Laurent
PHARMACEUTICALS

COVER PAGE FOR PROTOCOL

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

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CLINICAL TRIAL PROTOCOL

LAURENT PHARMACEUTICALS INC.

PROTOCOL NO: LAU-20-01

Study title: **RESOLUTION**: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE II/III STUDY OF THE EFFICACY AND SAFETY OF LAU-7b IN THE TREATMENT OF ADULT HOSPITALIZED PATIENTS WITH COVID-19 DISEASE

Sponsor: Laurent Pharmaceuticals Inc.

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

Protocol Date: Amendment 5, August 4th, 2023

Confidentiality Statement

Signature Page for Sponsor:

Product: LAU-7b
Study No. LAU-20-01

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

Approved by the following:

_____ _____
Larry Lands, MD, PhD — Date
Chief Medical Adviser
Laurent Pharmaceuticals Inc.
[redacted]

_____ _____
Jean-Marie Houle, B.Sc.Pharm., M.Sc., PhD — Date
Vice President of Clinical Development,
Laurent Pharmaceuticals Inc.
and Study Director
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_____ _____
Diane Potvin, M.Sc. — Date
Study Statistician
Senior Statistical Advisor, Biometrics
Innovaderm Research Inc.
[redacted]

Signature Page for Investigator:

Product: LAU-7b
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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/State + Postcode/Zipcode	Country

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	**RESOLUTION**: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE II/III STUDY OF THE EFFICACY AND SAFETY OF LAU-7b IN THE TREATMENT OF ADULT HOSPITALIZED PATIENTS WITH COVID-19 DISEASE
Investigational Product	LAU-7b (fenretinide) oral capsules
Sponsor	Laurent Pharmaceuticals Inc.
Study Objectives	**Primary objective:** To evaluate the efficacy of LAU-7b therapy + Standard-of-Care (SOC) relative to placebo + SOC in patients with COVID-19 disease with confirmed SARS-CoV-2 infection (target population). **Secondary and exploratory objectives:** 1- To assess the safety of LAU-7b therapy in all patients who received at least one dose of the study medication (Safety Population), compared to placebo + SOC. 2- To assess the efficacy of LAU-7b therapy at decreasing the rate of COVID-19 disease related aggravation in the target population (such as a worsening of one category on the ordinal scale, onset of severe categories on the ordinal scale, need for transfer to Intensive Care Unit (ICU), need for mechanical ventilation and death, among others), compared to placebo + SOC. 3- To measure the impact of LAU-7b therapy on the time course of the COVID-19 disease in the target population, as depicted by mean ordinal scale change from baseline at each assessment time, and by time-to-event analyses (time to an improvement of one category on the ordinal scale, time to recovery (defined), time to ICU transfer, time to mechanical ventilation, and time to death), compared to placebo + SOC. 4- To assess the benefit of LAU-7b therapy on the Quality of Life, compared to placebo + SOC.

Study Rationale	SARS-CoV2 is a novel coronavirus identified as the cause of the coronavirus disease 2019 (COVID-19) that began in Wuhan, China in late 2019, and rapidly qualified as a pandemic. No effective therapy currently exists for treatment. While most patients with COVID-19 disease are thought to have a favorable prognosis, older patients and those with chronic underlying conditions may have worse outcomes with hyper-inflammation in the lungs and rapid progression to acute respiratory distress syndrome (ARDS) that may result in a requirement for mechanical ventilation, thus creating an unsustainable burden for the health care system and a rapidly escalating crisis [6]. One of the main mechanisms for ARDS is cytokine storm, a deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokines[10]. Anti-inflammatory treatments that aggressively inhibit inflammation, such as corticosteroids, are less expected to have a significant benefit during the viral response phase of the disease, when the immune response is required to effectively fight the infection and prevent its escalation to lung hyper-inflammatory phase that may require respiratory support[11]. However, mild non-steroidal anti-inflammatory drug (NSAID)s (such as ibuprofen and acetaminophen) are useful for decreasing fever in coronavirus patients[12]. Recent results from the RECOVERY clinical study with

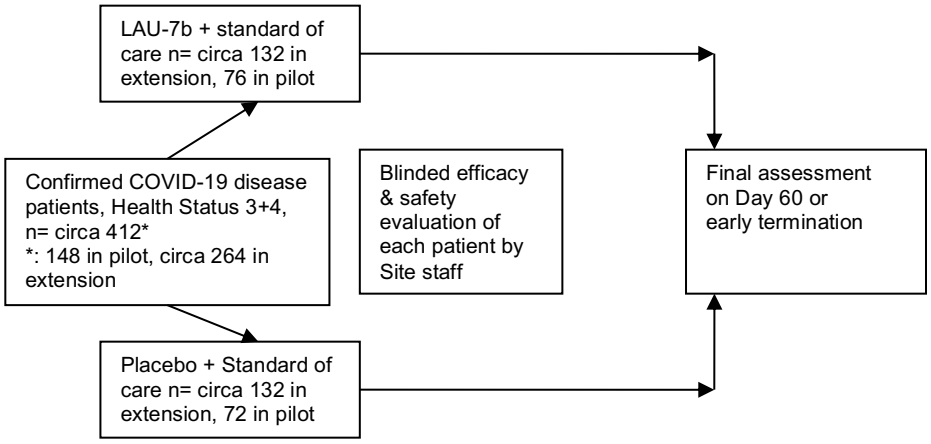
Study Rationale (cont'd)	dexamethasone corticosteroid therapy in hospitalized COVID-19 patients showed a reduction in death incidence by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen without invasive mechanical ventilation. However, it did not reduce mortality in patients not receiving respiratory support at randomization [13]. Normally, the body is able to maintain a balance between the pro-inflammatory and the resolution phases of inflammation. However, in certain conditions, this balance is disrupted and the pro-inflammatory phase becomes over-reactive. All current anti-inflammatory drugs work by inhibiting parts of the pro-inflammatory phase of the inflammation, modulated by the Arachidonic Acid (AA) metabolic cascade. LAU-7b is a novel once-a-day oral form of fenretinide that is under development by Laurent Pharmaceuticals for its ability to trigger the body's own resolution of inflammation without interfering with its immune response (a "pro-resolving" effect). LAU-7b is believed to act on the resolution phase of inflammation by endogenously modulating the metabolism of docosahexaenoic acid (DHA), an essential fatty acid involved in the process of healing and return to homeostasis after a pathogen attack or injury. Therefore, LAU-7b can be used as a balancing factor able to keep the inflammation process under control, complementing the action of typical anti-inflammatory drugs. During a drug-library screening effort conducted by scientists from the Institut Pasteur Korea, fenretinide was shown to also have potent antiviral activity (EC_{50} = 2.8µM) against Middle Est Respiratory Syndrome coronavirus (MERS-CoV), a virus that is structurally similar to the virus causing COVID-19[41]. Recent preliminary results using the same cellular model, showed that fenretinide exerts a similarly potent antiviral activity against several variants of the SARS-CoV-2 virus [redacted] a very relevant finding being confirmed by additional experiments. Independent *in vitro* evidence also showed that fenretinide inhibits SARS-CoV-2 spike protein-mediated cell-cell membrane fusion (SARS-CoV-205-2N, EC_{50} = 4.1µM) by decreasing host cell membrane lipids fluidity [42]. LAU-7b was evaluated in a Phase 2 clinical trial in adult patients with Cystic Fibrosis (CF) aiming to treat the exaggerated inflammatory response that leads to irreversible lung damage and a positive signal of efficacy was observed, paving the way to confirmatory Phase 3 studies. An earlier Phase 1b clinical data from CF adult patients, 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 AA and DHA pathways, with a favourable effect on certain biomarkers of inflammation (IL-6, IL-8, IL-10, neutrophils count) at the onset of a pulmonary exacerbation episode, suggestive of a protective effect on the lungs. LAU-7b' lipid modulation activity was shown to be in conjunction with pro-resolving pathways of inflammation (MAPK/ERK[37], NF-kB[54], cPLA2[14]), which also play a role in virus cellular entry, replication and avoidance of host defense system[14, 15, 17, 17]. By inhibiting these molecular pathways, LAU-7b may not only interfere with virus spread in the body, but also prevent the escalation of the pro-inflammatory response resulting during the infection process. Due to its antiviral properties and its pro-resolving effects on inflammation, LAU-7b is therefore being proposed as a therapeutic with potential to reduce COVID-19 disease severity, maintain a balanced immune-inflammatory response and prevent disease progression toward an Acute Respiratory Distress Syndrome, especially in patients at risk because of their age, underlying conditions, or both.

Study Endpoints	**Primary Endpoint:** The main efficacy variable is the 7-point ordinal scale of the patient status and the revised primary efficacy endpoint is the proportion of patients requiring mechanical ventilation (includes extra-corporeal membrane oxygenation - ECMO) AND/OR deceased (all causes) by Day 60 (Ordinal scale scores 6-7 inclusively), compared between the active and control (placebo) arms of the study; all patients will undergo the SOC at their institution. The ordinal scale is presented below and further definitions of categories 1-6 are presented in the body of the protocol Section 7.1.1. **Ordinal Scale** 1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities; 3. Hospitalized (under observation/admitted), not requiring supplemental oxygen; 4. Hospitalized (under observation/admitted), requiring supplemental oxygen; 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6. Hospitalized, on invasive mechanical ventilation or ECMO (extra-corporeal membrane oxygenation); 7. Death. The ordinal scale is an assessment of the health status on a given study day, identifying the worst health status during the previous day of observation. Each day, according to local practice in terms of time of assessment, the worst health status during the previous day gets scored with the scale and will be recorded. i.e. on Day 3, the worst Day 2 health status is obtained and recorded as Day 2 score in the CRF, with the assessment time. **Secondary Endpoints:** 1. Safety: The safety of LAU-7b therapy will be assessed through the monitoring of treatment emergent adverse events and serious adverse events, vital signs including oxygen saturation and body temperature, symptom-directed physical examinations and safety laboratory tests. It is important to note that most of these assessments are also SOC for hospitalized patients with COVID-19 disease and changes from baseline can depict improvement or worsening of the condition. 2. Efficacy: Rate of all-causes death, depicted by a change from baseline in the ordinal scale position to category 7 by Days 29 and 60, compared between the active and control (placebo) arms of the study. 3. Efficacy: Rate of COVID-19 disease-related transfer to mechanical ventilation or ECMO, depicted by a change from baseline in the ordinal scale position to category 6, compared between the active and control (placebo) arms of the study. 4. Efficacy: Proportion of patients alive and free of respiratory failure by Day 29 (ordinal scale scores 1-4, inclusively), compared between the active and control (placebo) arms of the study. 5. Efficacy: Proportion of patients re-hospitalized after discharge (any stay in the hospital of minimum overnight duration, all causes) up to Day 60, compared between the active and control (placebo) arms of the study. 6. Efficacy: Rate of COVID-19 disease-related aggravation, depicted by a change from baseline in the ordinal scale position of at least one category, compared between the active and control (placebo) arms of the study. 7. Efficacy: Rate of COVID-19 disease-related transfer to ICU, compared between the active and control (placebo) arms of the study. 8. Efficacy: Patient status on the 7-point ordinal scale on Days 14 and 29; compared between the active and control (placebo) arms of the study.

Study Endpoints (cont'd)	9. Efficacy: Mean change from baseline of the ordinal scale patient status as a function of assessment time, compared between the active and control (placebo) arms of the study. 10. Efficacy: Time to an improvement of one category on the ordinal scale patient status, compared between the active and control (placebo) arms of the study. 11. Efficacy: Time to recovery, defined here as a move from baseline to categories 2 or 1 on the ordinal scale patient status (first occurrence if more than one), compared between the active and control (placebo) arms of the study. 12. Efficacy: Time to mechanical ventilation, defined here as a move from baseline to category 6 on the ordinal scale patient status, compared between the active and control (placebo) arms of the study. 13. Efficacy: Time to death, defined here as a move from baseline to category 7 on the ordinal scale patient status, censored to Day 60 if it happens later than Day 60, compared between the active and control (placebo) arms of the study. 14. Efficacy: Duration of hospitalization (days) within the study period Days 1-60, compared between the active and control (placebo) arms of the study. 15. Quality-of-Life: The change from baseline to Days 14, 29, 45 and 60 in the score obtained on the EQ-5D-5L survey, a well-documented scoring system that has been widely used and validated as a QoL assessment tool, compared between the active and control (placebo) arms of the study, in patients reaching Days 14, 29, 45 and 60 and able to fill the questionnaire.
Study Design Overview	RESOLUTION is a randomized, double-blind (patients, investigators and blinded study staff), placebo-controlled Phase 2/3 Study of LAU-7b against confirmed COVID-19 disease. All patients, hospitalized for COVID because of their health condition and aggravating factors, confirmed to be infected with SARS-CoV-2 virus, will undergo the SOC for their stage of COVID-19 disease at their institution. This design is appropriate for this phase of development as it caters to individuals at a greater risk of aggravation but do not yet require intensive care. In the pilot Phase 2 portion of the study, a total of 232 patients have been randomized and upon analysis of the results, it has been decided to expand the enrolment in the subset of patients from the pilot portion responding best to LAU-7b therapy, relative to placebo, to reach an adequate statistical power for that target subset to be confirmatory. The best responders are patients with Health Status score 3 or 4 (moderate-to-severe, n=148) at baseline. This corresponds to patients deemed not to be in respiratory failure at baseline. Patients with a Health Status score of 5 at baseline (critical COVID, n=84) are deemed to have an established respiratory failure and did not respond positively to LAU-7b therapy in the pilot portion of the study. In the Phase 3 extension of the study, the overall design remains unchanged and so is the main efficacy variable, the Health Status score. Based on sample size calculation using the effect size observed in the pilot portion of the study for the revised Primary Efficacy Endpoint in the subset of patients with a Health Status score 3 or 4 at baseline and an alpha of 0.05, approximately 264 additional patients with Health Status score 3 or 4 at baseline will be recruited and randomized for the treatment phase of the study. Patients will be enrolled at approximately 25-30 centers in the United States of America and in Canada. To ensure the study extension is powered adequately and self-sufficient to be confirmatory, an interim sample size re-estimation including a futility analysis will occur once 42% (112) of the 264 planned patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early. A maximum of 462 patients total may be enrolled, dependent upon the results of the interim sample size re-estimation.

Study Design Overview (cont'd)

Below is a schematic of the study structure for Health Status 3 + 4 patients in the Phase 2 pilot and the Phase 3 extension:



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

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

Patients will continue the treatment with LAU-7b 200 mg per day (2 capsules of 100 mg each), once a day for the remaining 11 days, or a matching placebo administered in the same fashion, on top of SOC (the "Follow-up Treatment").

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

A Data and Safety Monitoring Board (DSMB) is overseeing this study.

Study Population

Study Inclusion Criteria:

1- Subjects must exhibit symptoms (including at least one lower respiratory symptom such as shortness of breath or dyspnea) of COVID-19 disease at screening and/or since the start of their hospitalization (may include treated symptoms);
2- Subjects must be 18 years and older, of either gender;
3- Subjects must have at least one of the following factors/co-morbidities:
   a) Controlled or uncontrolled diabetes;
   b) Pre-existing cardiovascular disease, including hypertension;
   c) Pre-existing respiratory disease such as COPD, asthma, emphysema;
   d) Active or a former smoker with a 20 pack-years of smoking history;
   e) Obesity as depicted by BMI≥30;
   f) Laboratory tests indicative of a higher risk of COVID-19-related complications, such as troponin >1.5 ULN, D-dimer >3.0 ULN and/or CRP >1.5 ULN;
   g) Patient aged 70 years and older who, based on the judgment of the Investigator, is at a higher risk of developing complications.

