DEVIATION

16.1 Compliance

It is very important that no modifications to the protocol should be made without the approval of Laurent Pharmaceuticals and Investigators. Changes that significantly affect the safety of the subjects, the nature, the scope and the scientific integrity of the study will require IRB/REB notification/approval before their implementation. Exceptions are cases where the modification is necessary to abrogate an apparent immediate risk to the subjects. Laurent Pharmaceuticals or designee will submit all protocol modifications to IRB/REB and the required regulatory authorities. When there is a need for immediate deviation from procedures enunciated in the protocol, the Investigator will contact Laurent Pharmaceuticals to discuss the course of action and possible alternatives, if at all possible, before any implementation of changes. Any deviation from protocol must be fully documented in the source documentation and in the study documentation on protocol deviations.

16.2 Protocol Amendment

Administrative amendments to the protocol will be classified as amendments of typographical errors, clarifications of confusing wording, name changes, and minor modifications that have no impact on the safety of the subjects or the science of the study. Administrative amendments will be submitted to the IRB/REB for information only. Laurent Pharmaceuticals will ensure that acknowledgement is received and filed. Any other amendment will be classified as a substantial amendment and will be submitted to the appropriate regulatory authorities and the IRBs/REBs for approval.

16.3 Protocol Deviation

Should a protocol deviation occur, Laurent Pharmaceuticals must be informed as soon as possible. Important protocol deviations and their reasons will be summarized in the clinical study report. In accordance with applicable regulatory authority mandates, the investigator is responsible for reporting specific types or all protocol deviations to the IRB/REB.

17 STUDY TERMINATION

At any time, Laurent Pharmaceuticals may terminate this study in its entirety or at specific clinical site. In addition, for reasonable cause, the IRB/REB and/or the Investigator at a clinical site may terminate the study at their center. In such cases, Laurent Pharmaceuticals should be informed immediately and if at all possible, before implementation.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Investigator noncompliance and/or lack of adherence to protocol procedures;
- Unsatisfactory subject enrollment;
- Lack of evaluable and/or complete data;
- Potentially unacceptable risk to subjects (see Section 7.2.3 for additional guidance);
- Changes in Laurent Pharmaceuticals drug development plans;
- Decision by Health Canada.

The reason(s) for clinical study termination must be properly documented.

18 ETHICAL CONSIDERATIONS

The study will be conducted according to current GCP, including any future revisions, all relevant local laws and regulations, as well as the principles of the Declaration of Helsinki and its amendments. IRB/REB committees will review and approve this protocol and informed consent. All subjects must provide a written informed consent before screening for participation in the study.

This study will be performed by qualified clinical investigators and in accordance with GCP. The study specifically incorporates all of the following features:

- Multicenter, randomized study design;
- Prospectively stated objectives and analytical plan;
- Accepted, pre-specified outcome measures for safety and efficacy;
- Investigator meeting (or equivalent) prior to study start and a detailed protocol to promote consistency across sites;
- Compliance with current GCP, with assessment via regular monitoring;
- Quality assurance procedures performed at study sites and during data management to ensure that safety and efficacy data are adequate and well documented.

The study will only be conducted at sites where IRB/REB approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/REB by the investigator or Laurent Pharmaceuticals, as allowable by local applicable laws and regulations.

19 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical trial agreement.

The Investigator/institution is required to have adequate current insurance to cover claims for negligence and/or malpractice according to national regulations. Laurent Pharmaceuticals will provide insurance coverage for the clinical study as required by national regulations.

20 PUBLICATION POLICY AND CLINICAL STUDY REPORT

20.1 Confidentiality and Publication Policy

Both the use of data and the publication policy are detailed within the clinical trial agreement.

Any and all scientific, commercial, and technical information disclosed by Laurent Pharmaceuticals in this protocol or any other documents and communications should be considered the confidential and proprietary property of Laurent Pharmaceuticals. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to the Investigator's staff on a "need to know" basis, as long as the said staff has been made aware that the information is confidential and who are bound to treat it as such.

The Investigator shall not use any and all information for any purpose other than determining interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study. The Investigator understands that the information developed from this clinical study will be used by Laurent Pharmaceuticals for the development of the study drug and therefore may be disclosed as required to other clinical Investigators, potential and current business partners and associates, Health Canada, the FDA, and possibly other agencies, without bearing any personally identifiable information. The Investigator also understands that, to allow for the use of the information derived from the clinical study, he/she has the obligation to provide Laurent Pharmaceuticals with complete results and accompanying data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Laurent Pharmaceuticals and the Investigator and/or the Investigator's clinical site. In all instances, personally and individually identifiable information shall not be published.

20.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

21 APPENDIX 1: Questionnaires in use in ESSOR

Figure 3: SF-36 English

36-Item Short Form Health Survey (SF-36 v 1.0)

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

Note: Laurent Pharmaceuticals Inc., acknowledges that the RAND-36-Short Form Health Survey (SF-36) was developed at RAND as part of the Medical Outcomes Study.

Figure 4: SF-36 French

Instrument d'enquête sur la santé, forme courte à 36 points (SF-36 v 1.0)

Pour chaque question, faites un choix.

