STUDY TITLE: Interferon Lambda for Immediate Antiviral therapy at Diagnosis (ILIAD): A phase II randomized, double-blind, placebo-controlled, multicenter, trial to evaluate the effect of peginterferon lambda for the treatment of COVID-19.

SHORT TITLE: Interferon Lambda for Immediate Antiviral therapy at Diagnosis (ILIAD)

PROTOCOL ID: JF-4-2020

SPONSOR: Jordan Feld, MD MPH
Toronto General Hospital, University Health Network

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2.1 December 22, 2020

PROTOCOL:

Interferon Lambda for Immediate Antiviral therapy at Diagnosis (ILIAD): A phase II randomized, double-blind, placebo-controlled, multicenter, trial to evaluate the effect of peginterferon lambda for the treatment of COVID-19.

This protocol has been approved by the Toronto Centre for Liver Disease, University Health Network. The following signature documents this approval.

_____ _____

Dr. Jordan Feld, MD Date

INVESTIGATOR SIGNATURE OF AGREEMENT FOR PROTOCOL

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Toronto Centre for Liver Disease, University Health Network. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

_____ _____

Site Principal Investigator Name (Printed) Signature

_____

Date

Interferon Lambda for Immediate Antiviral therapy at Diagnosis (ILIAD): A phase II randomized, double-blind, placebo-controlled, multicenter, trial to evaluate the effect of peginterferon lambda for the treatment of COVID-19.

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Amendment 6

Amendment rationale

Changes to the protocol
The major changes made to the protocol, and sections affected listed below

Section	Changes made
Cohort B Primary Outcome	**The primary has been revised to a clinical endpoint along an ordinal scale from a virologic endpoint. This change was made to reflect the importance of clinical outcomes for individuals hospitalized with COVID-19. A recently reported randomized trial of inhaled interferon-beta among inpatients with COVID-19 was associated with an improved odds of a beneficial outcome.**
Cohort B Study Procedures	**Reduced the number of sampling to align with the new primary endpoint and limit the need to expose research personnel to an individual with COVID-19. Replaced saliva sampling with mid-turbinate swabbing to allow for easier self-collection.**

4.0 Study Synopsis

OBJECTIVES	***Cohort A – Ambulatory*** *1. To evaluate the safety and tolerability of immediate treatment with Peginterferon Lambda 180 mcg in patients with mild to moderate COVID-19 discharged to home isolation.* *2. To compare the proportion of individuals with a nasopharyngeal swab negative for SAR-CoV-2 RNA at day 7 post-treatment in those treated with peginterferon lambda 180 mcg vs. placebo.* ***Cohort B - Hospitalized*** *1. To evaluate the safety and tolerability of immediate treatment with peginterferon-lambda 180 mcg on days 0 and 5 in patients hospitalized with moderate COVID-19 admitted to hospital.* *2. To compare clinical outcomes on an ordinal scale in those treated with peginterferon lambda 180 mcg at Days 0 and 5 vs. placebo.*
STUDY DESIGN AND INTERVENTION	*The study uses an adaptive design. An ambulatory cohort (Cohort A) will be recruited first. Individuals diagnosed with COVID-19 in an Assessment Centre/Emergency Department who are deemed well enough for discharge to home isolation will be provided information related to the study through recruitment materials (posters) at the site. Participants that are interested in participating will contact the study coordinator through the contact information provided on the recruitment material at the site or found through study advertisements. Providers caring for patients with COVID-19 may also refer patients to the study team after obtaining verbal consent to share contact information with the study team. After speaking with research staff, eligible consenting participants confirmed to be COVID-19 positive will come to the ambulatory clinic and be randomized to receive a single subcutaneous (SC) injection of*

	peginterferon lambda 180 mcg or placebo. Patients will be observed for one hour in the clinic before discharge and followed through phone/videoconferencing at 4-6 hours post injection and then daily and will perform self-administered mid-turbinate nasal swabs on days 1, 2 and 3. For participants who cannot return to the outpatient clinic; a study nurse will perform a home visit on day 3 for nasopharyngeal swab collection and clinical assessment. Additional self-swabs will be taken on days 5 and 7 with a second clinic/home visit on day 7 and 14 for nasopharyngeal swab. Virtual visits will occur on the days of self-swabs until day 14. Self-swabs will be performed on days 0,1, 2, 3, 5, 7, 10 and 14. The primary endpoint will be the proportion in both groups negative for SARS CoV-2 RNA by nasopharyngeal swab on day 7. *After 50% enrollment (n=30) in Cohort A, the Data Safety Monitoring Committee will review safety data. If deemed safe, Cohort B (Hospitalized) will begin enrollment. Patients diagnosed with COVID-19 without evidence of severe disease but requiring hospitalization will be consented and randomized to receive a SC dose of peginterferon-lambda 180 mcg on Days 0 and 5 or placebo Patients will be monitored with blood tests and mid-turbinate swabs from day 0 to day 28, with swab frequency decreasing after day 7. The primary endpoint will be clinical status on an ordinal scale at Day 14. Numerous secondary endpoints will be evaluated.*
STUDY POPULATION AND NUMBER OF PATIENTS	*Cohort A – Ambulatory – 60* *Cohort B – Hospitalized - 200*
ROLL-IN PHASE	*After the first 10 patients randomized (Cohort A) have completed 7 days of follow-up, the independent DSMC will review the totality of the safety data. Review will occur after each 10 patients complete 7*