Study Population (cont'd)	4- Subjects must have a documented positive test for the SARS-CoV-2 virus (co-infection with other viral respiratory infections is allowed and must be documented in medical history); 5- Subjects must be under observation by, or admitted to a controlled facility or hospital and receive SOC for COVID-19 disease; 6- Subject's health status must be 3 or 4 on the Ordinal Scale and not previously a "5 or a 6"; 7- 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 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 must be negative at the Screening Visit; 8- Subjects must have the ability to understand and give informed consent, which can be verbal with a witness, according to local requirements; 9- Subjects deemed capable of adequate compliance including attending scheduled visits for the duration of the study; 10- Subjects must be able to swallow the study drug capsules. **Study Exclusion Criteria:** 1. Pregnancy or breastfeeding; 2. Health condition deemed to possibly interfere with the study endpoints and/or the safety of the patients. For example, the following conditions should be considered contraindicated for participation in the study, but this is not an exhaustive list. In case of doubt, the Investigator should consult with the Sponsor's medical representative: a) Presence of inherited retinitis pigmentosa; b) Presence or history of liver failure (Child-Pugh B or C); c) Presence or history of stage 4 severe chronic kidney disease or dialysis requirement; d) Febrile neutropenia; e) Presence of end-stage cancer. 3. 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; 4. Participation in another drug clinical trial within 30 days (or a minimum of 5 elimination half-lives) prior to screening, except ongoing participation in non-interventional studies; 5. Calculated creatinine clearance (CrCL, using the Cockroft-Gault equation for example) <30 ml/min, (see footnote in Section 8.2); 6. Presence of total bilirubin >1.5 x ULN (in the absence of demonstrated Gilbert's syndrome), ALT and/or AST > 2.5 x ULN; 7. Patient expected to be transferred to ICU or die in the next 24 hours.
Dose and Mode of Administration	**Dose rationale in COVID-19 disease.** An initial load dose of 300 mg will be administered PO once-a-day, in the first three days of treatment, for a faster achievement of fenretinide plasma concentrations eliciting antiviral effect. A maintenance dose of 200 mg will then be administered PO once-a-day on Days 4-14, to maintain a plasma concentration expected to have both antiviral activity and a pro-resolving effect on inflammation. On the exposure standpoint, this regimen should achieve average circulating level of circa 2 μM, which corresponds to the concentrations eliciting the cytokine storm protection in the mice

Dose and Mode of Administration (cont'd)	model of sepsis (1-2 μM) and close to the EC_{50} range for the antiviral activity against the MERS-CoV virus (2.8 μM) and the SARS-CoV-2 virus (0.46 to 4.1 μM). A study treatment consisting of up to fourteen (14) consecutive days of treatment with LAU-7b or placebo, administered as follows: • Initial Treatment on Days 1-3: LAU-7b 300 mg per day (3 capsules of 100 mg each), or matching placebo, once a day for 3 days in the fed state, preferably the main meal of the day, followed by the • Follow-up Treatment on Days 4-14: LAU-7b 200 mg per day (2 capsules of 100 mg each), or matching placebo, once a day in the fed state, preferably the main meal of the day. • The capsules <u>should not</u> be broken down to administer their content through a feeding tube if the patient is intubated and cannot ingest anymore the capsules intact. Study treatment will be administered on top of current Standard of Care therapies.
Statistical Analysis	**Sample size:** A target of circa 264 SARS-CoV-2 positive patients with a Heath Status score of 3 or 4 at baseline total sample size is required in this Phase 3 study extension to be self-sufficient and confirmatory. Consequently, once additional enrolment is completed, considering the sample size re-estimation (below), a minimum of 412 patients with Heath Status score of 3 or 4 at baseline will have been randomized in this Phase 2/3 study, for a total of 496 patients including the 84 subjects with a Health Status score of 5 randomized in the Phase 2 Pilot. Sample size rationale: With the expansion of recruitment of patients with a Heath Status score of 3 or 4 at baseline, an informed sample size calculation has been carried out using the observed effect size in the pilot portion of the study (with n=148 patients) for the updated Primary Efficacy Endpoint "The proportion of patients requiring mechanical ventilation AND/OR deceased by Day 60", the observed rate of patients withdrawing consent to be followed up. Using the proportion of patients requiring invasive mechanical ventilation AND/OR deceased by Day 60 in the pilot portion of the study, an effect size of 7% change (i.e. 7% in the control group vs. 0% in the investigational group), comparing the active arm versus the control (placebo) arm, and a minimum of 90% statistical power of detecting a difference in proportions of 7% as statistically significant using a two-tailed Fisher Exact test with a nominal alpha of 0.05 (5%), a total sample size of 264 patients (132 per arm) with a Heath Status score of 3 or 4 at baseline is required. To ensure the study is powered adequately if the effect size is smaller than initially estimated, an interim sample size re-estimation (Mehta and Pocock, 2011)[85] including a futility analysis will occur once 42% (112) of the planned 264 patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early. If the conditional power is within the promising zone, the sample size may be increased up to a maximum of 462 patients, dependent upon the results of the interim sample size re-estimation. If the conditional power is below the promising zone, the futility criteria will be deemed met and a recommendation to stop further enrollment will be communicated to the DSMB and the Sponsor. **Primary Efficacy Endpoint Analysis:** The primary hypothesis test will be based on a test of a null hypothesis that the proportions of patients requiring mechanical ventilation OR deceased by Day 60 for the two treatment groups are the same against the alternative hypothesis that the investigational group is superior to the control group. The statistical analyses for the other study parameters are summarized in the Statistical Analysis, Section 12, and will be detailed in the SAP.

2 SCHEDULE OF EVENTS

	Screening Pre-randomization on Day -1 or 1 (no Day 0 in this study)	Randomization on Day 1	In-Hospital Days 2, 3, 4 , 6 , 7, 9, 10, 11, 13	In-Hospital Days 5, 8, 12 (+/- 1 day)	End-of–Hospital Stay or Day 14	Contacts in hospital after Day 14 or after discharge every 3 days up to Day 29 (+/- 2 days)	Contacts on Day 29 and Day 45 (+/- 3 days)	End-of-Study / Long term follow-up Day 60 (+/- 3 days)	Early termination
Visit number	**0**	**1**	**2, 3, 4 , 6 , 7, 9, 10, 11, 13**	**5, 8, 12**	**n/a**	**variable**	**n/a**	**n/a**	**n/a**
Verification of ID and age	X								
Informed consent	X								
Inclusion/Exclusion criteria	X	X							
Demographics and Medical History	X								
Concomitant Meds	X			X	X	X	X		X
Standard of Care procedures									
Directed Physical Examination	X			X	X[3]				
Height, weight and Body Mass Index calculated[1]	X				X				
Vital Signs including respiratory rate, oxygen saturation and body temperature[2]	X	X	X	X	X				X
COVID-19 symptom check	X	X	X	X	X	X	X	X	
Safety laboratory tests, including hematology with differentials[4], serum chemistry[5] and urinalysis[6]	X			X	X[3]				
Study-specific procedures									
Pregnancy Test for women (serum or urine)	X				X				X
Health status using Ordinal Scale	X		X	X	X	X	X	X	X
QOL: EQ-5D-5L	X				X		X	X	
Randomization		X							
Dispensing of Initial Treatment		X							
Dispensing of Follow-up Treatment			X on Day 4 only						
Study drug verification[7]					X	X			
Open-ended safety questions				X	X[3]	X	X		
Adverse Events	X	X	X	X	X	X	X	X	X

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

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3 GLOSSARY OF TERMS AND ABBREVIATIONS

AA: Arachidonic Acid
AE: Adverse Event
ALT: Alanine Aminotransferase
AMD: Age Related Macular Degeneration
ANCOVA: analysis of covariance
AST: Aspartate Aminotransferase
ATRA: All-Trans Retinoic Acid
AUC: Area Under the Curve
BID: *Bis In Die* (Latin), twice daily
BHA: Butylated Hydroxyanisole
BMI: Body Mass Index
BW: Body Weight
CBC: Complete Blood Count
CF: Cystic Fibrosis
CFTR: Cystic Fibrosis Transmembrane Conductance Regulator
Cmin : Minimal Concentration in Matrix (plasma, blood….etc)
Cmax: Maximal Concentration in Matrix (plasma, blood…etc)
CrCL: Creatinine clearance
CRF: Case Report Form
CRO: Contract Research Organization
CTCAE: Common Terminology Criteria for Adverse Events
CV: Curriculum Vitae
Css: Concentration at Steady State
DHA: Docosahexaenoic Acid
DILI: Drug Induced Liver Injury
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: Study Informed Consent Form
IL-1ra: Interleukin 1 receptor antagonist
IL-6: Interleukin 6
IL-8: Interleukin 8
IL-10: Interleukin 10
IP: Intra-Peritoneal
IRB: Institutional Review Board
ITT : Intent-to-Treat
IV : Intravenous
IWRS: Interactive Web Response System

KO : Knock-Out
MedDRA: Medical Dictionary for Regulatory Activities
MTD: Maximally Tolerated Dose
MUHC: McGill University Health Centre
NF-κB: Nuclear Factor-kappaB
NSAID: Non-steroidal anti-inflammatory drug
PD: Pharmacodynamic
PI: Principal Investigator
PK: Pharmacokinetic
PO: *per os* (Latin), by mouth, orally
PP: Per Protocol
PPAR: Peroxisome Proliferator Activating Receptor
PsA: *Pseudomonas aeruginosa*
QD: *Quaque Die* (Latin), every day/daily
QTc: QT corrected for heart rate
RAR: Retinoic Acid Receptor
RBC: Red Blood Cells
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
SC: Subcutaneous
SD: Standard Deviation
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
VLCC: Very Long Chain Ceramides

4 STUDY PERSONNEL

Sponsor:
Laurent Pharmaceuticals Inc.
[redacted]
Montreal, Quebec
[redacted]

Larry Lands, MD, Ph.D.,
Chief Medical Adviser
[redacted]

Jean-Marie Houle, B.Sc.Pharm., M.Sc., Ph.D.
Vice President of Clinical Development
and Study Director
[redacted]

Sarah Bezzaoucha, MSc
Associate Director Clinical Development
[redacted]

Monitors:
The sponsor has contracted with Contract Research Organizations (CRO) to help manage the trial. Specific Contact information for the below CRO contacts and each study monitor is maintained in the study monitoring plan and on file at each investigator's site.

CRO Senior Contacts:

[redacted]

Manufacturer:
Genvion Corporation
[redacted]
Winnipeg, MB [redacted]
Canada

Serious Adverse Event (SAE) Reporting:
Dr. Radhika A, MD
Medical Monitor
[redacted]
Laurent Safety Line: +1 877-914-4242
[redacted]

5 INTRODUCTION

5.1 Investigational product

LAU-7b is a solid oral dosage form of fenretinide (100 mg capsules). Fenretinide, a small molecule synthetic retinoid derivative, is an investigational drug (new chemical entity) with well-documented history of safety in non-clinical and clinical studies ([redacted] US National Cancer Institute (NCI) since 1992). The active product ingredient is N-(4-hydroxyphenyl)retinamide, also referred to as 4-HPR or FRD, and is a synthetic amide of all-trans retinoic acid with a molecular formula $C_{26}H_{33}NO_2$.

Fenretinide is an investigational synthetic retinoid that was 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.

LAU-7b is a novel and improved oral formulation of fenretinide. [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 Rationale 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-patient 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 so far, particularly in the pediatric population.

In the past, fenretinide has also been formulated in a lipid matrix, Lym-X-Sorb (LXS) [2], containing 2% of fenretinide and administrated as an oral powder delivered in non-milk fat-containing foods, and especially as a slurry in non-milk fat-containing, or soy-based nutritional supplements. However, this formulation has been shown to be associated with significant gastrointestinal side-effects, especially at higher doses[3], as well as to significant patient withdrawal due to the taste and texture of the medication.

There was thus a need for new pharmaceutical dosage form of fenretinide, especially for oral administration, capable of overcoming the poor oral bioavailability of corn-oil based formulation and the fair patient compliance. Dosage forms such as hard gelatin capsules, tablets, caplets, suspensions, or powders for suspensions were to be considered.

Laurent Pharmaceuticals has 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 new formulation (LAU-7b) [redacted] was successfully tested by Laurent Pharmaceuticals in a Phase 1b study involving adult Cystic Fibrosis (CF) patients [4]. [redacted] large Phase 2 study in CF [redacted] and will also be used in this study, [redacted]

5.2 COVID-19 Disease Overview

SARS-CoV2 is a novel coronavirus identified as the cause of the coronavirus disease 2019 (COVID-19 disease) that began in Wuhan, China in late 2019, and rapidly qualified as a pandemic. Coronaviruses are a large family of RNA viruses that are found diversely in animal species. They are known to cause diseases of the respiratory, hepatic, nervous system, and gastrointestinal systems in humans.

Although the outbreak is likely to have started from a zoonotic transmission event associated with a large seafood market that also traded in live wild animals, it soon became clear that efficient person-to-person transmission was also occurring [5]. The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death, with many patients who got hospitalized with pneumonia in Wuhan [6, 7, 8].

A retrospective analysis of the risk factors of severity and mortality in a sizeable cohort of patients in China using multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95% CI 1.03–1.17, per year increase; p=0.0043), higher Sequential Organ Failure Assessment score (5.65, 2.61–12.23; p<0.0001), and d-dimer greater than 1 µg/L (18.42, 2.64–128.55; p=0.0033) on admission. Median duration of viral shedding was 20.0 days (IQR 17.0–24.0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days [9].

While most patients with COVID-19 disease are thought to have a favorable prognosis, older patients and those with chronic underlying conditions may have worse outcomes with 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 [5].

One of the main mechanisms for ARDS is cytokine storm, a deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokine [10]. Anti-inflammatory treatments that aggressively inhibit inflammation, such as corticosteroids, are less expected to have a significant benefit during the viral response phase of the disease, when the immune response is required to effectively fight the infection and prevent its escalation to lung hyper-inflammatory phase that may require respiratory support [11]. However, mild anti-inflammatory NSAIDs (such as ibuprofen and acetaminophen) are useful for decreasing fever in coronavirus patients [12]. Recent results from the RECOVERY clinical study with dexamethasone corticosteroid therapy in hospitalized COVID-19 patients, showed a reduction in deaths by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen without invasive mechanical ventilation. However, it did not reduce mortality in patients not receiving respiratory support at randomization [13].

The controversy around the use of typical anti-inflammatory drugs in severe inflammatory diseases is not new. On one hand, during the viral phase of the disease it is desired to have the right amount of inflammation capable to stimulate an immune response and fighting the infection, and on the other hand, there is a need to avoid the inflammation process to become excessive, uncontrolled and potentially harmful. Normally, the body is able to maintain a balance between the pro-inflammatory and the resolution phases of inflammation. However, in certain conditions, this balance is disrupted and the pro-inflammatory phase becomes over-reactive, the disease enters into a lung hyper-inflammatory phase leading to ARDS, and a certain level of immune-suppression may be required.

Recent publications have cited MAPK/ERK [14, 15, 16], NF-κB [17] and cPLA2 [14, 16] as important molecular pathways required for coronavirus cellular entry, replication and avoidance of the host defense system, all potential targets against the virus spread. These are all potential targets for limiting the virus spread in the body and the COVID-19 disease.

Tracing a parallel with CF, the CF patients display an increased level of arachidonic acid (AA), having role in pro-inflammatory pathways, and a low level of docosahexaenoic acid (DHA) involved in anti-inflammatory, protective and pro-resolving roles during the inflammatory process [18]. AA and DHA are essential fatty acids that cannot be synthesized *de-novo* by humans, and are derived from nutritional intake. Their metabolism is the source for the synthesis of eicosanoids (AA-derived, such as prostaglandins, leukotrienes and lipoxins), and docosanoids (DHA-derived, such as resolvins and protectins). Eicosanoids and docosanoids are key inflammatory mediators involved in the modulation of the innate immune-inflammatory response following bacterial challenge or other type of injury. Thus, the timely homeostasis of eicosanoids and docosanoids is crucial in maintaining an efficient and balanced immune-inflammatory response.
The persisting, high AA levels displayed in CF patients may increase the pro-inflammatory factors and stimulate mucus secretion, while the low DHA levels, important in the anti-inflammatory defense and the resolution of inflammation, may explain why CF patients have an exaggerated and unresolved inflammatory response that, paradoxically, is unable to fight opportunistic infections [19, 20, 21].

5.3 Treatment of COVID-19 Disease

No all-encompassing and overly effective therapy currently exists for the treatment of established COVID-19 infection. Therefore, COVID vaccination, social distancing, hygiene and isolation remain the most effective measures for the prevention and the containment of COVID-19. The SARS-CoV-2 coronavirus, has continuously mutated since the beginning of the pandemic and nowadays, at the time of this Amendment 2, the Delta variant is the most prevalent variant circulating, being more infectious than the original form of the virus [22, 23], with Omicron starting to spread rapidly. At the time of initiation of this trial, no specific antiviral medication or vaccine was available [24]. In the matter of less than a year, effective preventive vaccines were developed, approved and are being administered worldwide but with regional disparities in the success or access to vaccination [22]. However, with the virus mutating rapidly and the danger of this disease becoming endemic, there is a need to develop effective COVID-19 therapeutics that can complement the vaccination campaigns, in order to prevent serious COVID-19 illness and death.

Therefore, the treatment of COVID-19 is tailored to the degree of advancement and severity of the infection, the inflammatory status, and may include symptomatic care and oxygen therapy. Non-hospitalized subjects with mild-to-moderate infections at risk of complications require early supportive management to which neutralizing antibodies (single or multiple in combination) can be administered to patients at risk of complications, to reduce the risk of hospitalization [25, 26]. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy [27]. Hospitalized patients with severe (non-critical) infections may also receive remdesivir, a specific and moderately effective antiviral therapy to help reduce the viral load, to speed up the recovery of hospitalized patients [28]. However, there is no evidence that remdesivir can reduce mortality in COVID-19 patients. These patients are currently in need of preventative and therapeutic agents capable of reducing the odds of aggravating further, such as established respiratory failure, the need for intensive care and invasive mechanical ventilation and ultimately, avoid death.