1. En général, diriez-vous que votre santé est:

- ◯ 1 – Excellente
- ◯ 2 – Très bonne
- ◯ 3 – Bonne
- ◯ 4 – Passable
- ◯ 5 – Mauvaise

2. **Comparativement à il y a un an**, diriez-vous que, en général, votre santé **actuelle** est:

- ◯ 1 – Nettement meilleure qu'il y a un an
- ◯ 2 – Meilleure qu'il y a un an
- ◯ 3 – À peu près pareille à il y a un an
- ◯ 4 – Moins bonne qu'il y a un an
- ◯ 5 – Nettement moins bonne qu'il y a un an

Les questions suivantes portent sur les activités que vous êtes susceptible de faire dans une journée typique. **Votre santé actuelle vous limite-t-elle** dans ces activités? Si oui, à quel point?

	Oui, beaucoup	Oui, un peu	Non, pas du tout
3. **Activités vigoureuses**, comme courir, soulever des objets lourds, participer à des sports intenses	◯ 1	◯ 2	◯ 3
4. **Activités modérées**, comme déplacer une table, pousser un aspirateur, jouer aux quilles ou au golf	◯ 1	◯ 2	◯ 3
5. Soulever ou transporter un sac d'épicerie	◯ 1	◯ 2	◯ 3
6. Monter **plusieurs** volées de marches	◯ 1	◯ 2	◯ 3
7. Monter **une** volée de marches	◯ 1	◯ 2	◯ 3
8. Vous pencher ou vous agenouiller	◯ 1	◯ 2	◯ 3
9. Marcher **plus de 1,6 kilomètre**	◯ 1	◯ 2	◯ 3
10. Marcher pendant **plusieurs pâtés de maisons (coins de rue)**	◯ 1	◯ 2	◯ 3
11. Marcher pendant **un pâté de maisons (coin de rue)**	◯ 1	◯ 2	◯ 3
12. Prendre un bain ou vous habiller	◯ 1	◯ 2	◯ 3

Au cours des **4 dernières semaines**, avez-vous vécu l'un ou l'autre des problèmes suivants dans le cadre de votre travail ou de vos autres activités quotidiennes régulières **à cause de votre santé physique**?

	Oui	Non
13. Diminuer **le temps** que vous consacrez à votre travail ou à vos autres activités	◯ 1	◯ 2
14. **Accomplir moins de choses** que vous l'auriez souhaité	◯ 1	◯ 2
15. Être limité(e) dans le **type** de travaux ou d'autres activités	◯ 1	◯ 2
16. Avoir de la **difficulté** à faire votre travail ou d'autres activités (par exemple : effort supplémentaire)	◯ 1	◯ 2

Au cours des **4 dernières semaines**, avez-vous vécu l'un ou l'autre des problèmes suivants dans le cadre de votre travail ou de vos autres activités quotidiennes régulières **à cause de problèmes émotionnels** (comme un sentiment de dépression ou d'anxiété)?

	Oui	Non
17. Diminuer **le temps** que vous consacrez à votre travail ou à vos autres activités	◯ 1	◯ 2
18. **Accomplir moins de choses** que vous l'auriez souhaité	◯ 1	◯ 2
19. Faire votre travail ou vos autres activités de manière moins **soignée** qu'à l'habitude	◯ 1	◯ 2

20. Au cours des **4 dernières semaines**, à quel point votre santé physique ou vos problèmes émotionnels ont-ils interféré dans vos activités sociales normales avec les membres de votre famille, vos amis, vos voisins ou vos groupes?

◯ 1 – Pas du tout
◯ 2 – Légèrement
◯ 3 – Moyennement
◯ 4 – Beaucoup
◯ 5 – Énormément

21. À quel point avez-vous souffert **physiquement** au cours des **4 dernières semaines**?

◯ 1 – Pas du tout
◯ 2 – Très légèrement
◯ 3 – Légèrement
◯ 4 – Moyennement
◯ 5 – Beaucoup
◯ 6 – Énormément

22. Au cours des **4 dernières semaines**, à quel point votre **douleur** a-t-elle interféré dans vos travaux habituels (en incluant le travail à l'extérieur du domicile et les tâches ménagères)?

- ◯ 1 – Pas du tout
- ◯ 2 – Un peu
- ◯ 3 – Moyennement
- ◯ 4 – Beaucoup
- ◯ 5 – Énormément

Les questions suivantes portent sur votre ressenti **au cours des 4 dernières semaines**. Pour chaque question, choisissez la réponse qui se rapproche le plus de votre ressenti.

	Tout le temps	La plupart du temps	Une bonne partie du temps	Parfois	Une petite partie du temps	Jamais
23. Vous êtes-vous senti(e) plein d'entrain?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
24. Vous êtes-vous senti très nerveux ou nerveuse?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
25. Vous êtes-vous senti(e) si déprimé(e) que rien ne pouvait vous remonter le moral?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
26. Vous êtes-vous senti(e) calme et serein(e)?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
27. Aviez-vous beaucoup d'énergie?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
28. Vous êtes-vous senti(e) découragé(e) ou abattu(e)?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
29. Vous êtes-vous senti(e) épuisé(e)?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
30. Vous êtes-vous senti(e) heureux ou heureuse?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6
31. Vous êtes-vous senti(e) fatigué(e)?	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5	◯ 6

32. Au cours des **4 dernières semaines**, à quelle fréquence **votre santé physique ou vos problèmes émotionnels** ont-ils interféré dans vos activités sociales (visites à des amis ou des proches, etc.)?