	days of follow-up until 50% enrollment. The DSMC will advise the steering committee whether to halt or continue enrollment based on their findings. After 50% enrollment, if the DSMC recommends continued enrollment, recruitment in Cohort B will begin.
STUDY DURATION	*Approximately 3 months (2 months for enrollment, 1-2 weeks of treatment, 1-2 weeks of follow-up).*
ELIGIBILITY CRITERIA	***Inclusion Criteria Cohort A*** *1. Adult patients between the ages of 18 and 75 years.* *2. Confirmed COVID-19 infection by PCR within 7 days of symptom onset.* *3. Discharged to home isolation.* *4. Willing and able to sign informed consent.* *5. Willing and able to follow-up by daily phone videoconference.* *6. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication. Female patients of childbearing potential are all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least 1 year postmenopausal.* ***Exclusion Criteria Cohort A*** *1. Requirement for hospital admission* *2. Current immunosuppression due to medication (steroids, biologics, chemotherapy) or underlying condition such as organ/bone marrow transplant or untreated HIV or HIV infection with detectable HIV RNA and/or CD4 count of <500.* *3. Pregnancy (or positive urine pregnancy test) or lactating* *4. The following pre-existing medical conditions:*

	a. *Known seizure disorder* b. *Known retinal disease requiring therapy* c. *Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (rheumatoid arthritis, lupus, inflammatory bowel disease)* d. *Known history of chronic obstructive pulmonary disease (COPD) or asthma associated with functional impairment* e. *Known cirrhosis with any history of decompensation (ascites, variceal bleeding or hepatic encephalopathy)* f. *Known chronic kidney disease with estimated creatinine clearance < 50 mL/minute or need for dialysis* g. *Severe psychiatric disorder – schizophrenia, bipolar disorder, depression with prior suicidality* h. *Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of peginterferon lambda* 5. *Advanced cancer or other illness with life expectancy of < 1 year* 6. *Known alcohol or drug dependence that in the opinion of the investigator would impair study participation* 7. *Known prior intolerance to interferon treatment* 8. *Enrolment in another clinical trial with use of any investigational agent in the prior 30 days* 9. *Use of off-label therapy for COVID-19* ***Cohort B Inclusion Criteria*** 1. *Adult patients over age 18* 2. *SARS-CoV-2 RNA-positive on nasopharyngeal swab/respiratory specimen within 10 days of symptom onset*

	3. Admitted to hospital for management of COVID-19 *4. Willing and able to provide informed consent* *5. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication. Female patients of childbearing potential are all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least 1 year postmenopausal.* ***Cohort B Exclusion Criteria*** *1. Severity of illness* *a. Respiratory failure (requiring>6L O_2 or intubation in the ER)* *b. Shock – systolic BP<90 mmHg or mean arterial BP<60 mmHg after fluid resuscitation* *2. Current immunosuppression due to medication (steroids, biologics, chemotherapy) or underlying condition such as organ/bone marrow transplant or untreated HIV or HIV infection with detectable HIV RNA and/or CD4 count of <500.* *3. Pregnancy (or positive urine pregnancy test) or lactating* *4. The following pre-existing medical conditions:* *a. Known seizure disorder* *b. Known retinal disease requiring therapy* *c. Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (rheumatoid arthritis, lupus, inflammatory bowel disease)* *d. Known cirrhosis with any history of decompensation (ascites, variceal bleeding or hepatic encephalopathy)* *e. Known chronic kidney disease with estimated creatinine clearance < 30 mL/minute or need for dialysis*

	f. Severe psychiatric disorder – uncontrolled schizophrenia or bipolar disorder or depression with prior suicidality *g. Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of peginterferon lambda* *5. Known prior intolerance to interferon treatment* *6. Enrolment in another clinical trial with use of an antiviral agent in the prior 30 days (co-enrollment with immunomodulatory agents permitted)* *7. Use of off-label therapy for COVID-19* *8. Any of the following abnormal laboratory indices* *a. Hemoglobin < 100 mg/dL* *b. Platelet count < 75,000 cells/mm^3* *c. Absolute neutrophil count < 1,000 cells/mm^3* *d. Estimated creatinine clearance < 30 cc/mL* *e. Total bilirubin > 2x upper limit of normal (ULN)* *f. Alanine aminotransferase (ALT) > 5x ULN* *g. Aspartate aminotransferase (AST) > 5x ULN* *h. Lipase or amylase > 2x ULN* *i. Random blood glucose > 20 mmol/L*
PRIMARY ENDPOINTS	***Cohort A*** ***Primary efficacy endpoint:*** *The proportion of participants with negative SARS-CoV-2 RNA on nasopharyngeal swab at day 7 post-randomization.* ***Primary safety endpoint:*** *The rate of treatment-emergent and treatment-related serious adverse events (SAEs)* ***Cohort B***