Critically ill patients require high flow oxygen, invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) and glucocorticoid therapy [27]. Early during the pandemic, the administration of systemic corticosteroids was not recommended to treat ARDS. However, large clinical studies have since demonstrated the benefit of systemic corticosteroids for patients in need for supplemental oxygen, the critically ill patients benefiting the most [29, 30, 28]. In the same vein, the hyperinflammation seen in the most severely affected patients can benefit from the strong anti-inflammatory effect afforded by anti-IL-6 monoclonal antibodies and the like [31, 32]. Moreover, unnecessary administration of antibiotics should also be

avoided. Patients with respiratory failure may require intubation, mechanical ventilation, high-flow nasal oxygen, or non-invasive ventilation. ECMO should be considered in patients with refractory hypoxemia despite undergoing assisted ventilation. Treatment of septic shock requires hemodynamic support with the administration of vasopressors. Organ function support is necessary for patients with multiple organ dysfunction [24].

Therapeutically, aerosol administration of alpha-interferon (5 million units twice daily), chloroquine phosphate, and lopinavir/ritonavir have been suggested [24], however the recently reported results were deceptive so far and the use of these drugs is not recommended.

So far, each drug or treatment added to the standard of care for COVID-19 have only contributed modestly to patient benefit, no single treatment modality is a game-changer [33, 34], especially for hospitalized mild-to-severe COVID-19 patients. With mutations continuing to appear and variability in vaccine access or resistance to vaccination, preventative therapeutics and supportive care used in combination to achieve a measurable benefit remains the mainstream of care for patients.

5.4 Study Rationale

LAU-7b is being proposed for its dual antiviral and inflammation-controlling properties, with potential benefits during the viral response phase of the COVID-19 disease by reducing the severity of the viral infection, as well as having potential benefits in the prevention of the hyper-inflammation of the lung.

LAU-7b lipid modulation and the pro-resolving effects on inflammation

LAU-7b is being developed for its potential to trigger the body's own ability to damping down inflammation without interfering with its immune response (a "pro-resolving" effect). Therefore, LAU-7b can be used as a balancing factor able to keep the inflammation process under control, complementing the action of typical anti-inflammatory drugs.

This effect was first observed in preclinical models of CF, then reproduced in CF exacerbating patients. There are many similarities between the aberrant inflammatory response in the lung of exacerbating CF patients and the pathogenesis of pulmonary complications associated with the COVID-19 infection.

CF is characterized by an abnormally activated inflammatory response in the lung, which overreacts in the presence of pathogens and leads to irreversible lung damage. Due to its abnormality and chronic manifestations, the regulation of inflammatory response remains one of the most important and unaddressed pathogenic mechanisms in CF. Previous attempts to control inflammation in the inflamed CF lungs by various anti-inflammatory drugs have been unsuccessful and in some cases resulted in frequent lung exacerbations and serious adverse events [35]. This is likely due to the fact that inhibition of the innate inflammation pathways can also inhibit the ability of patient's immune system to fight infections [36].

All current anti-inflammatory drugs work by inhibiting parts of the pro-inflammatory phase of the inflammation, modulated by the AA metabolic cascade. LAU-7b is believed to act on the resolution phase of inflammation by endogenously modulating the metabolism of DHA cascade, involved in the process of healing and return to homeostasis after a pathogen attack or injury. [redacted]

[redacted]

[redacted]

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* [37], CF mice model of inflammation and infection induced by *Pseudomonas aeruginosa* [38], mice models of allergic asthma [39] and spinal cord injury [40].

LAU-7b antiviral effects

Fenretinide was recently shown during a drug-library screening effort conducted by scientists from the Institut Pasteur Korea, to have potent antiviral activity (50% effective (inhibitory) concentration (EC_{50}) of 2.8uM) against the Middle Est Respiratory Syndrome coronavirus (MERS-CoV), a virus that is structurally similar to COVID-19 virus [41]. Recent preliminary results using the same cellular model, showed that fenretinide exerts a similarly potent antiviral activity against several variants of the SARS-CoV-2 virus (unpublished data). This information is presented below in Table 1. These are very relevant findings being confirmed by additional experiments. Independent *in vitro* evidence also showed that fenretinide inhibits SARS-CoV-2 spike protein-mediated cell-cell membrane fusion (SARS-CoV-205-2N, EC_{50} = 4.1µM) by decreasing host cell membrane lipids fluidity [42]. This is in line with the dose rationale for fenretinide in inflammatory diseases. Previous studies have also shown fenretinide's broad antiviral potential in preclinical testing against Dengue fever [43], Zika virus [44] and HIV [45].

			EC_{50}	
SARS-CoV-2 variant	**Institution**	**Cell line**	**Fenretinide**	**Remdesivir**
Delta B.1.617.2	Utah State University (Logan UH, USA)	VeroE6	0.46 µM	3.4 µM
Alpha B.1.1.7	Utah State University (Logan UH, USA)	VeroE6	0.87 µM	3.2 µM
Québec/21697/2020	Laval University (Quebec, Canada)	VeroE6	1.57 µM	1.16 µM
USA-WA1/2020	Utah State University (Logan UH, USA)	Vero76	2.6 µM	
SARS-CoV-205-2N *	Teikyo University (Tokyo, Japan)	VeroE6	4.1 µM	

*: Independent validation: Hayashi Y. *et al*, 2021 [42]

Table 1: Fenretinide and remdesivir antiviral activity against SARS-CoV-2 variants

Treatment goal and expected clinical benefits

Due to its antiviral properties and its pro-resolving effects on inflammation, LAU-7b is being proposed to potentially reduce COVID-19 disease severity, maintain a balanced immune-inflammatory response and prevent disease progression toward Acute Respiratory Distress Syndrome, especially in patients at risk because of their age, underlying conditions, or both.

A host-directed antiviral is expected to have a broader utility 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 destruction of lung tissue, and ultimately to lung insufficiency and impairment [21, 46].

It is unlikely that a single defect in one pathway accounts for the entirety of the exaggerated inflammatory response. For example, airway surface fluid from CF patients contains large concentrations of pro-inflammatory mediators including the tissue necrosis factor alpha (TNF-α), IL-1β, IL-6, IL-8, IL-17, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [47]. The synthesis of these mediators is promoted by a few transcription factors including AP-1, nuclear factor (NF)-κB, and mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinase (ERK1/2). In addition to a heightened pro-inflammatory arm, there appear to be inappropriately decreased counter-regulatory pathways, particularly those involving IL-10 and nitric oxide.

5.4.1 Proposed Mechanism of Action in COVID-19 disease

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 COVID-19 disease, for its antiviral properties and the potential to maintain a balanced inflammatory response.

Fenretinide is not a typical retinoid; it does not have a terminal carboxyl group believed to be an essential feature for active retinoids. However, it has been shown to have certain biological activities associated with the retinoid class. 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 [48].

Reprogramming of membrane lipids metabolism is a key feature of virus-host interaction, required for both virus entry and replication [17]. Although the complete mechanism of action in COVID-19 is not fully elucidated, fenretinide is hypothesized to work in COVID-19 by modulating cell membrane lipids fluidity and reducing *de-novo* lipogenesis via inhibiting dihydroceramide fatty acids desaturases (delta-4-desaturase, delta-9-desaturase) [42, 49, 50], which are described to be important factors for coronavirus entry and replication in the host cells [16, 17, 51]. 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 [52].

It was shown in animal models and in humans that fenretinide corrects the AA/DHA imbalance and inhibits macrophage inflammatory mediators via the ERK 1/2 pathway [53]. Fenretinide was also shown to inhibit the activation of the pro-inflammatory transcriptional NF-κB [54], as well as inhibit the downregulation of PPARγ, which is known to have a role in lipid metabolism [55]. More recently, it was demonstrated that fenretinide has the ability to inhibit the activity of calcium-dependent cytosolic phospholipase 2 (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 [56] and to increase the function of CFTR surface protein through its activity on the lipid microdomains (rafts) in the cell membrane.

Considering the involvement of previously cited MAPK/ERK[14, 15, 16] NF-κb[17] and cPLA2[14, 16] pathways in the various steps of viral entry, replication and immunological avoidance, and the fact that these pathways are also inhibited by fenretinide as part of its pro-resolving effect on inflammation, by modulating these pathways, LAU-7b may not only interfere with virus entry and replication, but also prevent the escalation of the pro-inflammatory response resulting during the infection process (Figure 1).

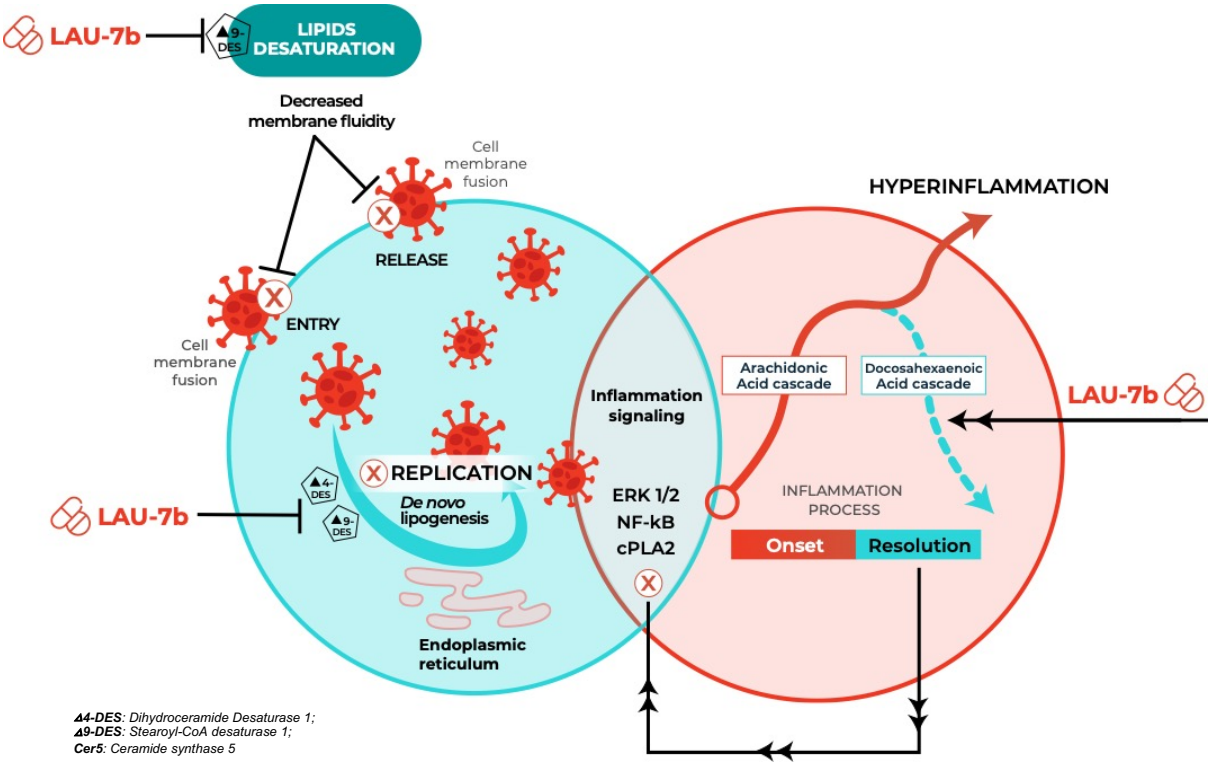


Figure 1: Fenretinide proposed mode of action in COVID-19 disease

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 [57, 58, 59, 60]. 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]

[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 [62, 63]. 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 [64]. 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) [65, 66], whereas additional minor metabolites, 4-oxo-N-(4 hydroxyphenyl)retinamide (4-oxo-fenretinide) and 4-hydroxy-N-(4 hydroxyphenyl)retinamide (4-OH-fenretinide), have been subsequently reported [67]. In contrast to rodents, 4-oxo-fenretinide is present at low concentrations in humans. Although 4-MPR is now generally considered to be inactive [68, 69], 4-oxo fenretinide was found to be an active metabolite that inhibits cell proliferation [67, 70].

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 [71]. The oxidative metabolism (phase1) is predominantly carried out by cytochromes P450 (CYP)s 3A4, 2C8, 2C9 and 2B6. This has been confirmed very recently by in-vitro metabolic stability experiments in human liver microsomes and hepatocytes (unpublished data) showing a low intrinsic clearance of fenretinide in human liver microsomes. Glucuronidation was shown to not playing a major role in the metabolism and clearance of fenretinide and its metabolites at clinically relevant levels [72]. Recently carried in-vitro drug metabolism, including inhibition and induction experiments showed the fenretinide is not a significant inhibitor or inducer of cytochrome P450 enzymes, in human liver microsomes and hepatocytes (unpublished data). Moreover, 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 metabolic profile of fenretinide in human indicates a low potential for drug-drug interactions.

5.4.2 Direct and Supportive Clinical Evidences

5.4.2.1 Safety and Efficacy Results to Date in This Study

At the time of Amendment 2, the RESOLUTION study has successfully achieved its initial randomization objective for the pilot portion, with 240 patients screened and 232 randomized. The rate of screen failure was lower than expected with most patients being consented, screened and randomized within hours of first contact by the site staff. Also, all screened patients already had a positive test for SARS-CoV-2. This avoided to withdraw patients before Day 4 from the study because of a negative test. The randomization stratified by site worked well and almost all 14 participating sites had a balanced active/placebo sample. A total of 6 sites

in Canada and 8 sites in the USA enrolled all patients starting on 18 August 2020 and ending on 15 May 2021.

Study demographics:
Overall, the two treatment arms were very well balanced (117 and 115 patients, in the LAU-7b and placebo arms, respectively). No bias due to an odd distribution of baseline characteristics was noted. The Health Status score distribution is such that the bulk of the overall study sample was either Score 4 or 5 (severe or critical, as per the widely accepted FDA COVID-19 disease severity definitions). The mean patient age was 57.5 and 56.7 years old (LAU-7b/placebo); about 60 % of all subjects were male and the vast majority were of a white, Caucasian race; mean BMI was 33.95 and 35.06 (LAU-7b/PBO); and more than 60 % of patients 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 patients (LAU-7b and placebo, respectively). Finally, both treatment arms were well balanced in terms of use of most COVID Standard of Care concomitant medications, such as remdesivir and systemic corticosteroids.

Safety summary:
In the RESOLUTION safety population (all randomized patients 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 patients. Almost all AEs (99.2%+) 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 patients did not report adverse events. The majority of the subjects (56 to 60%) experienced mild to moderate events while 10 to 16% of the patients 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.

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

Across most body systems, 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. The safety profile remains well balanced across the treatment arms when sorted by Health Status subgroup.

Efficacy Summary:
The primary analysis of efficacy is performed on the ITT population (randomized and took a minimum of one dose of study medication, n=232). The protocol also pre-specified a per-protocol (PP) population (randomized and took at least 12 days of study treatment administered in accordance with the protocol (i.e. without major protocol deviations as pre-identified prior to the database lock) and without interruption triggering withdrawal from further treatment, n=132). Also prespecified were the efficacy analysis by age categories, health status subgroup (Scores 3, 4 and 5), and number of comorbidities, as well as the logistic

regression analysis to determine if there are baseline factors affecting the response of patients. Along with full safety evaluation, a number of efficacy variables were pre-identified as topline results and obtained shortly after the database lock. These are the primary efficacy endpoint (the proportion of patients 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 ITT population, no statistically significant differences between LAU-7b and Placebo were found for the primary endpoint or for the secondary endpoints selected for topline results. However, the pre-planned logistic regression analysis of the impact of baseline factors on efficacy endpoints indicated that the Health Status at Baseline is a highly significant factor impacting the outcome. Based on the above, the pre-planned analyses by Health Status subgroup are justified for the key endpoints.

In addition, justified by the non-significance of Heath Status as a factor in a logistic regression analysis performed on these two subgroups separate from the Health Status 5 subgroup, $p>0.1$) a set of ad-hoc analyses on a pool of subgroups 3 and 4 was performed and resulted in identifying this pooled subgroup as the population targeted in the extension of the RESOLUTION study. Contrary to Patients with a Heath Status of 5 at baseline, these patients are not in respiratory failure at baseline.

In subgroups 3 and/or 4 (and the combined 3+4 subgroup as well) LAU-7b plus standard of care showed a 100% reduction in the risk of all-causes death and the risk of progressing to invasive mechanical ventilation by Day 60, when compared to placebo plus standard of care, as well as an improvement in the proportion of patients alive and without respiratory failure at Day 29, a faster recovery and shorter hospitalization.

More specifically, none of the 76 moderately to severely ill COVID-19 patients treated with LAU-7b died or progressed to mechanical ventilation, while 4 patients died (4/72, 5.6%, $p=0.053$) and 5 progressed to mechanical ventilation (5/72, 6.9%, $p=0.025$) in the placebo arm. For some endpoints, the positive trend is more evident in subgroup 3 while for others, it is subgroup 4 which shows the higher benefit. Combining them increases the sample size and approaches statistical significance. This is indicative that the combined 3+4 population should be studied further to confirm the results above. 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 patients didn't show an improvement in the LAU-7b arm over placebo, suggesting that patients already in respiratory failure at baseline may be too severely affected by the disease to benefit from LAU-7b treatment.

Summary:
In conclusion, patients 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 further evaluation in this patient subset. Safety was excellent in the overall Safety population and particularly in the Moderate-to-Severe COVID patients.