- ○ 1 – Tout le temps
- ○ 2 – La plupart du temps
- ○ 3 – Parfois
- ○ 4 – Rarement
- ○ 5 – Jamais

Diriez-vous que **chacun** des énoncés suivants est VRAI ou FAUX ?

	Très vrai	Plutôt vrai	Je ne sais pas	Plutôt faux	Très faux
33. Je semble tomber malade un peu plus facilement que les autres	○ 1	○ 2	○ 3	○ 4	○ 5
34. Je suis en aussi bonne santé que n'importe qui	○ 1	○ 2	○ 3	○ 4	○ 5
35. Je m'attends à ce que ma santé empire	○ 1	○ 2	○ 3	○ 4	○ 5
36. Je suis en excellente santé	○ 1	○ 2	○ 3	○ 4	○ 5

Remarque : Laurent Pharmaceuticals Inc., reconnaît que le questionnaire court RAND de 36 questions sur l'état de santé a été élaboré par RAND dans le cadre de l'étude « Medical Outcomes Study ». Les normes de RAND Health sont respectées pour la traduction.

Figure 5: PGI-C English

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

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

Figure 6: PGI-C French

IMPRESSION GÉNÉRALE DE CHANGEMENT DU PATIENT (PGIC)

En général, comment décririez-vous le changement dans votre capacité à faire vos activités quotidiennes habituelles depuis le début de l'étude ?

☑ *Veuillez cocher une seule case :*

[1] ☐ Une énorme amélioration

[2] ☐ Une grande amélioration

[3] ☐ Une légère amélioration

[4] ☐ Aucun changement

[5] ☐ Une légère détérioration

[6] ☐ Une grande détérioration

[7] ☐ Une énorme détérioration

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-35.

Figure 7: FACIT-Fatigue Scale English

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

English (Universal)
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16 November 2007

Figure 8: FACIT-Fatigue Scale French

FACIT-Fatigue Scale (Version 4)

Vous trouverez ci-dessous une liste de commentaires que d'autres personnes atteintes de la même maladie que vous ont jugés importants. **Veuillez indiquer votre réponse en entourant un seul chiffre par ligne et en tenant compte des 7 derniers jours.**

		Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
HI7	Je me sens épuisé(e)	0	1	2	3	4
HI 12	Je ressens une faiblesse générale	0	1	2	3	4
An1	Je suis sans énergie [lessivé(e)]	0	1	2	3	4
An2	Je me sens fatigué(e)	0	1	2	3	4
An3	J'ai du mal à commencer les choses parce que je suis fatigué(e)	0	1	2	3	4
An4	J'ai du mal à terminer les choses parce que je suis fatigué(e)	0	1	2	3	4
An5	J'ai de l'énergie	0	1	2	3	4
An7	Je suis capable de faire ce que je fais d'habitude	0	1	2	3	4
An8	J'ai besoin de dormir dans la journée	0	1	2	3	4
An 12	Je suis trop fatigué(e) pour manger	0	1	2	3	4
An 14	J'ai besoin d'aide pour faire mes activités habituelles	0	1	2	3	4
An 15	Je suis frustré(e) d'être trop fatigué(e) pour pouvoir faire ce que je veux	0	1	2	3	4
An 16	Je dois limiter mes activités sociales parce que je suis fatigué(e)	0	1	2	3	4

French (Universal)
Copyright 1987, 1997

10 July 2012

Figure 9: DePaul Symptom Questionnaire English

DePaul Symptom Questionnaire - Post-Exertional Malaise short form (DSQ-PEM)

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

Source: Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post- Exertional Malaise. *Diagnostics (Basel).* 2018;8(3):66. Published 2018 Sep 11. doi:10.3390/diagnostics8030066

Figure 10: DePaul Symptom Questionnaire French

Questionnaire de DePaul - Formulaire abrégé de malaise post-effort (DSQ-PEM)

Pour chaque symptôme ci-dessous, veuillez entourer un chiffre pour indiquer sa fréquence et un chiffre pour sa gravité :
Veuillez remplir le tableau de gauche à droite.

Symptômes	Fréquence : Au cours des **6 derniers mois**, **a quelle fréquence** avez-vous eu ce symptôme ? Pour chaque symptôme listé ci-dessous, entourez un chiffre parmi : **0 = jamais**, **1 = de temps en temps**, **2 = environ la moitié du temps**, **3 = la plupart du temps**, **4 = tout le temps**	Sévérité : Au cours des **6 derniers mois**, **a quel degré** ce symptôme vous a-t-il dérangé ? Pour chaque symptôme listé ci-dessous, entourez un chiffre parmi : **0 = symptôme non présent**, **1 = faible**, **2 = modéré**, **3 = sévère**, **4 = très sévères**
1. Sensation d'assommement, de lourdeur après avoir débuté un exercice physique	0 1 2 3 4	0 1 2 3 4
2. Douleur ou fatigue le lendemain d'activités ordinaires non intensives	0 1 2 3 4	0 1 2 3 4
3. Fatigué(e) mentalement après le moindre effort	0 1 2 3 4	0 1 2 3 4
4. Faire un minimum d'exercice vous fatigue physiquement	0 1 2 3 4	0 1 2 3 4
5. Epuisé(e) physiquement ou malade après une activité légère	0 1 2 3 4	0 1 2 3 4

Pour chaque question ci-dessous, choisissez la réponse qui décrit le mieux vos symptômes de malaise post-effort.

6. Si vous étiez épuisé(e) après avoir participé activement à des activités extrascolaires, sportives ou à des sorties avec des amis, vous en remettriez-vous en une heure ou deux après la fin de 1'activité?	Oui	Non
7. Ressentez-vous une aggravation de votre **fatigue / maladie liée à l'énergie** après avoir fourni un effort physique minime?	Oui	Non
8. Ressentez-vous une aggravation de votre **fatigue / maladie liée à l'énergie** après avoir fourni un effort mental?	Oui	Non
9. Si vous vous sentez moins bien après des activités, combien de temps cela dure-t-i1?	< 1 h, 2-3 h, 4-10h	11-13 h, 14-23 h, > 24h
10. Si vous ne faites pas d'exercice, est-ce parce que 1'exercice aggrave vos symptômes?	Oui	Non

Source: Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post- Exertional Malaise. *Diagnostics (Basel).* 2018;8(3):66. Published 2018 Sep 11. doi:10.3390/diagnostics8030066

Figure 11: EQ-5D-5L English

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 = ☐

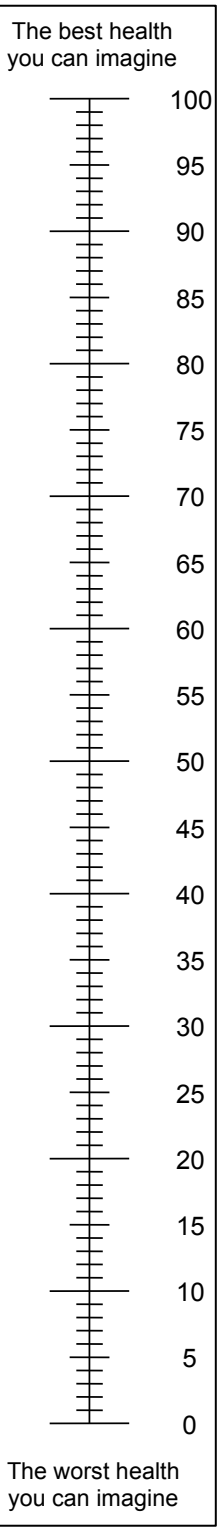

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Figure 12: EQ-5D-5L French

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

MOBILITÉ

Je n'ai aucun problème pour me déplacer à pied	❑
J'ai des problèmes légers pour me déplacer à pied	❑
J'ai des problèmes modérés pour me déplacer à pied	❑
J'ai des problèmes sévères pour me déplacer à pied	❑
Je suis incapable de me déplacer à pied	❑

AUTONOMIE DE LA PERSONNE

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e)	❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e)	❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e)	❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e)	❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e)	❑

ACTIVITÉS COURANTES *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes	❑
J'ai des problèmes légers pour accomplir mes activités courantes	❑
J'ai des problèmes modérés pour accomplir mes activités courantes	❑
J'ai des problèmes sévères pour accomplir mes activités courantes	❑
Je suis incapable d'accomplir mes activités courantes	❑

DOULEURS / INCONFORT

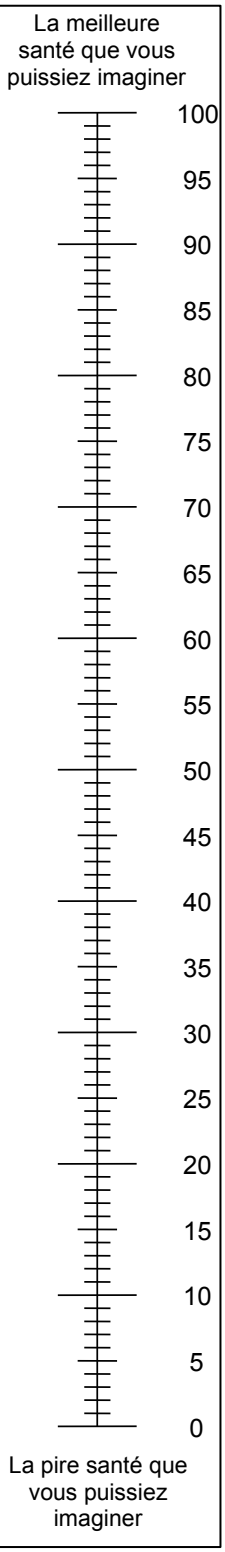
Je n'ai ni douleur ni inconfort	❑
J'ai des douleurs ou un inconfort léger(ères)	❑
J'ai des douleurs ou un inconfort modéré(es)	❑
J'ai des douleurs ou un inconfort sévère(s)	❑
J'ai des douleurs ou un inconfort extrême(s)	❑

ANXIÉTÉ / DÉPRESSION

Je ne suis ni anxieux(se) ni déprimé(e)	❑
Je suis légèrement anxieux(se) ou déprimé(e)	❑
Je suis modérément anxieux(se) ou déprimé(e)	❑
Je suis sévèrement anxieux(se) ou déprimé(e)	❑
Je suis extrêmement anxieux(se) ou déprimé(e)	❑

- Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.
- Cette échelle est numérotée de 0 à 100.
- 100 correspond à la meilleure santé que vous puissiez imaginer. 0 correspond à la pire santé que vous puissiez imaginer.
- Veuillez faire un X sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.
- Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