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 [4]. It was a single-site, double-blind, placebo-controlled escalating multiple oral dose study of fenretinide (LAU-7b formulation) in adult CF patients with a FEV-1 predicted of 40% and above, non-pregnant and with no serious skin or ocular disorders. It involved 15 patients randomized 3:1 (active:placebo) who received each dose level in a sequential fashion, for cycles of 21 days 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 morning meal in addition to current Standard of Care therapies. Three (3) ascending dose levels of fenretinide as LAU-7b were administered (100 mg, 200 mg and 300 mg/day). The rationale behind the dose selection was to achieve, on average, a mean plasma concentration at steady state (Css) between 1-2 µM. This target was based on pre-clinical evidences in the mouse model.

The three main objectives of the study were:

- To establish the safety and tolerability of fenretinide in adult CF patients, using a novel oral formulation designed to optimize fenretinide bioavailability.
- To evaluate the PK profile of fenretinide at multiple dose levels;
- To determine the recommended doses of fenretinide to be used in future Phase II trials;

Results and conclusions of the study

SAFETY:

Overall, fenretinide was shown to be safe at all three doses studied for 21 days. The vast majority of adverse events (AEs) reported 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 fenretinide dosing. Many of these events were expected within the CF population studied, such as pulmonary exacerbations, characteristic of CF evolution, as well as reversible nyctalopia and dry skin which have been reported for fenretinide in other patient populations. Biochemical and hematological safety parameters were not affected by fenretinide at all dose levels. The safety and tolerability of fenretinide in adult CF patients was comparable with the reported safety profile associated with the use of this drug in other patient populations over similar or longer periods of treatment, and with comparable systemic exposure levels.

PHARMACOKINETICS:

Following single and multiple doses of fenretinide as 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. The concentration at 8 hours (C_{8h} and C_{ss8h}, following the first and last doses, respectively) reached the fenretinide plasma concentration target range of 1–2 µM at the 200 mg dose level with mean values of 1.32 µM and 1.85 µM following single and multiple doses of fenretinide, [redacted]

Mean $t_{1/2}$ values at PK steady-state ranged from 8.25 h to 16.65 h.

[redacted]

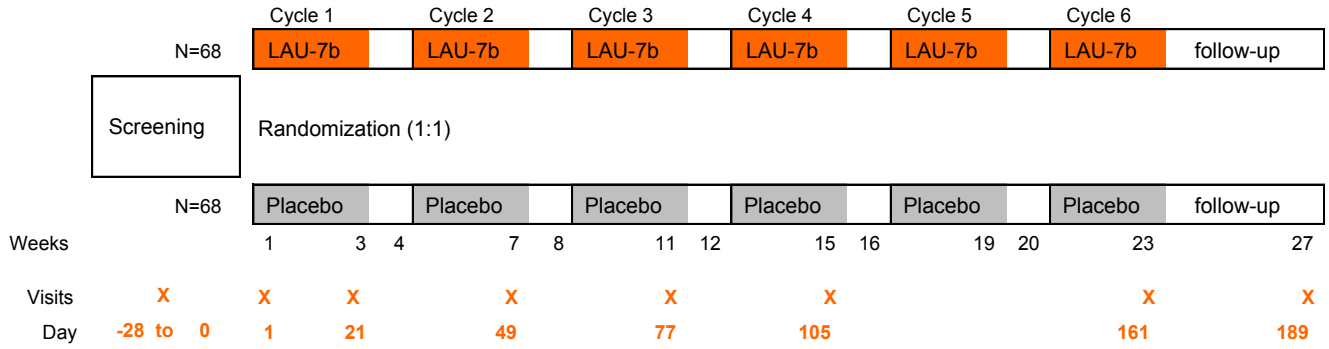
EFFICACY:

In this study, we showed an association between a fenretinide 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. The improvement of the CF-associated AA/DHA imbalance, as well as a decreased oxidative stress in a majority of patients, appears to produce a shift towards an anti-inflammatory pattern, particularly at the highest dose. 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 effect on AA and DHA was superior to what was measured at onset and during the treatment of PEx with antibiotics in the previous, non-interventional, cohort characterization study conducted in the same type of CF patient cohort of the same clinical site in Montreal [4]. At the highest dose (300mg), the improvement of the anti-inflammatory profile at onset of PEx in the Phase 1b study was comparable (IL-6 and neutrophils) or better (IL-8 and IL-10) than at the end of the PEx treatment in the cohort characterization study. A better systemic anti-inflammatory profile at onset of PEx was shown to correlate with increased odds to better respond to antibiotics for PEx [73, 4].

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

Laurent Pharmaceuticals conducted APPLAUD, a randomized, double-blind, placebo-controlled Phase II study in adult CF patients across 39 clinical sites located in Canada, the United States of America and Australia, and a positive signal of efficacy was observed, paving the way to confirmatory Phase 3 studies. To be eligible for the study, patients must have undergone at least one IV or oral antibiotic-treated PEx in the year prior, have a FEV-1 predicted of 40% and above and meet all other study inclusion/exclusion criteria at screening. Eligible patients are randomized 1:1, after stratification, to either LAU-7b (active) group or placebo (control) group. All patients continued their CF Standard of Care. Below is an illustration of the overall study structure:



The study's revised enrolment, to compensate for the impact of the COVID-19 pandemic on patient's access to clinical sites or interest to continue in the study, has been met with a total of 166 adults with CF randomized and dosed with LAU-7b or placebo (1:1)., Out of the 166 patients, a total of 119 patients have completed the 6-months treatment period and the study as per protocol, 12 patients have completed the study but with missing key endpoint data due to COVID restrictions, and 35 patients have ended prematurely their participation, mainly for the following reasons: personal choice/burden of study, termination due to starting a new CFTR modulator treatment or termination due to COVID-19 restrictions at clinical sites or personal choice due to COVID-19 concerns.

The aggregated demographics as of May 17th, 2021 data cutoff (safety population, n=166) are as follows: Mean age: 32.7 years (range 18-70), 60% women and 40% men, of which 96% white, 1% American Indian, 3% black and 1% other.

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, the latest on June 22nd, 2021, and on all five occasions, the Committee recommended to continue the study unchanged owing to no safety concerns.

Overall, the safety observations, including 29 treatment-emergent AEs of Pulmonary Exacerbation reaching the criteria of seriousness due to the hospitalization required to administer intravenous antibiotics, are typical of those found in CF studies with patients with moderate disease. The typical adverse events of fenretinide have been observed and their incidence remain low, such as the perception of changes in vision under dark and bright light conditions (around 9% of TEAEs) and in great majority of mild intensity. Three resulted in study discontinuation due to inconvenience. No SUSAR were reported.

5.4.2.4 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 [74, 75, 76, 77]. 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

Toxicity of oral chronic doses achieving 1-2 µM plasma levels of fenretinide in chemoprevention clinical trials has been minimal [74, 75, 78].

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[74, 77, 78, 79, 80, 81,]. 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 in one month following discontinuation of fenretinide [80, 81].

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 [82, 75, 83]. Presence of food increased significantly the plasma levels of the drug and has been used since as standard recommendation for fenretinide dosing[75]. 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 patients 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.

<u>High-dose clinical trials</u>

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 [76, 79, 84].

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) toxicity [76, 84]. 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 toxicity (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 toxicity. 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 toxicity [79]. 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).

5.4.2.5 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 tolerable toxicity.

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 toxicity/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 toxicity 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 4000mg/m^2 and fenretinide plasma peak levels of 14.5 µM.

Fenretinide reduces plasma retinol levels and retinol binding protein 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.

Based on the Phase Ib study data in adult CF patients, the dose of 300mg/day (equivalent to 800 mg/day of corn-oil formulation of fenretinide) resulted in steady state 8-hour plasma concentration of fenretinide on Day 21 of 2.7 µM and average drug plasma concentration of 2.06 µM, at the upper range of "low doses". There were no serious adverse events related to fenretinide recorded in the study, and the overall number of adverse events tended to decrease with the increase of the dose. The incidence of nyctalopia symptoms reported in this study is consistent with the incidence of symptoms of diminished dark adaptation reported in other clinical trials with fenretinide. Ad-hoc and scheduled ophthalmological examinations did not reveal any abnormality or signs of retinal damage in these patients. The reduction of serum retinol levels, as compared to baseline, appears to be smaller in CF patients than other patient populations for which lower doses of fenretinide were used. [redacted]

The recently completed APPLAUD Phase 2 clinical trial also has an aggregated 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.

Of direct relevance for the expansion of the RESOLUTION trial is the confirmation of a good safety profile in the 117 patients who received LAU-7b therapy so far, and most favorable in the proposed subset of patients for the expansion, those with a Heath Status of 3 or 4 (Moderate-to-Severe COVID, n=76). The positive efficacy signal seen across several endpoints in these subgroups is a good justification for expanding the enrollment of such patients, presently underserved by treatment option to prevent the onset of respiratory failure.

Moreover, with antivirals such as Paxlovid® and molnupiravir and the past usage of neutralizing antibodies, which are all used in an outpatient setting, a successful outcome of the expanded RESOLUTION trial will bode well for a once-a-day treatment option which can be administered to the underserved moderate to severe hospitalized COVID-19 patient population, allowing patients to continue the treatment at home after discharge from the hospital.

These collective results are supporting the safety of the selected Initial Treatment and Follow-up Treatment dose of 300 mg and 200 mg/day, respectively with LAU-7b formulation in this Phase 2 study in adults with COVID-19 disease, to exert the maximal antiviral activity and the pro-resolving effects on inflammation.

5.4.3 Specific Rationales for the proposed expansion of this Phase II study

5.4.3.1 Design/Structure and Dosing Regimen

This Phase 3 study extension aims at confirming the positive efficacy signal observed with LAU-7b in patients with COVID-19 disease susceptible to aggravate owing to the presence of risk factors. In the pilot portion of the study, patients with a baseline Health Status of 3 or 4 (not in respiratory failure) showed a clear

benefit while patients with a Health Status of 5 (in respiratory failure) did not. This justifies not pursuing the latter in the study expansion but pursuing in the Moderate-to-Severe COVID patients. It will guide further development in larger well-controlled clinical trials.

Since time is of the essence during the COVID-19 pandemic to identify useful treatments for affected patients, the study is simple in design, is short in duration and makes use of assessments commonly done in patients hospitalized for the disease. The primary objective of the study remains to measure the impact of LAU-7b on the recovery rate and on the frequency, severity and timing of COVID-19 disease aggravation and outcomes.

This is a randomized, double-blind (patients, Investigators and blinded study staff), placebo controlled, Phase II/III study (details are presented in Section 7.2). 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 patients will undergo the Standard of Care at their institution. A randomized, double-blind study design will avoid observer bias and reduce symptoms or outcomes arising from the patients' knowledge of treatment. A parallel design is most appropriate for this type of acute indication and with a short impactful period.

While the Phase Ib study with fenretinide was conducted in adult CF patients and there is a Phase 2 in the CF indication in adult CF patients which showed a positive signal of efficacy, the treatment paradigm for the treatment of COVID-19 disease is very different; it is a short, one-time 14-Day usage while the CF indication calls for longer term chronic administration.

5.4.3.2 Rationale for dose selection:

In the previous Phase Ib study in CF, three doses of LAU-7b were investigated and all showed good tolerability. Doses for that study were chosen based on the enhanced bioavailability that LAU-7b capsule formulation conferred to fenretinide, the active product ingredient, [redacted]

In essence, the Phase Ib was a concentration-driven study, while aiming at finding a maximum tolerated dose. On the exposure standpoint, the Phase Ib dose of 200 mg (middle dose) achieved the average circulating level (circa 2 µM Css) which corresponds to the concentrations eliciting the cytokine storm protection in the mice model of sepsis (1-2 µM) [37] and close to the IC50 for the antiviral activity against the MERS-CoV virus (2.8 µM)[41] and the SARS-CoV-2 virus [redacted].

Because CF patients have a different pharmacokinetic profile than other patient populations, usually requiring higher doses, it is expected that in COVID patients, the 300mg dose should achieve a concentration slightly higher than seen with CF patients, and this is why this dose will be administered in the first three days, for a faster onset of a concentration eliciting antiviral effect.

The maintenance dose of 200 mg, administered on Days 4-14, is expected to maintain a plasma concentration expected to have both antiviral activity and a pro-resolving effect on inflammation. Since a low LAU-7b dose is used in this study, no dose reductions are planned.

The administration of the study treatment is split in two regimens:

1. Initial Treatment (Days 1-3) is given to all randomized patients in order to start the treatment as early as possible. The Initial Treatment daily dose is higher (300 mg) for a faster onset of a concentration eliciting antiviral effect.

2. Follow-up Treatment (Days 4-14) is lower (200 mg) to maintain plasma concentrations that support both antiviral and inflammation-controlling effects.

The study regimen is justified by the good safety profile observed in the 117 patients who received it so far, even more favorable in the proposed subset of patients for the expansion, those with a Heath Status of 3 or 4 (Moderate-to-Severe COVID, n=76).

This expanded study is now intended to be confirmatory for hospitalized moderate-to-severe COVID-19 patients who are at risk to progress to respiratory failure, in order to inform further development and potentially support an Emergency Use Authorization application.

5.4.3.3 Rationale for Study Assessments

The study assessments are generally part of the SOC for patients hospitalized for suspected or confirmed SARS-CoV-2 infection with the presence of underlying conditions or measurement associated with a greater risk of complications. Most are frequently assessed during hospitalization and includes vital signs, symptom check, safety laboratory tests, assessing the need or not for supplemental oxygenation or for a transfer to the intensive care unit (ICU), as well as determining if hospitalization can end (patient discharge). It is recognized that during the pandemic, institution/departmental policies for preventative reasons can change very rapidly and affect the hospitalization thresholds.

EQ-5D-5L Quality of Life 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. It will be filled at screening and by fully eligible patients (confirmed SARS-CoV-2 infection) reaching Days 14, 29 and 45 (and at the longer term safety/QoL assessment, around 2 months after study start), and able to fill the questionnaire. This is not part of Standard of Care, but this is relevant for outcomes since patients with varying degrees of functionality will represent a variable pharmacoeconomic weight.

Scoring the Heath Status of the patients using the ordinal scale: Performed on specific days by the study coordinators or other delegated and trained staff, this assessment aims at formally determine in which category the patient is, each period of 24 hours (a study Day) once at a time. This is not done as part of SOC, but is key for this study. Several variables are derived from it.

Serial oropharyngeal swabs to detect SARS-CoV-2 virus: This was an optional objective measurement of the virus presence and allows to determine how long the virus shedding lasts from the oropharyngeal cavity. Unfortunately, none of the clinical sites volunteered to perform it due to the complexity of accessing repeatedly the patient on the COVID wards and the lack of resources. This assessment will not be pursued in the expansion of the study.

6 STUDY OBJECTIVES

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

Secondary objectives:
1- To assess the safety of LAU-7b therapy in all patients who received at least one dose of the study medication (Safety Population), compared to placebo + SOC.

2- To assess the efficacy of LAU-7b therapy at decreasing the rate of COVID-19 disease related aggravation in the target population (such as a worsening of one category on the ordinal scale, onset of severe categories on the ordinal scale, need for transfer to Intensive Care Unit (ICU), need for mechanical ventilation and death, among others), compared to placebo + SOC.
3- To measure the impact of LAU-7b therapy on the time course of the COVID-19 disease in the target population, as depicted by mean ordinal scale change from baseline at each assessment time, and by time-to-event analyses (time to an improvement of one category on the ordinal scale, time to recovery (defined), time to ICU transfer, time to mechanical ventilation, and time to death), compared to placebo + SOC.
4- To assess the benefit of LAU-7b therapy on the Quality of Life, compared to placebo + SOC.

Rationale for the selection of objectives:

The primary objective of this study has been selected because it is simple and clinically relevant; what impact LAU-7b therapy has on hospitalized patients in terms of outcomes by Days 29 and 60 post-randomization. In the context of limited ICU resources and equipment, any reduction in the burden of intensive care, in particular invasive mechanical ventilation or ECMO, will free up resources and have a huge pharmacoeconomic impact. Moreover, since patient who remain mildly affected recover more rapidly from COVID-19 disease, it allows a better flattening of the prevalence as a function of time.

The secondary objectives, besides safety, are aligned with the properties of LAU-7b/fenretinide demonstrated in humans and preclinical studies, such as the protection from an excessive pro-inflammatory response, the promotion of the resolution of inflammation and the demonstrated antiviral properties.

This will help guiding further development of LAU-7b in the treatment of COVID-19 disease, and may also contribute to its development in CF, due to the possible commonality between CF Pulmonary Exacerbations and the exaggerated inflammatory response seen in aggravated COVID-19 patients. Furthermore, the knowledge derived from this study may find applications with other acute infections causing dysregulated inflammation in the lung.