VOTRE SANTÉ AUJOURD'HUI = ☐



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22 APPENDIX 2: BIOMARKER SAMPLING SUB-STUDY

22.1 Sub-Study Schedule of Events

	Randomization	Post-Cycle 1 visit (15+/-2 days)	Post-Cycle 3 visit (70+/-2 days)
Main Protocol Visit number, where applicable	**2**	**3**	**n/a**
Informed consent for companion sub-study	X		
Blood sampling for biomarkers of interest[1]	X	X	X

[1] List of biomarkers: calprotectin, CD40L, CRP, CXCL10, interferon-gamma (IFN-γ), IFNL1 (IL-29), IFNL3 (IL-28B), IL-1β, IL-6, IL-8, IL-10, retinol, serotonin, tumor necrosis factor-alpha (TNF-α), tryptophan and taurine as well as absolute neutrophil, platelet, reticulocytes and lymphocyte counts.

22.2 Rationale for the Sub-Study

The ESSOR adaptive Phase 2/3 study aims at investigating the potential benefit and safety of LAU-7b against LONG COVID in non-hospitalized subjects with at least one moderate-to-severe core LONG COVID symptom. The ESSOR study targets the enrolment of LONG COVID patients that are not hospitalized but have sufficiently severe LONG COVID symptoms to interfere with their usual daily activities. The current SOC for such patients diagnosed with LONG COVID generally consists of addressing each symptom with symptomatic relief tailored to each patient's spectrum of symptoms.

This companion sub-study aims at exploring if, in addition to the potential benefits on clinically relevant endpoints of the study, there could be some changes from baseline in a series of select systemic biomarkers present in the blood, at specific timepoints during study participation.

While there are published references in the literature that suggest that patients with LONG COVID do not exhibit marked differences in several biomarkers from non-LONG COVID or LONG COVID recovered controls, mainly due to their high variability[73, 74] and considering that there is no known disease-modifying treatment for LONG COVID yet, it is appropriate and desirable to monitor an array of biomarkers susceptible to change upon administration of LAU-7b, earmarked as a potential disease-modifying LONG COVID treatment [75]. Since the presence of at least one moderate to severe core LONG COVID symptom is assumed to affect the energy level of the participants, this biomarker sampling sub-study was offered on a voluntary basis to ESSOR subjects at about 2-3 interested participating clinical sites in Protocol Version 1.3 and is integral to the participation in ESSOR at all participating clinical sites in this Protocol Version 1.4.

22.2.1 Sub-Study Inclusion Criteria

Written informed consent.

22.2.2 Sub-Study Exclusion Criteria

None.

22.3 Sub-Study Objective and Assessments

Primary objective:
To evaluate the ability of LAU-7b at modifying from baseline a select panel of systemic blood biomarkers 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)).

Secondary objective:
To establish correlations between the measured biomarkers and effects on clinically relevant endpoints measured in the ESSOR study.

The main sub-study objective is to evaluate if LAU-7b modifies the systemic levels of certain biomarkers at various timepoints during participation into ESSOR, compared to pre-intervention (Baseline). If indeed LAU-7b treats LONG COVID in a disease modifying manner, it may be apparent in the levels of these biomarkers and may provide some explanations for some effects (if any) on the clinically relevant endpoints measured in the ESSOR study. Furthermore, since sampling for the biomarkers will occur both after the first and last cycle of 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.

22.3.1 Biomarker Assessments and Specific Rationales

Blood samples for the scheduled determination of systemic markers of inflammation will be obtained at participating clinical sites at the time points listed in the Schedule of Events, Page 13 and above, Section 22.1, specifically at baseline and on Days 15 and 70, the first and second corresponding to ESSOR Visits #2 and #3, respectively, carried out in-person. The Day 70 visit only serves to collect samples.

Select biomarkers in serum: calprotectin, CD40L (CD154), CRP, CXCL10 (IP10), interferon-gamma (IFN-γ), IFNL1 (IL-29), IFNL3 (IL28B), IL-1β, IL-6, IL-8, IL-10, retinol, serotonin, tumor necrosis factor-alpha (TNF-α), tryptophan and taurine.

Select biomarkers in blood: absolute neutrophils, platelets, reticulocytes and lymphocytes counts.

Specific Rationales:

Biomarkers of Inflammation: Calprotectin, CRP, IL-1β, IL-6, IL-8, IL-10, IFN-γ, TNF-α are the biomarkers of inflammation to be measured in this sub-study. As a drug with a potential to modulate pro-inflammatory and pro-resolving inflammation cascades, the effect of LAU-7b on a series of inflammation biomarkers will be measured serially in this sub-study, building on the knowledge from the APPLAUD Phase 2 study in CF, and the RESOLUTION Phase 2/3 study in patients hospitalized with acute COVID-19.

Calprotectin is a complex of two mammalian proteins with antimicrobial, proinflammatory and prothrombotic properties. Calprotectin constitutes up to 60% of soluble protein content in the cytosol of neutrophil granulocytes, it can also be found in monocytes, macrophages, and squamous epithelial cells and it is secreted during the inflammatory response. It is now known that calprotectin also has antibacterial and antifungal properties that arise from its ability to sequester manganese and iron.

CRP (C-reactive protein) is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP in the liver during the acute phase of an inflammatory/infectious process. Its circulating concentrations rise in response to inflammation.

IL-1β is a member of the interleukin 1 family of cytokines. It is produced by activated macrophages, monocytes and certain dendritic cells. This cytokine is an important mediator of the inflammatory response

and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. The induction of COX-2 by this cytokine in the central nervous system is found to contribute to inflammatory pain hypersensitivity. This cytokine also induces expression of a number of interleukins, and suggests its involvement in the modulation of autoimmune inflammation. Its increased production can cause a number of different auto-inflammatory syndromes. Intestinal dysbiosis has been noted to induce osteomyelitis through an IL-1β dependent manner.

IL-6 is a multifunctional cytokine produced by many different cell types, including immune cells, endothelial cells, fibroblasts, myocytes and adipose tissue, mediating inflammatory as well as stress-induced responses. It is an interleukin that acts as a pro-inflammatory cytokine and an anti-inflammatory myokine. It is promptly and transiently produced in response to infections and tissue injuries, contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions. IL-6's role as an anti-inflammatory myokine is mediated through its inhibitory effects on TNF-alpha and IL-1 and its activation of IL-1ra and IL-10. It is capable of crossing the blood-brain barrier and initiating synthesis of PGE_2 in the hypothalamus, thereby changing the body's temperature setpoint as an important mediator of fever and of the acute phase response.

IL-8 is a chemokine produced by macrophages and other cell types such as epithelial cells, airway smooth muscle cells and endothelial cells. It induces chemotaxis in target cells, primarily neutrophils but also other granulocytes, causing them to migrate toward the site of infection and inducing neutrophil degranulation. IL-8 also stimulates phagocytosis once they have arrived. IL-8 is also known to be a potent promoter of angiogenesis.

IL-10 is a key anti-inflammatory cytokine that can inhibit proinflammatory responses of both innate and adaptive immune cells; it can block NF-κB activity, and is involved in the regulation of the Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling pathway. IL-10 cytokine is produced primarily by monocytes, it maintains the balance of the immune response, allowing the clearance of infection while minimizing damage to the host.

IFN-γ is a cytokine that plays an important role in inducing and modulating an array of innate and adaptive immunity responses against viral, some bacterial and protozoan infections. Cellular responses to IFN-γ are mediated by its heterodimeric cell-surface receptor (IFN-γ R), which activates downstream signal transduction cascades, ultimately leading to the regulation of gene expression. It is primarily secreted by activated T cells and natural killer (NK) cells, and can promote macrophage activation, mediate antiviral and antibacterial immunity, enhance antigen presentation, orchestrate activation of the innate immune system, coordinate lymphocyte–endothelium interaction, regulate Th_1/Th_2 balance, and control cellular proliferation and apoptosis.

TNF-α (tumor necrosis factor), is an adipokine and a cytokine, identified as a major regulator of inflammatory responses that make up the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. The primary role of TNF is in the regulation of immune cells. TNF, as an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, and inflammation, inhibit tumorigenesis and viral replication, and respond to sepsis via IL-1 and IL-6-producing cells. Dysregulation of TNF production has been implicated in a variety of human diseases including Alzheimer's disease, cancer, major depression, psoriasis and inflammatory bowel disease.

Biomarker of Pharmacodynamic Activity: As it was the case in the APPLAUD study, retinol will be measured serially in this sub-study, to monitor the pharmacodynamic effect of LAU-7b on circulating retinol levels, and upon cessation of LAU-7b, the return of retinol to pre-intervention levels. These analyses will be performed at the clinical site's clinical laboratories.

Indirect Biomarkers of Inflammation Status: The absolute neutrophil, platelet, reticulocytes and lymphocyte counts will be measured serially in this sub-study as representative of the involvement of cellular immunity and these analyses will be performed at the clinical site's clinical laboratories.

CXCL10 (IP-10) is secreted by several cell types in response to IFN-γ. It has been attributed to several roles, such as chemoattraction for monocytes/macrophages, T cells, NK cells, and dendritic cells, promotion of T cell adhesion to endothelial cells, antitumor and inhibition of bone marrow formation and angiogenesis. CXCL9, CXCL10 and CXCL11 have proven to be valid biomarkers for the development of heart failure and left ventricular dysfunction, suggesting an underlining pathophysiological relation between levels of these chemokines and the development of adverse cardiac remodeling.

CD154, also called CD40 ligand or CD40L is a protein that is primarily expressed on activated T cells and is a member of the TNF superfamily of molecules. CD40L plays a central role in co-stimulation and regulation of the immune response via T cell priming and activation of CD40-expressing immune cells such as memory B-cell and dendritic cell maturation as well as in secretion of some cytokines. CD40L is primarily expressed on activated CD4+ T lymphocytes but is also found in a soluble form.

The cytokines IFNL1 (interferon lambda 1, also known as IL-29), and IFNL3 (interferon lambda 3) known as IL28B are part of the type III interferon family, which is distantly related to type I interferons and the IL-10 family. Type III interferons are induced by viral infection and interact with a heterodimeric class II cytokine receptor that consists of interleukin 10 receptor, beta (IL10RB) and interferon lambda receptor 1 (IFNLR1) to signal via the JAK-STAT anti-viral pathway. These interferons play an important role in the immune response against pathogens and especially viruses by mechanisms similar to type I interferons.