7 STUDY DESIGN

7.1 Endpoints

7.1.1 Efficacy Variable:

The main efficacy variable is the 7-point ordinal scale of the patient status. The ordinal scale is presented below, and categories 1-6 are further detailed/clarified to help categorization at baseline:

Ordinal Scale

1. Not hospitalized, no limitations on activities
    a. Able to carry on regular daily activities;
    b. May experience light symptoms that do not interfere with daily activities.
2. Not hospitalized, limitation on activities
    a. Cannot carry on daily activities like prior to COVID-19;
    b. Lingering symptoms of sufficient intensity to interfere with daily activities;
    c. Periods of rest during the day to help recovery.
3. Hospitalized (under observation/admitted), not requiring supplemental oxygen

   a. Remain bedridden most of the day;
   b. Ambulates without significant help;
   c. Under room air, able to maintain oxygen saturation at 93% and above;
   d. Does not require oxygen cannula, even at low flow of oxygen.
4. Hospitalized (under observation/admitted), requiring supplemental oxygen at ≤4 L/min [1]
   a. Remain bedridden most of the day;
   b. Ambulates with help;
   c. Unable to maintain an adequate oxygen saturation.
5. Hospitalized, on non-invasive ventilation or high flow oxygen supplementation at >4 L/min
   a. Bedridden;
   b. Does not ambulate easily and requires help;
   c. Unable to maintain an adequate oxygen saturation with a cannula at an oxygen flow ≤4 L/min., or
   d. Requires non-invasive ventilation with instruments such as a Continuous Positive Airway Pressure (CPAP) machine to maintain adequate oxygen saturation.
6. Hospitalized, on invasive mechanical ventilation or ECMO (extra-corporeal membrane oxygenation);
   a. Bedridden in ICU
   b. Intubated and connected to a mechanical ventilator, or
   c. Connected to an ECMO.
7. Death.

The ordinal scale is an assessment of health status on a given study day, identifying the worst health status during the previous day of observation. Each day, according to local practice in terms of time of assessment, the worst health status during the previous day gets scored with the scale and will be recorded. i.e. on Day 3, the worst Day 2 health status is obtained, scored and recorded as Day 2 score in the CRF, with the assessment time.

7.1.2 Primary Efficacy Endpoint

The revised primary efficacy endpoint is the proportion of patients requiring mechanical ventilation AND/OR deceased (all causes) by Day 60, compared between the active and control (placebo) arms of the study using the 7-point ordinal scale described above.

Justification for the main Efficacy Variable and the revised Primary Efficacy Endpoint

LAU-7b is proposed to act through a multi-prong approach against COVID-19 disease. It is hypothesized that these effects will reduce the odds of aggravation for the at-risk population that is under observation/admitted at the hospital for the COVID-19 disease. This will translate in a higher proportion of patients that recover and are discharged earlier from the hospital compared to those treated with the SOC alone + placebo. The use of the 7-point Ordinal Scale proposed by the World Health Organization for COVID-19 clinical trials is ideally suited for establishing the proportion of patients requiring invasive mechanical ventilation (and this includes ECMO) AND/OR deceased (all causes) (WHO Ordinal Scale scores 6-7 inclusively) as primary endpoint, particularly if assessed regularly during the course of the study. The time course of the COVID-19 disease is quite short but its complications are devastating and entail a huge burden on caretakers. This efficacy variable and the proportion of patients requiring mechanical

[1] Patients receiving up to 6L/min with a low-flow device can also qualify as an Ordinal Scale "4" if they have a pre-existing health condition (COPD, heart failure, for example) that causes higher oxygen supplementation needs and if the Investigator judges that the patient is NOT in respiratory failure. Other patients are subject to the ≤4L/min threshold.

ventilation AND/OR deceased (ordinal scale scores 6-7 inclusively) by Day 60, coined here as the revised primary efficacy endpoint, will permit both an overall picture of the impact of LAU-7b on patient outcomes, and a clinically meaningful assessment of the impact of LAU-7b on the proportion of patients avoiding the invasive mechanical ventilation and/or death.

In addition, changes in the health status depicted by the Ordinal Scale category changes will permit to derive several secondary endpoints listed below.

7.1.3 Secondary Endpoints

1. Safety: the safety of LAU-7b therapy will be assessed through the monitoring of treatment emergent adverse events and serious adverse events, vital signs including oxygen saturation and body temperature, symptom-directed physical examinations and safety laboratory tests. It is important to note that most of these assessments are also SOC for hospitalized patients with COVID-19 disease and changes from baseline can depict improvement or worsening of the condition.
2. Efficacy: Rate of all-causes death, depicted by a change from baseline in the ordinal scale position to category 7 by Days 29 and 60, compared between the active and control (placebo) arms of the study.
3. Efficacy: Rate of COVID-19 disease-related transfer to mechanical ventilation, depicted by a change from baseline in the ordinal scale position to category 6, compared between the active and control (placebo) arms of the study.
4. Efficacy: Proportion of patients alive and free of respiratory failure by Day 29 (ordinal scale scores 1-4, inclusively), compared between the active and control (placebo) arms of the study.
5. Efficacy: Proportion of patients re-hospitalized after discharge (any stay in the hospital of minimum overnight duration, all causes) up to Day 60, compared between the active and control (placebo) arms of the study.
6. Efficacy: Rate of COVID-19 disease-related aggravation, depicted by a change from baseline in the ordinal scale position of at least one category, compared between the active and control (placebo) arms of the study.
7. Efficacy: Rate of COVID-19 disease-related transfer to ICU, compared between the active and control (placebo) arms of the study.
8. Efficacy: Patient status on the 7-point ordinal scale on Days 14 and 29; compared between the active and control (placebo) arms of the study.
9. Efficacy: Mean change from baseline of the ordinal scale patient status as a function of assessment time, compared between the active and control (placebo) arms of the study.
10. Efficacy: Time to an improvement of one category on the ordinal scale patient status, compared between the active and control (placebo) arms of the study.
11. Efficacy: Time to recovery, defined here as a move from baseline to categories 2 or 1 on the ordinal scale patient status (first occurrence if more than one), compared between the active and control (placebo) arms of the study.
12. Efficacy: Time to mechanical ventilation, defined here as a move from baseline to category 6 on the ordinal scale patient status, compared between the active and control (placebo) arms of the study.
13. Efficacy: Time to death, defined here as a move from baseline to category 7 on the ordinal scale patient status, censored to Day 60 if it happens later than Day 60, compared between the active and control (placebo) arms of the study.
14. Efficacy: Duration of hospitalization (days) within the study period Days 1-60, compared between the active and control (placebo) arms of the study.
15. Quality-of-Life: The change from baseline to Days 14, 29, 45 and 60 in the score obtained on the EQ-5D-5L survey, a well-documented scoring system that has been widely used and validated as a QoL assessment tool, compared between the active and control (placebo) arms of the study, in patients reaching Days 14, 29, 45 and 60 and able to fill the questionnaire.

7.2 Study Overview

7.2.1 Description

RESOLUTION is a multicentre, randomized, double-blind (patients, Investigators and blinded study staff), placebo-controlled Phase II study of LAU-7b for the treatment of COVID-19 disease in patients at a higher risk than the general COVID-19 disease population to develop complications while hospitalized.

To be eligible for the study, patients must be symptomatic of COVID-19, confirmed by PCR (or alternates but excluding rapid antigen tests)) to have a SARS-CoV-2 infection, be aged 18 years and above, and meet all other study inclusion and none of the exclusion criteria at screening. There is no time limit between the onset of symptoms or the confirmation of SARS-CoV-2 infection and screening.

Eligible patients will be randomized 1:1, at each clinical site, to either LAU-7b (active) group or placebo (control) group. After randomization, patients will enter the treatment phase of the study. There will be no active control treatment but patients will undergo the COVID-19 disease SOC at their institution.

Since the study randomizes only confirmed cases of SARS-CoV-2 infection, the screen failure rate is very low. It is estimated that based on sample size calculation using the effect size observed in the pilot portion of the study for the revised Primary Efficacy Endpoint in the subset of patients with Health Status score 3 or 4 at baseline, up to a total of approximately 264 patients with a Health Status score 3 or 4 at baseline will be recruited in the expansion. Patients will be enrolled at approximately 25-30 centers in the United States of America and in Canada. The study treatment (LAU-7b or matching placebo) will be administered once a day in the fed state (with the main meal of the day if possible) for up to 14 days on treatment.

Patients will be evaluated at pre-specified times during and after the study treatment period, for efficacy, safety, as well as for Quality of Life.

This design is appropriate for this phase of development (confirmatory Phase 3 portion) and will ensure that the highest quality of data is collected with minimal bias and the patient's safety and wellbeing are preserved. A Data and Safety Monitoring Board (DSMB) is monitoring this study.

The overall study structure for Health Status 3+4 patients in the Phase 2 pilot and the Phase 3 extension is presented below in Figure 2.

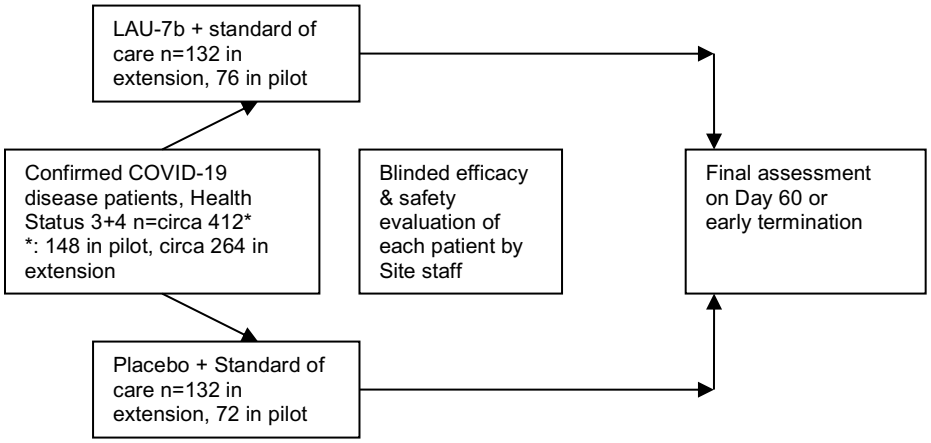


Figure 2: Overall structure of the study

To ensure the study is powered adequately if the effect size is smaller than initially estimated, an interim sample size re-estimation (Mehta and Pocock, 2011)[85] will occur once 42% (112) of the planned 264 patients have either completed the Day 60 primary endpoint assessment or terminated their study participation early. If the conditional power is within the promising zone, the sample size may be increased up to a maximum of 462 patients, dependent upon the results of the interim sample size re-estimation. If the conditional power is

below the promising zone, the futility criteria will be deemed met and a recommendation to stop further enrollment will be communicated to the DSMB and the Sponsor.

7.2.2 DSMB

Throughout the study, the DSMB monitors blinded and unblinded safety measures and demographics 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 disease 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 patient 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.
- 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 a third of the enrolled patients have completed their LAU-7b (or placebo) treatment period and corresponding safety information was available. This was an unblinded safety analysis of Active versus Placebo and occurred in March 2021;
    - When a minimum of half of the enrolled patients have completed their LAU-7b (or placebo) treatment period and corresponding health status/efficacy information at Day 29 was available, a formal futility analysis (stopping rule) focusing on the proportion of patients alive and free of respiratory failure by treatment group, was performed and presented to the DSMB, seeking recommendation to pursue or stop the study, details can be found in the statistical analysis Section 12.7.2 and the analysis resulted in a DSMB recommendation to continue the study on 30Mar2021, since the criteria for futility was not met;
    - When a minimum of two thirds of the enrolled patients have completed their LAU-7b (or placebo) treatment period and corresponding safety data is available for review. This was an unblinded safety analysis of Active versus Placebo and occurred in June 2021;
    - During the Phase 3 expansion of the study, considering the excellent safety profile observed so far, when one third and two-thirds of the required supplemental patients have completed their

LAU-7b (or placebo) treatment period and corresponding health status/efficacy information at Day 29 is available, again an unblinded safety analysis of Active versus Placebo;
- Review the interim sample re-estimation/futility analysis data and results. The DSMB will convey the recommendation to either continue the study with the planned sample size or increase the sample size (up to the maximum) according to the pre-defined criteria or to stop enrollment if the futility criteria has been met.
- 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 and/or further drug administration in the study for safety reasons. This is in addition to the stopping rule based on the futility analysis (already performed) outlined in Section 12.7.2. Other considerations may be used to arrive at such decisions, which must involve Laurent Pharmaceuticals Executive Management. Taking in consideration the sizeable proportion of these at-risk patient population to develop severe complications, including death from COVID-19 disease:

- Occurrence of any case of death that is attributable to fenretinide (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 *probable* causality relationship) that raise the DSMB/Investigators concerns about patients' safety.

7.3 Blinding and Randomization

Given the potential for bias in the interpretation of the study endpoints, the RESOLUTION study must be placebo-controlled, double-blinded, 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 COVID-19 disease.

7.3.1 Rationale for Placebo Control

It is appropriate that this study be placebo-controlled since there is no consensual effective treatment at this point in time. In this pandemic circumstance where search for a treatment of COVID-19 disease is extreme, participation in this study will not exclude co-administration with new SOC treatments, as they become available (for example remdesivir and dexamethasone). This will be evaluated on a case-by-case basis. However, co-enrolment in other interventional studies of unproven COVID-19 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 patients on their standard of care 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. Patients, Investigators and Site Staff, sponsor and CRO personnel, 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, duly identified members of the CRO managing the study 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 patient(s).

The study blind may be broken for an individual patient or several patients in the event of an emergency in which knowledge of the treatment assignment is needed for the safety of the patient(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 CRO'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 and captured on the patient(s) electronic case report form (e-CRF).

7.3.3 Randomization Scheme and Stratification

Computer-generated randomization sequences will be programmed into the IWRS. At the time of Randomization, not before, the IWRS will assign a Subject number (Randomization Number) to each patient. Randomization will be stratified by clinical site and randomized in a 1:1 double-blinded fashion to either LAU-7b (active) group or the placebo (control) group. Stratification by clinical site is appropriate when each site is expected to randomize a sizeable number of patients; this will enable an even distribution of patients among the two treatment groups, by site. Detailed instructions for randomization will be provided separately.

8 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Screening Inclusion Criteria

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

1- Subjects must exhibit symptoms (including at least one lower respiratory symptom such as shortness of breath or dyspnea) of COVID-19 disease at screening and/or since the start of their hospitalization (may include treated symptoms);
2- Subjects must be 18 years and older, of either gender;
3- Subjects must have at least one of the following factors/co-morbidities:
   a) Controlled or uncontrolled diabetes;
   b) Pre-existing cardiovascular disease, including hypertension;
   c) Pre-existing respiratory disease such as COPD, asthma, emphysema;
   d) Active or a former smoker with a 20 pack-years of smoking history;
   e) Obesity as depicted by BMI≥30;
   f) Laboratory tests indicative of a higher risk of COVID-19-related complications, such as troponin >1.5 ULN, D-dimer >3.0 ULN and/or CRP >1.5 ULN
   g) Patient aged 70 years and older who, based on the judgment of the Investigator, is at a higher risk of developing complications.
4- Subjects must have a documented positive test for the SARS-CoV-2 virus (co-infection with other viral respiratory infections is allowed and must be documented in medical history);
5- Subjects must be under observation by, or admitted to a controlled facility or hospital and receive SOC for COVID-19 disease;
6- Subject's health status must be 3 or 4 on the Ordinal Scale and not previously a "5 or a 6";

7- 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 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 must be negative at the Screening Visit;
8- Subjects must have the ability to understand and give informed consent, which can be verbal with a witness, according to local requirements;
9- Subjects deemed capable of adequate compliance including attending scheduled visits for the duration of the study;
10- Subjects must be able to swallow the study drug capsules.

8.2 Screening Exclusion Criteria

Patients are to be excluded from the study at the time of screening for *any* of the following reasons:

1. Pregnancy or breastfeeding;
2. Health condition deemed to possibly interfere with the study endpoints and/or the safety of the patients. For example, the following conditions should be considered contraindicated for participation in the study, but this is not an exhaustive list. In case of doubt, the Investigator should consult with the Sponsor's medical representative:
    a) Presence of inherited retinitis pigmentosa;
    b) Presence or history of liver failure (Child-Pugh B or C);
    c) Presence or history of stage 4 severe chronic kidney disease or dialysis requirement;
    d) Febrile neutropenia;
    e) Presence of end-stage cancer;
3. 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;
4. Participation in another drug clinical trial within 30 days (or a minimum of 5 elimination half-lives) prior to screening, except ongoing participation in non-interventional studies;
5. Calculated creatinine clearance (CrCL, using the Cockroft-Gault equation for example) <30 ml/min[2];
6. Presence of total bilirubin >1.5 x ULN (in the absence of demonstrated Gilbert's syndrome), ALT and/or AST > 2.5 x ULN;
7. Patient expected to be transferred to ICU or die in the next 24 hours.

8.3 Study Drug Discontinuation and Withdrawal of Patients

Patients should discontinue permanently the study drug in the event of any of the following (Since a low LAU-7b dose is used in this study, no dose reductions are planned):

1. If a patient is escalated to invasive mechanical ventilation preventing the administration of the study medication intact;
2. Occurrence of a SAE deemed related to the study drug that is a life-threatening adverse reaction or one resulting in prolonged non-COVID-19 disease-related hospitalization;

[2] When a factor that may potentially affect renal function by hemodynamic mechanisms is known or suspected on admission (Ex: dehydration), it is recommended to rule out a possible renal impairment by addressing the issue whenever possible (Ex: rehydration) and reassessing CrCL prior to signing the ICF.