Interferon-induced reduction in blood levels of serotonin and its precursor tryptophan as well as the amino-acid taurine were recently associated with LONG COVID[79]. Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs) which reduce serotonin through diminished tryptophan uptake and hypercoagulability. Peripheral serotonin deficiency impairs cognition via reduced vagal signaling. Viral infection and type I interferon-driven inflammation reduce serotonin through three mechanisms: diminished intestinal absorption of the serotonin precursor tryptophan; platelet hyperactivation and thrombocytopenia, which impacts serotonin storage; and enhanced monoamine oxidase (MAO)-mediated serotonin turnover. Peripheral serotonin reduction, in turn, impedes the activity of the vagus nerve and thereby impairs hippocampal responses and memory.

The large majority of circulating serotonin is produced in the gastrointestinal tract, where it is synthesized from dietary tryptophan in enterochromaffin cells. Individuals with acute COVID-19 showed reduced plasma tryptophan levels. Moreover, tryptophan levels were decreased in LONG COVID patients suggesting that lower tryptophan availability may cause serotonin reduction by substrate limitation.

22.3.2 Visit by Visit description and Sample Handling

The overall sub-study visit, sample volume, aliquot size and destinations for analyses are summarized in the below Table 8:

Table 8: Biomarker Sub Study visits, sample/aliquot types/volumes and destinations for analyses

Test/Biomarker	Matrix	Sample/ Aliquots	Volume/ sample or aliquot	Randomization	Post-Cycle 1 D15 +/-2 days	Post-Cycle 3 D70 +/-2 days	Storage Temperature	Analysed at	Blood Volume
Hematology w/ Differential Counts	Whole blood	1	3 mL	x	x	x	Refrigerated	Local laboratory	3mL
CRP	Serum	1	2 mL	x	x	x	Refrigerated		10mL
Retinol	Serum*	1	2 mL	x	x	x	Refrigerated		
CD40L	Serum	2	500 µL	x	x	x	-80 C	IRCM	3mL
CXCL10 (IP10)	Serum			x	x	x	-80 C		
IFN-γ	Serum			x	x	x	-80 C		
IFNL1 (IL-29)	Serum			x	x	x	-80 C		
IFNL3 (IL-28B)	Serum			x	x	x	-80 C		
IL-1β	Serum			x	x	x	-80 C		
IL-6	Serum			x	x	x	-80 C		
IL-8	Serum			x	x	x	-80 C		
IL-10	Serum			x	x	x	-80 C		
TNF-α	Serum			x	x	x	-80 C		
Calprotectin	Serum			x	x	x	-80 C		
Serotonin	Serum	2	500 µL	x	x	x	-80 C	IRCM	3mL
Tryptophan	Serum			x	x	x	-80 C		
Taurine	Serum			x	x	x	-80 C		

* Protected from light
Blood (K_2EDTA)
Serum (Red Cap SST BD Vacutainer)

22.3.2.1 Baseline (ESSOR Randomization Visit 2, in-person, Day 1)

As mentioned earlier, some analyses are to be locally performed at each site's clinical laboratory during the course of the study and the others are to be centrally performed at the IRCM laboratory in a planned single occasion after acquiring the majority if not all the study samples. In either case, procedures are to be in place to prevent the clinical investigators from receiving identifiable results.

Whole blood for hematology with differential counts (including reticulocytes)

Using the standard procedure in effect at your site for collecting samples destined for hematology, or the below suggested handling steps,

- take one 3mL Lavender Cap BD Vacutainer (K_2EDTA) and properly identify it with subject ID.
- fill completely the Vacutainer tube (approximately 3mL of whole blood).
- gently mix the content by inversion of the tube 8-10 times.
- send the sample to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database.

Serum (CRP and retinol)

Using the standard procedure in effect at your site for collecting samples destined for CRP and retinol analysis, or the below suggested handling steps,

- take one 10mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tube (approx. 10mL of whole blood).
- Immediately after the blood is drawn, the tube should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.
- spin the tube at 1700-1800 x g during 10 min., at room temperature.

- harvest serum from the Red Cap SST BD Vacutainer and transfer into two cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
  - 2 mL – for CRP
  - 2 mL – for retinol (protect from light by covering with aluminum foil).
- send the samples to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database

For the following tests, to be done at the IRCM laboratory, locate the Baseline tubes and the pre-printed label kit provided by Laurent/IRCM, and pull out the various tubes: Vacutainers and cryotubes, with corresponding labels. Use the following procedure:

Serum (inflammation biomarkers)

- take two 3mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tubes (approx. 3mL of whole blood each).
- Immediately after the blood is drawn, the tubes should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.
- spin the tube at 1700-1800 x g during 10 min., at room temperature.
- harvest serum from the Red Cap SST BD Vacutainers and transfer into four cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
  - 2 x 500µL – for calprotectin, CD40L, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-28B(IFN-lambda3, Il-29, IP-10 and TNF-α
  - 2 x 500µL – for serotonin, tryptophan and taurine
- according to instructions provided by Laurent, either:
  - Store at -80°C until instructed to ship to IRCM in dedicated shipping containers (on dry ice);
  - Place the transport cryotubes in a provided subject sample box, keep temporarily at -20°C before shipping in dedicated shipping containers (on dry ice) under Frozen transport to IRCM.
- IRCM to proceed with batch analysis after all the samples have been collected from participating sites.
- results are to be kept in a secure location at IRCM, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.