3. If the patient, Investigator, or Laurent determines that it is not in the best interest of the patient to continue treatment;
4. If a patient is serially and persistently noncompliant with study procedures and/or assessments, the investigator or the sponsor may withdraw the patient from further treatment;
5. A patient's treatment is unblinded by the Investigator;
6. If a female patient has a confirmed pregnancy (with the exception of a pregnancy resulting from *in-vitro* fertilization), this should be immediately reported to the Medical Monitor and Laurent Pharmaceuticals (within 24 hours awareness) and the patient shall discontinue the study drug. Pregnancy, whether in a patient or in a partner of a patient should be followed up until conclusion, with an assessment of child health at birth;
7. Considering the safety observed so far in the study, patients showing possible kidney impairment as depicted by either:
    a. An increase from screening in serum creatinine of 0.5 mg/dL or 2x the screening value if the serum creatinine was within normal range at screening and the calculated CrCL was ≥ 30 ml/min;
    b. An increase of serum creatinine ≥ 2x the screening value if the screening value was above the normal range and the calculated CrCL was ≥ 30 ml/min.
8. Notwithstanding that the study so far confirms the lack of a particular drug-related liver toxicity, patients showing possible liver impairment as assessed with the liver safety algorithm based on the Drug Induced Liver Injury (DILI) algorithm, described in Section 11.4
9. As soon as the site is informed, patients missing two consecutive doses or more than two non-consecutive doses at any point during the treatment period.

Patients 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 Day 60. In all cases, the reason for study drug discontinuation will be noted on the CRF. This is in the view of maximizing the number of patients with actual follow-up information and minimizing patients lost to follow-up.

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

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

The patient has the right to withdraw from the study at any time. Nevertheless, investigators will be trained to minimize full withdrawals from study wherever possible. Survival status and the requirement for invasive mechanical ventilation up to Day 60 are absolutely necessary for all randomized participants and should still be reported for participants who withdraw from the study, where permitted by local guidelines. Site staff should make multiple attempts to contact patients who miss a study visit; it is better to have a late visit than a missed visit.

The reason for patient withdrawal from the study will be noted on the CRF. Where applicable, the investigator should attempt to follow patients withdrawn from study until resolution of any adverse events. Upon withdrawal, no further dosing should be performed for these patients. Investigators shall make reasonable attempts to contact lost-to-follow-up patients for evaluation.

8.4 Replacement of Patients

Patients who withdraw their consent or are screen-failed prior to randomization, will be replaced to ensure that at least 264 patients with a Health Status of 3 or 4 enroll in the Phase 3 confirmatory portion of the study. Patients who withdraw (study or further treatment) after randomization will not be replaced.

9 STUDY CONDUCT

9.1 Timing of Assessments

For the sake of simplicity, the timing of assessments is not specified. Investigator and their staff should however use their judgment to avoid the interference of more invasive procedures on sensitive procedures.

9.2 Study Visits and Procedures

9.2.1 Screening and Eligibility Assessments (Visit 0, pre-randomization on Day -1 or (no Day 0 in this study)):

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

1. Verification of identity and age;
2. Prior to any study specific screening activities, all potential patients will sign the Study Informed Consent Form (ICF), since paper copies are deemed contaminated, it is possible to take a picture of the signed page when possible. The consent can also be obtained verbally per COVID-19 regulatory requirements or local recommendations and use a witness to attest of the verbal consent. The consent forms will comply with all applicable regulations governing the protection of human subjects. An ICF Form, approved by Laurent Pharmaceuticals and the site's institutional review board (IRB or REB, as applicable), must be used. At this point, the patient's initials are used for identification purposes and to identify the patient at the time of randomization in the IWRS. 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 patient.
3. Verification of all inclusion and exclusion criteria;
4. Obtain demographic information and recent & relevant medical history (typically the previous 6 months). Particular attention will be put on confirming the underlying disease or factors (including COVID vaccination) susceptible to affect the prognosis of COVID-19 disease progression and used to determine eligibility;
5. Verification of the concomitant medications, including any supplemental oxygen currently in use, along with recording the oxygen flow in use;
6. Body weight, height, with BMI calculated (measured if possible but self-reporting is accepted);
7. Directed physical examination (symptom- and disease-driven);
8. From SOC, collect the vital signs including heart rate, respiratory rate, oxygen saturation (under room air if possible, or value obtained prior to administering supplemental oxygen, from patient chart) and body temperature;
9. COVID-19 symptom check (including but not limited to, fever, myalgia, coughing, dyspnea, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
10. SOC laboratory tests including at a minimum, urinalysis (dipstick), hematology, serum chemistry (while they should be preferably done during the screening, it is acceptable that they be obtained from the Standard-of-Care performed between the start of hospitalization and screening but in no case more than 48 hours prior to screening; with the exception that when a patient is only eligible based on an abnormal biomarker (troponin, D-dimer or CRP, for example), such a value should have been obtained no more than 24 hours prior to screening) and urine (or serum) pregnancy test if applicable (details on the

minimum laboratory testing can be found in Section 11.2). The pregnancy test result must be available before randomization and it must be negative;
11. Health status determination using the 7-point ordinal scale;
12. Quality-of-Life questionnaire: EQ-5D-5L questionnaire.

The clinical site or Investigator may request additional procedures/tests that are part of the COVID-19 disease SOC at the institution or are required based on the patient's condition; these will not be captured in the CRF but should be recorded in the patient's source documentation.

9.2.1.1 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 patient is eligible for the study.

9.2.1.2 Rescreening

Not applicable.

9.2.2 Randomization and First Dosing (Visit 1, Day 1)

It is expected and desirable that once all screening procedures are complete and eligibility is confirmed, that the patient transitions directly to randomization, without delay. Randomization will be performed on the IWRS platform and the assigned Initial treatment container (9 capsules) will be retrieved from the pharmacy (where applicable) and stored in the ward's refrigerator, as per site procedures.

Randomized patients will receive their first dose of 3 capsules of study treatment, under fed condition. As patient is hospitalized, there is no mandatory supervision period.

9.2.3 In-Hospital Days

For this study in hospitalized patients with confirmed COVID-19 disease, the hospital stay duration will vary as a function of complications/improvement observed with each given patient, the bed and resources availability, rules and restrictions imposed by Health Authorities (Institution, Governmental…etc.). In order to minimize the burden of this study on the hospital resources, the in-hospital study requirements will piggyback on the SOC, with some exceptions. The overall scheme can be found in the Schedule of Event on page 11. Details are presented below.

1. **Pre-Dose on Day 4 only**:
   If the patient has tolerated the Initial treatment of 3 days, if not done previously, a replenishment will be requested in the IWRS and the Follow-up treatment container (22 capsules) will be retrieved from the pharmacy (where applicable) and stored in the ward's refrigerator.

2. **On Days 5, 8 and 12 (visits 5, 8 and 12, with a window of +/- 1 day while in hospital)**, the following assessments will be done:
   a. Concomitant medication verification, including any supplemental oxygen currently in use;
   b. Directed physical examination (symptom- and disease-driven);
   c. From SOC, collect the vital signs including heart rate, respiratory rate, oxygen saturation and body temperature (can be done multiple times during each day as part of SOC, but at a minimum twice);

d. COVID-19 symptom check (including but not limited to, fever, myalgia, coughing, dyspnea, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
e. SOC laboratory tests including at a minimum, urinalysis (dipstick), hematology and serum chemistry, as per Section 11.2 (the laboratory test can be performed within +/- 1 day from the target visit day);
f. Health status determination using the 7-point ordinal scale;
g. Handing study medication for intake during the main meal of the day;
h. Asking safety-focused open-ended questions:
    i. How is your health today?
    ii. How is your vision today?
    iii. How is your skin today?
i. Adverse event verification and follow-up on ongoing adverse events.

3. **On Day 14 or on the Day of hospital discharge (not a preset visit number)**, the following assessments will be done;
    a. Concomitant medication verification, including any supplemental oxygen currently in use;
    b. Directed physical examination (symptom- and disease-driven, will not be repeated if assessment done within 2 days from the discharge day);
    c. Body weight with BMI calculated (measured if possible);
    d. From SOC, collect the vital signs including heart rate, respiratory rate, oxygen saturation and body temperature;
    e. COVID-19 symptom check (including but not limited to, fever, myalgia, coughing, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
    f. SOC laboratory tests including at a minimum, urinalysis (dipstick), hematology and serum chemistry (will not be repeated if assessment done within 2 days from the discharge day), as per Section 11.2;
    g. Urine (or serum) pregnancy test if applicable;
    h. Health status determination using the 7-point ordinal scale;
    i. Quality-of-Life questionnaire: EQ-5D-5L questionnaire;
    j. If applicable, dispensing to the patient the remaining study drug treatment with instructions for storage in the home refrigerator, self-administration, and return of unused study drug in a pre-labeled envelope;
    k. Asking safety-focused open-ended questions:
        i. How is your health today?
        ii. How is your vision today?
        iii. How is your skin today?
    l. Adverse event verification and follow-up on ongoing adverse events.

4. **On all other Days in Hospital until the day before discharge or before Day 14 (Visit numbers = Day of the study)**: The following assessments will be done:
    a. From SOC, collect the vital signs including heart rate, respiratory rate, oxygen saturation and body temperature (can be done multiple times during each day as part of SOC, but at a minimum twice);
    b. COVID-19 symptom check (including but not limited to, fever, myalgia, coughing, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
    c. Health status determination using the 7-point ordinal scale;
    d. Handing study medication for intake during the main meal of the day;
    e. Adverse event verification and follow-up on ongoing adverse events.

5. Early-Termination Visit

This visit may happen anytime a patient elects to withdraw consent or becomes unable to be followed-up, as detailed in Section 8.3. The following assessments can be performed, sometimes indirectly since the patient may not be able to contribute.

a. Concomitant medication verification, including any supplemental oxygen currently in use, including the oxygen flow;
b. If possible, collect the vital signs including heart rate, respiratory rate, oxygen saturation and body temperature;
c. Urine (or serum) pregnancy test if applicable;
d. Adverse event verification and follow-up on ongoing adverse events.

9.2.4 Contacts in hospital after Day 14 or after discharge once every 3 days (±2 days from target) and up to Day 29

(not a preset visit number)

The following assessments will be done, either at the hospital, or by phone or using an electronic platform compatible with mobile phones or tablets.

e. Concomitant medication verification, including any supplemental oxygen currently in use including the oxygen flow;
f. COVID-19 symptom check (including but not limited to, fever, myalgia, coughing, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
g. Health status determination using the 7-point ordinal scale;
h. Verification of the study drug intake and accountability, where applicable;
i. Asking safety-focused open-ended questions:
    i. How is your health today?
    ii. How is your vision today?
    iii. How is your skin today?
j. Adverse event verification and follow-up on ongoing adverse events.

9.2.5 Contacts on Days 29 and 45 (window of +/- 3 days)

(not a preset visit number)

The following assessments will be done, either by phone or using an electronic platform compatible with mobile phones or tablets. Based on the patient responses, actions may be taken including inviting the patient to visit the hospital or meet a health professional.

a. Concomitant medication verification, including any supplemental oxygen currently in use including the oxygen flow;
b. COVID-19 symptom check (including but not limited to, myalgia, coughing, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
c. Health status determination using the 7-point ordinal scale;
d. Quality-of-Life questionnaire: EQ-5D-5L questionnaire;
e. Asking safety-focused open-ended questions:
    i. How is your health today?
    ii. How is your vision today?
    iii. How is your skin today?
f. Adverse event verification and follow-up on ongoing adverse events.

9.2.6 End-of-Study / Long-term Follow-up

(Day 60 (window of +/- 3 days) after randomization, not a preset visit number)

The following assessments will be done, either by phone or using an electronic platform compatible with mobile phones or tablets.

a. COVID-19 symptom check (including but not limited to, myalgia, coughing, smell and taste alteration, headache, gastrointestinal disorders...etc.) as per SOC;
b. Health status determination using the 7-point ordinal scale;
c. Quality-of-Life questionnaire: EQ-5D-5L questionnaire;
d. Adverse event verification and follow-up on ongoing adverse events.

9.3 Study Drug Treatment

The total duration of study treatment is up to 14 consecutive days of either LAU-7b or placebo, as follows:

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

From Day 4, patients will continue the treatment with LAU-7b 200 mg per day (2 capsules of 100 mg each), once a day for the remaining 11 days, or a matching placebo administered in the same fashion (the "Follow-up Treatment").

All eligible and confirmed patients will be treated and closely monitored for a period of up to 2 weeks or until early termination. The last day of study drug treatment will be on Day 14 or earlier due to aggravation preventing oral intake of study medication or death, whichever comes first. Specifically, patients undergoing intubation preventing oral intake of study medication will not receive the drug by other means such as through a feeding tube. Patients 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 SOC therapies for COVID-19 disease.

9.3.1 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 either 9 capsules (Initial Treatment) or 22 capsules (Follow-up Treatment). Study medication will be handled as follows:

- Shipped refrigerated (2 to 8°C, 36-46°F) to the Hospital pharmacy;
- Stored refrigerated (2 to 8°C, 36-46°F) in the Hospital pharmacy and wards, and where applicable,
- Stored refrigerated (2 to 8°C, 36-46°F) at the patient's home.

9.3.2 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 either 9 capsules (Initial Treatment) or 22 capsules (Follow-up Treatment). Study medication will be handled as follows:

- Shipped refrigerated (2 to 8°C, 36-46°F) to the Hospital pharmacy;

- Stored refrigerated (2 to 8°C, 36-46°F) in the Hospital pharmacy and wards, and where applicable,
- Stored refrigerated (2 to 8°C, 36-46°F) at the patient's home.

9.3.3 Packaging, Labeling, and Shipping

Study medication will be provided in appropriately-sized HDPE bottles containing enough medication for either the Initial Treatment phase (9 capsules) or the Follow-up Treatment phase (22 capsules). Study drug will be specifically identified 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 refrigerated temperature (target 2 to 8°C, 36-46°F), a temperature data logger may accompany the shipment to ensure an adequate chain of custody.

9.3.4 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 not be administered until instructed otherwise.

At the clinical sites, the study drug bottles will initially be stored in a suitable refrigerator (2 to 8°C, 36-46°F) in a secure location with limited access. Most preferably, the storage refrigerator 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 refrigerator is acceptable as long as the thermometer readings are taken daily during weekdays, at a minimum. On the hospital ward, the drug should also be stored in the refrigerator, and most preferably, also monitored similarly.

Upon instructions from the IWRS, the pharmacy/site staff will, at the time of dispensing, formally identify and remove the assigned treatment bottle from the secure refrigerator and will check the expiry date on the labels, at a minimum. Where applicable, the necessary treatment bottle will be sent to the site staff on the ward actually dispensing the study drug to the patients.

To avoid incorrect patient dosing, the instructions/paperwork/bottles must bear clearly the "subject number" and site staff **must be trained** to **correlate the treatment bottle with the target patient**, since there will be multiple patients active on the study medication at any point in time.

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

9.3.5 Administration of Study Drug Treatment

On each inpatient Day at the Hospital, the patient will be handed the required quantity of capsules to ingest with the main meal of the day (if possible). The capsules should not be broken down to administer their content through a feeding tube if the patient is intubated and cannot ingest anymore the capsules intact. If the patient is discharged from the clinical site before Day 14 (the last day of study drug intake), the patient will be dispensed the remaining capsules of study drug and will receive instructions to continue the intake until Day 14.

9.3.6 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 patient in the study. Patients discharged from hospital prior to the end of study drug treatment will be given a pre-labeled+paid return envelope and will be instructed to keep the

bottle and any content remaining after completing the study drug intake until the next phone contact, which will enable a verbal reconciliation. Patients will then be instructed to return the study medication in the provided envelope. At the site, any used study drug 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 from the sponsor, the study drug 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.

9.4 Treatment and Protocol Compliance

Patients are expected to receive oral daily doses based on the protocol schedule and have all procedures done within the allowable time windows (outlined in the Schedule of Events, page 11 and further detailed in Study Visits and Procedures).

Regardless of allowable visit windows, study drug treatment should target a total of 14 days. In the event a patient misses an outpatient dose, he/she should not double-dose on the next dosing day; instead, he/she should continue as planned and take a note of this omission for disclosure at the next outpatient contact.

In the event a patient misses a scheduled in-hospital/outpatient contact, this should be rescheduled for the earliest possible date. Patients who are persistently noncompliant may be withdrawn from the study at the investigator's or the sponsor's discretion.

9.5 Allowed and Disallowed Concomitant Medications

The standard of care for patients with COVID-19 disease is continually evolving and may include several medications and procedures destined to improve their outcome, treat symptoms and prevent aggravation. Considering the very short study treatment duration and the lack of clinically proven drug interactions for fenretinide, there is only a limited number of disallowed medications for this study. The COVID-19 SOC should be used, with the following restrictions, always weighing the risk versus benefit of co-administration. Co-enrolment in other interventional studies of unproven COVID-19 treatments is not permitted.