22.3.2.2 Day 15 (Visit 3, In-person)

Whole blood for hematology with differential counts (including reticulocytes)

Using the standard procedure in effect at your site for collecting samples destined for hematology, or the below suggested handling steps,

- take one 3mL Lavender Cap BD Vacutainer (K_2EDTA) and properly identify it with subject ID.
- fill completely the Vacutainer tube (approximately 3mL of whole blood).
- gently mix the content by inversion of the tube 8-10 times.
- send the sample to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database.

Serum (CRP and retinol)

Using the standard procedure in effect at your site for collecting samples destined for CRP and retinol analysis, or the below suggested handling steps,

- take one 10mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tube (approx. 10mL of whole blood).
- Immediately after the blood is drawn, the tube should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.
- spin the tube at 1700-1800 x g during 10 min., at room temperature.
- harvest serum from the Red Cap SST BD Vacutainer and transfer into two cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
  - 2 mL – for CRP
  - 2 mL – for retinol (protect from light by covering with aluminum foil).
- send the samples to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database

For the following tests, to be done at the IRCM laboratory, locate the Baseline tubes and the pre-printed label kit provided by Laurent/IRCM, and pull out the various tubes: Vacutainers and cryotubes, with corresponding labels. Use the following procedure:

Serum (inflammation biomarkers)

- take two 3mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tubes (approx. 3mL of whole blood each).

- Immediately after the blood is drawn, the tubes should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.
- spin the tube at 1700-1800 x g during 10 min., at room temperature.
- harvest serum from the Red Cap SST BD Vacutainers and transfer into four cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
    - 2 x 500µL – for calprotectin, CD40L, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-28B(IFN-lambda3, Il-29, IP-10 and TNF-α
    - 2 x 500µL – for serotonin, tryptophan and taurine
- according to instructions provided by Laurent, either:
    - Store at -80°C until instructed to ship to IRCM in dedicated shipping containers (on dry ice);
    - Place the transport cryotubes in a provided subject sample box, keep temporarily at -20°C before shipping in dedicated shipping containers (on dry ice) under Frozen transport to IRCM.
- IRCM to proceed with batch analysis after all the samples have been collected from participating sites.
- results are to be kept in a secure location at IRCM, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.

22.3.2.3 Day 70 (biomarker sampling visit, in-person)

Whole blood for hematology with differential counts (including reticulocytes)

Using the standard procedure in effect at your site for collecting samples destined for hematology, or the below suggested handling steps,

- take one 3mL Lavender Cap BD Vacutainer (K_2EDTA) and properly identify it with subject ID.
- fill completely the Vacutainer tube (approximately 3mL of whole blood).
- gently mix the content by inversion of the tube 8-10 times.
- send the sample to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database.

Serum (CRP and retinol)

Using the standard procedure in effect at your site for collecting samples destined for CRP and retinol analysis, or the below suggested handling steps,

- take one 10mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tube (approx. 10mL of whole blood).
- Immediately after the blood is drawn, the tube should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.

- spin the tube at 1700-1800 x g during 10 min., at room temperature.
- harvest serum from the Red Cap SST BD Vacutainer and transfer into two cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
  - 2 mL – for CRP
  - 2 mL – for retinol (protect from light by covering with aluminum foil).
- send the samples to your clinical laboratory for analysis.
- results are to be kept in a secure location in the clinical laboratory, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.
- at regular intervals during the study, the results will be electronically transmitted to an unblinded data management staff at Alimentiv, for merging with the clinical database

For the following tests, to be done at the IRCM laboratory, locate the Baseline tubes and the pre-printed label kit provided by Laurent/IRCM, and pull out the various tubes: Vacutainers and cryotubes, with corresponding labels. Use the following procedure:

Serum (inflammation biomarkers)

- take two 3mL Red Cap SST BD Vacutainer tube and properly identify it with subject ID, on the labels provided.
- fill completely the Vacutainer tubes (approx. 3mL of whole blood each).
- Immediately after the blood is drawn, the tubes should be gently inverted 5 times to mix the content.
- allow blood to clot for a minimum of 30 minutes at room temperature in a vertical position and observe to determine the presence of a dense clot.
- spin the tube at 1700-1800 x g during 10 min., at room temperature.
- harvest serum from the Red Cap SST BD Vacutainers and transfer into four cryotubes properly labeled with subject ID and verify the identity against the Vacutainer label:
  - 2 x 500µL – for calprotectin, CD40L, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-28B(IFN-lambda3, Il-29, IP-10 and TNF-α
  - 2 x 500µL – for serotonin, tryptophan and taurine
- according to instructions provided by Laurent, either:
  - Store at -80°C until instructed to ship to IRCM in dedicated shipping containers (on dry ice);
  - Place the transport cryotubes in a provided subject sample box, keep temporarily at -20°C before shipping in dedicated shipping containers (on dry ice) under Frozen transport to IRCM.
- IRCM to proceed with batch analysis after all the samples have been collected from participating sites.
- results are to be kept in a secure location at IRCM, to ensure that no identifiable results are communicated back to the clinical investigator or his/her team, in order to maintain the blinded nature of the study.

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