Based on the available *in-vitro* and *in-vivo* data from animal studies and human clinical trials, the short term fenretinide treatment in the RESOLUTION study (only 14 days) is not expected to cause any clinically significant Drug-Drug Interactions in COVID-19 patients with concomitant administration of most commonly used drugs for diseases such as Type-2 diabetes, hypertension or asthma, some being metabolized by CYP enzymes. There is no real risk either for clinically significant interactions with drugs potentially added to SOC, such as remdesivir and dexamethasone, for the same reasons. Furthermore, since fenretinide is marginally eliminated in urine and eventually co-administered antibiotics are mostly eliminated by the kidneys, the risk of interactions with these drugs is improbable.

9.5.1 Disallowed medications:

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

1. Concomitant use of Narrow Therapeutic Index drugs that are sensitive CYP substrates (e.g.: amiodarone, carbamazepine, cyclosporine, digitoxin, theophylline, phenytoin, warfarin, etc. See list in study reference manual) is authorized but the adverse events of these drugs should be monitored as per standard of care. In the study so far, the following drugs were co-administered with LAU-7b with no relevant adverse events: amiodarone (3 patients), carbamazepine (1 patient) and warfarin (1 patient);
2. Concomitant use of known strong inducers or inhibitors of hepatic CYP450 isoenzyme (e.g.: ketoconazole, fluoxetine, clopidogrel, rifampin, etc. See list in study reference manual) is authorized but the known adverse events of fenretinide should be monitored. In the study so far, the following drugs

were co-administered with LAU-7b with no adverse events: fluconazole (2 patients), fluoxetine (1 patient) and clopidogrel (4 patients);

3. Concomitant use of medications that may potentially act as modulators of intracellular ceramide levels or ceramide cytotoxicity, sphingolipids transport, or p-glycoprotein "MDR1" or "MRP1" drug/lipid transporters, such as: cyclosporine A or analogue; verapamil; tamoxifen or analogue; ketoconazole, chlorpromazine and thioridazine; RU486 (mifepristone); indomethacin; or sulfinpyrazone continue to be prohibited. In the study so far, the prohibition was respected.

While the concomitant use of drugs known to prolong QT significantly is permissible in this study, only in the event that such a drug is already used or planned to be added, the cardiac safety of the combination should be monitored by performing 12-lead ECG during the stay in the hospital; specifically, either before starting the study medication (can be obtained from SOC within 48 hours prior to screening) or before adding the QT-prolonging drug to the study medication, and approximately once every 2-3 days thereafter during the hospital stay. Appropriate actions may be taken subsequent to QT prolongation from baseline exceeding 50 msec or a treatment-emergent QT segment exceeding 500 msec. In the study so far, the following drugs were co-administered with LAU-7b with no relevant adverse events or ECG abnormalities including QT prolongations reported as adverse events: azithromycin (23 patients including 6 who also took another drug prolonging the QT segment), ciprofloxacin (2 patients including one who also took citalopram), citalopram ((2 patients including one who also took ciprofloxacin), levofloxacin (3 patients including 2 who also took ondansetron), fluconazole (2 patients), ondansetron (18 patients including 4 who also took another drug prolonging the QT segment). ECG monitoring will continue to be recommended in the study expansion when a known QT prolonging drug is started on-study or is part of a patient's regimen at baseline.

10 EFFICACY ASSESSMENTS

10.1 Health Status using the 7-point Ordinal Scale

This is the main efficacy variable of the study. It will be assessed post-randomization daily in hospital as listed in the Schedule of Events, page 11, and on Day 14 (or assessed upon discharge if discharged earlier than Day 14), and at each of the outpatient contacts (once every 3 days up to Day 29, and on Days 45 and 60). The ordinal scale is an assessment of the health status on a given study day, identifying the worst health status during the previous day of observation. Each day, according to local practice in terms of time of assessment, the worst health status gets scored on the Ordinal scale for the previous day and the score will be recorded. i.e. on Day 5, the worst Day 4 health status is scored and recorded as Day 4 score in the CRF. The scale is as follows and further details on each of the categories 1-6 are presented in 7.1.1.

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized (under observation/admitted), not requiring supplemental oxygen;
4. Hospitalized (under observation/admitted), requiring supplemental oxygen at ≤4 L/min[3];
5. Hospitalized, on non-invasive ventilation or high flow oxygen supplementation at >4 L/min;
6. Hospitalized, on invasive mechanical ventilation or ECMO (extra-corporeal membrane oxygenation);
7. Death.

[3] Patients receiving up to 6L/min with a low-flow device can also qualify as an Ordinal Scale "4" if they have a pre-existing health condition (COPD, heart failure, for example) that causes higher oxygen supplementation needs and if the Investigator judges that the patient is NOT in respiratory failure. Other patients are subject to the ≤4L/min threshold.

10.2 Body height, weight, with BMI calculated

Height (screening only) and weight will be measured (can also be self-reported) with shoes off at time points listed in the Schedule of Events, page 11, specifically at screening and on Day 14 (or earlier discharge from hospital). The body mass index (BMI) will be calculated using standard methods, most likely automatically by the eCRF platform.

10.3 Quality-of-Life evaluations

The patient's Quality of Life (QoL) will be assessed at time points listed in the Schedule of Events, page 11, specifically at screening, on Day 14 (or earlier discharge from hospital), on Days 29 and 45, and also be assessed at a longer-term time point approximately 2 months (Day 60) after randomization. A well characterized and widely used QoL instrument will be used, the EQ-5D-5L (EuroQol 5 dimensions) questionnaire. It is relevant to the condition being treated, the inpatient/outpatient settings, is short to answer and is available in both English and French.

11 SAFETY ASSESSMENTS

Safety evaluations will include reporting of Adverse Events (AEs), clinical laboratory assessments, and SOC evaluation of vital signs.

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 End-of-Study follow-up, on Day 60, 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. As the study subjects are hospitalized, planned surgical procedures for an illness or disease that existed before the patient 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.

Patients 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 patients about AEs and changes in pre-existing illnesses since their last visit and must record the information in the patients' 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.

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 End-of-Study follow-up, on Day 60, 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 until the end of the study participation of a patient that has or is believed to have a causal relationship to the study drug should be reported to Laurent Pharmaceuticals via telephone. Patients who experience AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. All AEs and 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 patient's medical record. Follow-up laboratory results should be filed with the patient's source documentation and CRF. For all AEs that require the patient to discontinue treatment, relevant clinical assessments and laboratory tests should be performed until final resolution or stabilization of the event(s). These assessments should be captured in the source data and SAE forms but will not be entered in the CRF.

Due to the critical nature of the COVID-19 infection and its expected complications in mechanically ventilated patients, a revised definition of reportable adverse events (AEs) was developed for use following the Canadian guidelines for AE/SAE reporting in academic critical care trials [4]. The following 2 categories of events will therefore not be reported in the eCRF:

- Any expected adverse complications related to treatments/procedures commonly administered in the context of invasive mechanical ventilation, such as right main bronchus intubation, lacerated lips, tongue, pharynx and trachea, vocal cord injury, chipped teeth, aspiration, introduction of infection, airway obstruction, hypoxia, hypotension, and cardiac arrhythmias.

- Abnormal Laboratory variations considered clinically significant (eg, leukopenia, transaminitis, lymphopenia, leukocytosis, hypokalemia, hyponatremia and elevated inflammatory markers like D-dimer) that could result from COVID related acute care procedures and medications.

All AEs for randomized patients will be recorded in the CRF and the patient's source documents. AEs for patients who are screened but not subsequently randomized in the study will be recorded in the patient'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);

[4] Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. CMAJ. 2008 Apr 22;178(9):1181-4

- 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 systematic treatment arm dose reduction or 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 4.03, (Cancer Therapy Evaluation Program website; available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm ; accessed 01 December 2015) 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 patient's source documents and e-CRF.

Severity will be assessed according to the following criteria:

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 patient, 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 patient lost to follow-up).

11.1.1.5 Treatment Administered

The Investigator will ensure adequate medical care is provided to patients for any AEs, including clinically significant laboratory values related to study drug. In addition, 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 Clinically Significant Assessments

Study assessments including laboratory tests and vital signs should be assessed and those deemed a clinically significant worsening from baseline documented as an AE. When possible, a clinical diagnosis for the study assessment should be provided rather than the abnormal test result alone (e.g. urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (e.g. bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the patient has one or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment;
- Further diagnostic testing or medical/surgical intervention;
- A change in the dose of study drug or discontinuation from study drug treatment.

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator. A laboratory abnormality judged to be Grade 4, in itself, may not constitute an SAE unless the clinical status of the patient indicates a life-threatening AE.

11.1.3 Serious Adverse Events

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study but within 30 days post-study (Day 90), 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 patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE**.

*An inpatient hospitalization is defined as an admission for any length of time. In this specific case of COVID-19 patients already hospitalized, other hospitalization for routine or planned clinical procedures, prolongation of hospitalization for any COVID-19-related adverse change in the patient's condition, or for "social" reasons, should not be considered an AE and should not be reported as a SAE.
** While prolongation of hospitalization and/or transfer to Intensive Care Unit per se shall not be considered a AE/SAE, if invasive mechanical ventilation/ECMO is started, the cause for it is an important medical event and therefore reaches the criteria of seriousness to be reported as a SAE.

Definition of Life-Threatening Adverse Experience:
An adverse experience is life threatening if the patient 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 serious form, might have caused death). For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.

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 patient's ability to carry out normal life functions.

Medical Monitor:
Dr. Radhika A., MD
Contact Number: +91 8728830894

Laurent Safety Line: +1 877-914-4242
Email: [redacted]

11.1.3.1 Serious Adverse Event Reporting

Any SAE that occurs during this study, including death from any cause other than disease progression, 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, patient evolution notes, laboratory test results, new con-meds, 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 patient health status (worsening of the initial event, death, or when the SAE has resolved completely).

Please see Section 11.2 for specific reporting requirements for laboratory tests related to a SAE on study, in particular once a patient is intubated and therefore ceases to receive the study medication. For concomitant medications, considering that patients in the ICU can receive multiple additional drugs with many dose adjustments and electrolytes for serious conditions as per SOC, and in order to simplify the reporting process, we recommend the following minimum data to be entered in eCRF:

- For every 24-hour period, all new prescribed drugs should be entered in eCRF, including the dose, the indication they were prescribed for, and the date of treatment initiation/end.
- For each drug, indicate only the highest dose administered during the specific 24-hour period (i.e., not every dose adjustment occurring during that day/night…).
- In the event that a patient gets intubated to start mechanical ventilation, the medications, the procedures and various electrolytes to support life and provide comfort do not need to be entered in the eCRF: Life support therapies and dose adjustments do not need to be reported in the eCRF for mechanically ventilated patients (eg, medications used for continuous sedation and muscle paralysis, fluid and electrolytes management, antibiotics, medications used to correct low blood pressure or hypotensive shock, medications for venous thromboembolism prevention, and procedures for cardiopulmonary resuscitation).

For the SAE report: All con-meds used to manage the SAE, including dosing adjustments should be summarized in the con-med 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 scheduled study follow-up, on Day 60, 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 patient'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 patient becomes pregnant during the study, the patient will be removed from the study without receiving further study medication. Follow-up regarding the outcome of the pregnancy and any postnatal sequelae in the infant is required. Pregnancies are considered immediately reportable AEs (within 24 hours of awareness) and are to be documented in the e-CRF.

11.1.3.2 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 (IECs)/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 patient or the patient population.

For the RESOLUTION study, the following AEs will not require expedited reporting based upon the judgment of the Investigator:

- AEs that occur due to Standard-of-Care COVID-19 therapies and are consistent with the package labels for such products;
- AEs due to aggravation of the COVID-19 disease, including death, and unrelated to the study drug.

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

11.2 Clinical Laboratory Assessments

Blood and urine samples will be collected according to the Schedule of Events (page 11) and analyzed locally at the clinical site's laboratory as per their SOC. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (as per Section 11.1.1). Screening laboratory results must be available and reviewed by the Investigator before randomization. The typical safety laboratory test panels are shown in Table 2 below (it is acceptable that SOC varies between clinical sites regarding some tests, but testing must include at the minimum tests evaluating the hematologic status, the kidney and the liver functions. The tests marked by a (+) are suggested:

Table 2: Laboratory Tests Panels

Serum Chemistry	Hematology	Urinalysis*
Albumin+	Hematocrit+	Nitrite
Creatinine+	Hemoglobin+	Urobilinogen+
Total protein	Red blood cells+	Protein+

Potassium	Mean corpuscular hemoglobin	pH+
Sodium	Mean corpuscular hemoglobin	Blood+
Calcium	Mean corpuscular volume	Leucocyte esterase
Bicarbonate	Reticulocytes	Specific gravity
Phosphate	Platelet count+	Ketones
Alkaline phosphatase+	Leucocytes+	Bilirubin+
ALT+	Differential (absolute and %)	Glucose+
AST+	Eosinophils	Appearance
GGT	Basophils	
Total bilirubin+	Neutrophils+	
Blood urea nitrogen+	Lymphocytes+	
Glucose	Monocytes	

* If urine is positive for leukocyte esterase, nitrite, urobilinogen, protein, or blood, if part of SOC, microscopic examination of urine will be performed for leukocytes, erythrocytes, crystals, bacteria, and casts, as per SOC.

For the purpose of this study conduct, the laboratory tests performed in the local laboratory are the primary tests. 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, pregnancy tests (β-human chorionic gonadotropin) for females of childbearing potential: Urine (or serum) samples will be obtained as specified in the Schedule of Events, page 11 and tested. The urine (or serum) pregnancy test pre-randomization must be negative before the first dose of study drug. Finally, clinical laboratory evaluations may be performed at other times if judged to be clinically appropriate by the Investigator.

Reporting requirements for laboratory tests performed to monitor a SAE, in addition to the protocol-requested safety laboratory tests: Patients experiencing a worsening of their condition (generally a life-threatening situation declared as a SAE) are subject to receiving numerous con-meds, spontaneous treatment adjustments, along with frequent safety laboratory testing.

- For the SAE report, all important safety lab tests performed to monitor the SAE during hospitalization should be summarized in the evolution notes section of the SAE report for a thorough review of the event by the Sponsor and the medical monitor.
- Safety lab tests performed to monitor the SAE during hospitalization will not be entered in the eCRF and only safety lab tests scheduled per protocol requirements will be entered.
- In addition, if the patient is intubated and therefore ceases to receive the study medication, there is no need to enter the laboratory tests results in the eCRF from this point in time.

11.3 Vital Signs and Physical Examinations

Consistent with the site's SOC, vital signs, directed Physical Examinations will be performed according to the Schedule of Events, page 11, and will be symptom- or disease-driven. After screening, any clinically significant abnormal findings in physical examination should be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature (oral or tympanic, consistently determined being a key COVID-19 sign), pulse rate, oxygen saturation and respiratory rate. Oxygen saturation may be performed while the patient is stabilized on room air, in the view of determining if oxygen supplementation is needed.

11.4 Liver Safety Algorithm for the Management of Hepatic Impairment

The following instructions are to be followed if liver function markers and clinical presentation suggest the onset of hepatic impairment on study. The hepatic safety of all randomized patients will be assessed through the use of the following algorithm based on FDA DILI management guidelines:

- If ALT or AST rises > 5x the Upper Limit of Normal (ULN): LAU-7b treatment is discontinued and patient is closely monitored until recovery;
- If subjects with abnormal baseline liver indices develop elevations of AST or ALT >2x the baseline values or total bilirubin (TBL) >1.5x the baseline values during the study, repeat testing should be performed within 48 -72 hours. If there are persistent elevations (ALT or AST >2x the baseline values or TBL >1.5x the baseline values) upon repeat testing, LAU-7b should be discontinued unless LAU-7b is clearly not the cause of the elevation;
- If baseline measurements were <2x ULN, discontinue LAU-7b if ALT or AST increases to > 4x the baseline values;
- If baseline values are ≥2x ULN but <5x ULN, discontinue LAU-7b if ALT or AST increases to > 2x the baseline values;
- Discontinue LAU-7b if ALT or AST increase >2x the baseline values *AND* the increase is accompanied by a concomitant increase in TBL >1.5x the baseline value *OR* the International Normalized Ratio (INR) concomitantly increases by >0.2
- Discontinue LAU-7b treatment if alkaline phosphatase increases to > 2x the baseline value.
- Discontinue LAU-7b in any subject with multiple signs or symptoms suggestive of liver injury such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

12 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will provide details of the methods of analysis to address all study objectives. The SAP may be amended during the course of the study, but 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 7-point Ordinal Scale, data will be tabulated in frequency tables to display the number and proportion of patients for each category by treatment group. For continuous variables, data will be summarized with the number of patients, 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 9.2.1.1, before the first dose of study drug. Statistical significance will be set at the 5% level (one-sided) for the pilot portion and at the 5% level (two-sided) for the extension. Consideration

will be given for adjusting for pre-specified prognostic baseline factors such as age, the ordinal scale health status at baseline and comorbidities, where applicable.

Diligent efforts will be made to prevent missing data in the study. For example, patients who discontinue the study treatment early should still be followed for all regularly scheduled visits for safety and relevant efficacy assessments, until the Day 60 follow-up. A clear distinction should be made between treatment discontinuation and study withdrawal. Efficacy assessments occurring after treatment discontinuation should not be included in the per-protocol analysis.

Database lock and statistical analyses will be performed for the pilot portion and the extension, separately.

12.1 Sample Size Determination

The main efficacy variable is the 7-point Ordinal Scale of the patient Health Status and the primary efficacy endpoint is the proportion of patients requiring mechanical ventilation and/or deceased (ordinal scale scores 6-7 inclusively) by Day 60 compared between the active and control (placebo) arms of the study. The sample size has been formally estimated for this revised primary efficacy endpoint, in the view of confirming the positive signals of efficacy obtained during the pilot portion of the trial (see Section 5.4.2.1 for a summary of these results.

The study showed so far that patients with a Health Status of 3 or 4 at baseline benefited from LAU-7b therapy while patients with a Health Status of 5 at baseline (with an established respiratory failure) were apparently too advanced to benefit from LAU-7b therapy. Therefore, going forward with this expansion, the enrolment will focus only on patients with a Health Status of 3 or 4 at baseline. The observed effect size for the revised primary efficacy endpoint in the pooled patients with a Health Status score of 3 or 4 at baseline in the pilot portion of the study (n=148) was 7% (0% in the LAU-7b arm, 6.9% in the placebo arm).

A target of circa 264 SARS-CoV-2 positive patients with a Heath Status score of 3 or 4 at baseline total sample size are therefore required in the Phase 3 portion of this study under the initial assumption of effect size (see below for the sample size re-estimation). Consequently, once additional enrolment is completed, a minimum of 412 patients with a Heath Status score of 3 or 4 at baseline will have been randomized in this study, for a total 496 patients including the 84 patients with a Health Status score of 5 enrolled during the Phase 2 pilot portion.

Sample size rationale: Based on the WHO Master Protocol [86], utilization of the main efficacy variable that uses an ordinal severity scale with 7 categories, enables the calculation of numerous study endpoints including the primary efficacy endpoint, the proportion of patients requiring mechanical ventilation AND/OR deceased by Day 60. The primary hypothesis test will be based on a test of a null hypothesis that the proportions of patients requiring mechanical ventilation AND/OR deceased by Day 60 for the two treatment groups are the same against the alternative hypothesis that the investigational group is superior to the control group.

Using the proportion of patients requiring mechanical ventilation AND/OR deceased by Day 60 in the pilot portion of the study, an effect size of 7% change (i.e. 7% in the control group vs. 0% in the investigational group), comparing the active arm versus the control (placebo) arm, and a minimum of 90% statistical power of detecting a difference of 7% using a two-tailed Fisher Exact test, with a nominal alpha of 0.05, a total sample size of 264 patients (132 per arm) with a Heath Status score of 3 or 4 at baseline is required for the Phase 3 confirmatory portion of this study.

12.2 Sample Size Re-estimation

To ensure the study is adequately powered, an interim sample size re-estimation/futility analysis is planned for this study, following the procedures proposed by Mehta and Pocock (2011) [85]. The sample size re-estimation will be performed by one unblinded study statistician, who will not have a decision-making role in the trial. The results will be presented to the DSMB for discussion in the closed session; no one else, including Sponsor or clinical team members, will see the data. When approximately 42% of the subjects have completed the Day 60 primary endpoint assessment or terminated the study, the data are considered "soft-locked" by data management, the data will be provided to the unblinded statistician in the DSMB. The proportion of patients requiring mechanical ventilation AND/OR deceased by Day 60 in each treatment arm will be estimated; and the conditional power (CP) will be calculated.

The maximum allowable sample size is set at 1.75 times the initial sample size (132 × 1.75 = 231 subjects per arm, or 462 in total), corresponding to a difference of 4% (i.e. 4% in the control group vs. 0% in the investigational group) using an alpha of 0.05 and 90% power. Given that the interim analysis is to be performed at 42% of the initial sample size of 264 patients, the targeted power is 90%, and the maximum allowable sample size is 1.75 times, the conditional power cut-off value (CPmin) is calculated as 38.6%. At the interim assessment, if the conditional power (CP), calculated based on the interim data, is between 38.6% and <90% (promising zone), the number of subjects will be increased, up to the maximum allowable sample size for this study. If the conditional power is below the promising zone, the futility criteria will be deemed met and a recommendation to stop further enrollment will be communicated to the DSMB. The communication plan from the DSMB is to report one of the three following statements based on the results: 1) "carry on with the original sample size"; 2) "increase sample size to XXX" or 3) "Stop the study for futility". Details about the DSMB and the data monitoring procedures are specified in the DSMB charter.

Since sample size re-estimation occurs only when the interim conditional power falls in the pre-specified "promising" range, the overall alpha will be protected. Furthermore, because the study will not stop for efficacy regardless of the conditional power, the final analysis will be carried out using conventional tests, without the need for weighing the stage 1 and 2 results or adjusting the alpha value. The operating characteristics obtained from simulation showed that the interim sample size re-estimation approach yields a slightly higher statistical power owing to the slightly higher number of final expected sample size, compared with a classical fixed sample size design.

12.3 Analysis Populations

- **The intent-to-treat (ITT) population** will include all patients randomized to a treatment group who are randomized and receive at least one dose of the study drug. The ITT population will be used for the primary analyses of all study endpoints, taking into consideration the specific populations described below. The patients will be kept in their randomized treatment arm for the analyses.
- **The per-protocol (PP) population** will include all patients randomized to a treatment group to whom at least 12 days of study treatment are administered in accordance with the protocol (i.e. without major protocol deviations as pre-identified prior to the database lock) and without interruption triggering withdrawal from further treatment (see Section 8.3). The PP population will serve as the basis for secondary analyses of all study endpoints. The patients will be kept in the treatment arm that they actually received for the analyses.
- **The safety population** will include all patients randomized to a treatment group who received at least one dose of study drug treatment. This population will serve as the basis for analyses of all safety endpoints. The patients will be kept in the treatment arm that they actually received for the analyses.

12.4 Estimand Strategy

Some types of intercurrent events are expected to possibly occur during the course of the study: treatment interruption; treatment discontinuation; and use of disallowed medication (see Section 9.5.1). The project estimands strategies, including those for handling each of these types of intercurrent events are summarized in Table 3 below.

Table 3: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events in Phase III

Objective: To evaluate the efficacy of LAU-7b therapy + Standard-of-Care (SOC) relative to placebo + SOC in patients with COVID-19 disease with confirmed SARS-CoV-2 infection.		
Target Population	Adult subjects with COVID-19 disease with confirmed SARS-CoV-2 infection and a Health Status score 3 or 4 at baseline.	
Variable/Endpoint	The 7-point ordinal scale of the patient status / The proportion of patients requiring mechanical ventilation AND/OR deceased (all causes) by Day 60	
Primary Estimand		
Intercurrent events 1.Treatment Interruption 2.Treatment Discontinuation for Other Reasons than death 3.Use of Disallowed Medication	Treatment Policy strategy	1. For temporary interruptions of study treatment (e.g. due to an adverse event), data collected will be analyzed as if treatment had continued normally throughout the study. If the treatment is interrupted and then never restarted (e.g. due to subject death, withdrawal) then it will be treated as per treatment discontinuation strategies below. 2. For endpoints where the subject has data available, the subject will continue to be analyzed as part of their treatment group even if they have discontinued treatment. Missing data are not considered part of this intercurrent event and are handled separately (see the appropriate Section 12.7 or 12.8 for handling depending upon endpoint). 3. If a subject is given disallowed medication (see Section 9.5.1) after enrollment, their safety and efficacy data will be analyzed as normal.
Intercurrent events 4. Treatment Discontinuation due to Lack of Efficacy (mechanical ventilation) or Safety Event (death)	Composite event strategy	4. Serious safety events and/or indications of lack of efficacy (e.g. death, mechanical ventilation) are included in study endpoints as part of analyses. Therefore, treatment discontinuation due to most anticipated types of safety/lack of efficacy events are accounted for in the endpoints and analyses
Population-Level Summary	The proportion of patients requiring mechanical ventilation (includes ECMO) AND/OR deceased by Day 60 will be analyzed using a Fisher	

	exact test to compare proportion of LAU-7b treated subjects relative to placebo.
Estimand Description	Superiority of LAU-7b on the proportion of patients requiring mechanical ventilation or deceased by Day 60 will be analyzed using Fisher exact test irrespectively from the interruption of treatment, early discontinuation of the treatment (for other reason than death) or use of disallowed medication.
Imputation/Data/Censoring Rule(s)	Missing observations will be treated as a non-response (i.e. patient considered as Health Status 6-7 inclusively) for the primary analyses on ITT.
Sensitivity Analysis	Sensitivity analyses where missing observations will be imputed using different methods will also be performed and will be further detailed in the SAP.

12.5 Subject Disposition and Discontinuations

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

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

12.6 Baseline and Demographic Characteristics

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 patient 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.

12.6.1 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 to the follow-up on Day 45 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.

12.6.2 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. If the last dose date of study drug is missing, the patient'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 population subset of the ITT population.

12.6.3 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]/(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 patients whose compliance is <80% or ≥80% will be summarized, by study group.

12.7 Efficacy Analysis

12.7.1 Analysis of Primary Endpoint

The proportion of patients requiring mechanical ventilation (includes ECMO) AND/OR deceased by Day 60 will be analyzed using a Chi-Square test (or a Fisher exact test if the expected values in any of the cells of the contingency table are below 5).

Logistic regression including treatment group, age group and other prognostic factors at baseline will also be performed.

Missing observations will be treated as a non-response (i.e. patient not considered as alive and free of respiratory failure) for the primary analyses on ITT. Sensitivity analyses where missing observations will be imputed using different methods will also be performed and will be further detailed in the SAP.

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

Full details will be specified in the SAP and its Addendum dedicated to the study expansion.

12.7.2 Analysis of Secondary Efficacy Endpoints

Pre-defined Clinical Parameters:

- The ordinal scale will be used to estimate a proportional odds model. The primary hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. The model fit using a goodness-of-fit likelihood ratio test will be evaluated. The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested. Participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These sensitivity analyses will be fully defined in the SAP.
- Count data variables: The number of days of hospitalization, the number of days in ICU, the number of days under mechanical ventilation…etc., will be tabulated by treatment and compared with an appropriate count data model, e.g., ANOVA model (if assumptions of normality and homogeneity of variance appear acceptable), Poisson regression, negative binomial regression, zero-inflated regression, etc., depending on their distribution.
- Time to event data variables: The time to mechanical ventilation, time to recovery, time to aggravation (worsening by one category on the ordinal scale), and time to death will be tabulated by treatment 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 survival (aggravation-free survival, survival) by treatment group and to estimate cumulative aggravation-free survival and survival rates by treatment group.
- Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).
- Mean change-from-baseline for the ordinal scale will be analyzed through time, using a mixed model repeated measure (MMRM) model.
- Body weight and BMI changes from screening will be summarized using descriptive statistics by treatment and compared between treatments using an analysis of covariance (ANCOVA) with treatment as fixed effect; and adjustment for screening Ordinal Scale Health Status, and weight or BMI at baseline as covariates.

Formal Futility Analysis (Pilot Portion):

When approximately 50 patients per arm were available for health status/efficacy data from Day 29 (actual 102 patients across the two treatment arms), a formal futility analysis based on the initial primary efficacy endpoint derived from the 7-point Ordinal Scale data was carried out and reported to the DSMB for formulation of a recommendation to the Sponsor. The aim of this futility analysis/stopping rule was to ensure that there is a high probability of stopping the study when there is a true underlying excess risk of disease deterioration with the use of the investigational product, and a low probability of stopping the study when there is no such risk.

In this study, the appropriate stopping rule was based on the proportion of patients alive and free of respiratory failure, corresponding to Ordinal Scale scores of 1 to 4 inclusively, on Day 29. The proportion of patients alive and free of respiratory failure has an expected frequency in the control arm of 78% (Kim *et al*. **Error! Bookmark not defined.**). The proportion of patients on the investigational product should be improved.

The rule was to stop the study if the observed investigational product rate was numerically lower than the

observed control (placebo) arm rate. Based on Kim *et al.* **Error! Bookmark not defined.**, assuming that the true underlying control arm (placebo) rate is 78% and using a normal approximation when comparing proportions, it is estimated that when using this rule:

the probability of stopping the study is ~5% if the true underlying investigational product rate is 90%.
the probability of stopping the study is ~50% if the true underlying investigational product rate is 78% (equal to the assumed true underlying control arm rate).
the probability of stopping the study is ~91% if the true underlying investigational product rate is 66%.

The Futility Analysis was performed and the DSMB provided their recommendation on 30Mar2021 to continue the study since the criteria for futility was not met.

Quality of Life Endpoints:

Quality-of-life data will be derived from the questionnaire according to the corresponding scoring manual and will be summarized by treatment group. Patients' health state will be derived from the EQ-5D-5L questionnaire. Data will be summarized by treatment group using descriptive statistics. Analysis of the absolute change from screening for the EQ-5D-5L will be performed using an ANCOVA with treatment as fixed effect and EQ-5D-5L score at baseline as a covariate.

12.8 Safety Analyses

The safety analyses will be performed at least five times, 1- when a minimum of one third of the initially enrolled patients have completed their LAU-7b (or placebo) treatment period and corresponding safety information is available, 2- when at least two thirds of the initially enrolled patients have completed their LAU-7b (or placebo) treatment period, 3- at the time of final analysis subsequent to the planned database lock on 15Sep2021 for the pilot part of the study, 4- when at least half of the expansion's enrolled patients have completed their LAU-7b (or placebo) treatment period, and 5- at the time of final analysis (after completion of the expanded enrolment and database lock). Safety analyses will be performed on the safety population (those patients who receive at least one dose of study drug). Blinded safety data will be assessed by the DSMB at regular meetings. The DSMB may request unblinding of patients for safety concerns in addition to receiving the unblinded interim analyses results. Like it was the case for the pilot portion of the study, the study expansion will be double blinded to the Investigators, patients and sponsor's staff until the revised end of the study, unless circumstances require unblinding.

Safety and tolerability will be assessed by the following:

- Adverse events described and categorized according to the MedDRA, version 16 or more recent.
- Clinically relevant changes from baseline in vital signs
- Clinically relevant changes from baseline in directed physical examinations
- Clinically relevant changes from baseline in safety laboratory assessments (hematology with differential count, biochemistry, and urinalysis).

12.8.1 Adverse Events

Adverse events will be tabulated with reported incidences by treatment, number of patients that presented adverse events by treatment, serious adverse events by treatment, number of adverse events by body system and by treatment. 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 and TEAEs. 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 at the last follow-up, on Day 60, or earlier if early terminated. Post-treatment AEs are not collected in this study. 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-and post-treatment AEs, will be presented in individual patient data listings.

The number and percentage of patients with at least one AE, as classified by preferred term and system organ class, will be summarized for each treatment group. For these summaries, patients with multiple events will be counted only once per preferred term. AEs will also be summarized by severity and relationship to study drug. At each level of summarization, the event with the highest level of severity or strongest drug relationship will be presented.

All AEs must be listed. In addition, detailed listings will be provided for patients who die, experience a SAE, or discontinue the study because of an AE. These listings will include treatment, patient's age, duration of follow-up, amount of fenretinide received, and time since last intake.

12.8.2 Clinical Laboratory Assessments

Safety laboratory variables (e.g., hematology, biochemistry, and urinalysis results) will be presented in SI units, if available, at each time point using descriptive statistics (mean, standard deviation, median, minimum, and maximum).

12.8.3 Vital Signs

Vital signs (blood pressure, temperature, heart rate, oxygen saturation and respiration rate) will be presented at each time point using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Change from baseline values for each variable will also be presented by treatment group.

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

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

No statistical analyses of vital signs are planned.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

All patient data generated by the study will be recorded in each patient'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 patients 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 hospital/institution that will allow verification of the existence of the patient 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/IEC and regulatory bodies, including the FDA 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/IEC 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 patient's CRF.

The study will be monitored to ensure the following:

- Data are authentic, accurate, and complete;
- The safety and rights of patients 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 medical institution (where applicable) 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 a in-person or remote study site visit 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. *During COVID-19-related site restrictions, some site qualification and initiation activities may be carried out remotely, with study documentation supporting in lieu the qualification until the time allows in-person confirmation to happen.*

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 patients, the nature, the scope and the scientific integrity of the study will require IRB/IEC notification/approval before their implementation. Exceptions are cases where the modification is necessary to abrogate an apparent immediate risk to the patients. Laurent Pharmaceuticals or designee will submit all protocol modifications to IRB/IEC 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 patients or the science of the study. Administrative amendments will be submitted to the IRB/IEC 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/IECs 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 protocol deviations to the IRB/IEC.

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/IEC 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 patient enrollment;
- Lack of evaluable and/or complete data;
- Potentially unacceptable risk to patients (see Section 7.2.3 for additional guidance);
- Changes in Laurent Pharmaceuticals drug development plans;
- Decision by the FDA or 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/IEC committees will review and approve this protocol and informed consent. All patients must provide written informed consent where applicable, before 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/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC 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 study 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 study 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 institution. 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 REFERENCES

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