	Primary clinical endpoint: *Clinical status on an ordinal scale at Day 14.* **Scale:** 1 death; 2 hospitalized with invasive ventilation; 3 hospitalized on non-invasive ventilation or high flow oxygen; 4 hospitalized on supplemental oxygen; 5 hospitalized not on supplemental oxygen; 6 not hospitalized with limitation of activity; 7 not hospitalized without limitation in activity ***Primary safety endpoint:*** *The rate of treatment-emergent and treatment-related serious adverse events (SAEs).*
SECONDARY ENDPOINTS	***Cohort A*** ***Secondary Endpoints:*** ***Clinical*** 1. *Time to resolution of symptoms (fever, cough, diarrhea)* 2. *Change in symptom scores (respiratory, gastrointestinal, fever) from day 0 to day 7* 3. *Need for hospital admission from day 0 to 14* 4. *Adverse events and serious adverse events by day 14* ***Virologic/Immunological*** 5. *Proportion negative for SARS-CoV-2 RNA by nasopharyngeal swab on day 3* 6. *Proportion negative for SARS-CoV-2 RNA by nasopharyngeal swab on day 14* 7. *Time to SARS-CoV-2 RNA negativity on mid-turbinate nasal swab* 8. *Proportion with SARS-CoV-2 RNA in blood at day 0 and 7* 9. *Proportion with SARS-CoV-2 antibodies in blood at day 0 and 7*

	10. *Correlation of response with interferon lambda 4 (IFNL4) genotype* 11. *Change in laboratory and inflammatory markers (hemoglobin, white blood cell count, lymphocyte count, liver profile, ferritin, lactate dehydrogenase, c-reactive protein, D-dimers, amylase) from day 0 to day 7 and day 7 to 14* 12. *Confirmed diagnosis of COVID-19 in household contacts from day 0 – 30.* ***Cohort B*** ***Secondary Endpoints*** 1. *Clinical status on the ordinal scale at Day 7, 21, and 28* 2. *ICU admission during hospitalization* 3. *Need for intubation from day 0 to 14 and to 28* 4. *Length of hospital stay* 5. *Change in respiratory symptom score from day 0 to 7, day 0 to 14, and day 0 to 28 (Appendix A)* 6. *All-cause mortality at day 28 and day 90* 7. *Readmission to hospital from day 0 - 28 and from day 0 - 90* 8. *COVID-19-related mortality at day 28* 9. *Adverse (AEs) and Serious Adverse Events (SAEs) from day 0 - 28* 10. *Frequency of dose reduction or dose omission for the second dose of peginterferon lambda* ***Virologic/Immunological*** 11. *Time to SARS-CoV-2 negativity* 12. *Proportion negative for SARS-CoV-2 RNA by mid-turbinate swab on days 0-7, 10, 12, 14, 18, 21, 25, 28*

	13. *Change in quantitative SARS-CoV-2 RNA by mid-turbinate swab over time* 14. *Correlation of clinical and virologic response with interferon lambda 4 (IFNL4) genotype* 15. *Change in laboratory and inflammatory markers hemoglobin, white blood cell count, lymphocyte count, liver profile, ferritin, lactate dehydrogenase, c-reactive protein, D-dimers, amylase) from day 0 to day 7 and to day 14, 21, and 28* 16. *Proportion with SARS-CoV-2 antibody at day 7, 14, 21, and 28* 17. *Proportion with SARS-CoV-2 RNA in blood at day 0, 7 and 14, 21, and 28*
SAMPLE SIZE	***Cohort A*** *With an expected clearance rate of 40% by day 7 in the placebo arm and 80% in the treatment arm, 23 patients are required in each arm for 80% power at alpha 0.05. With potential dropout of 20% due to either logistical problems or loss-to-follow-up, this translates to 30 patients per arm or 60 patients.* ***Cohort B*** *Powered based on the estimated odds of improvement on an ordinal scale using the distribution of outcomes from previous randomized treatment trials for COVID-19. For a suspected odds ratio of 2.1, similar to that observed for inhaled interferon-beta, and with 80% power the estimated sample size is 200, assuming 5% drop-out.*
RANDOMIZATION AND TREATMENT ASSIGNMENT	*In both cohorts, patients will be randomly assigned 1:1 in blocks of 4 using centralized computer-generated randomization to receive either treatment with peginterferon lambda or placebo.*

	Randomization in Cohort B will be stratified by sex (male/female) and country of site.
DATA TO CAPTURE	*Demographic data: Age, sex, ethnicity, country of birth* *Living arrangements: house/apartment, long-term care, number of household contacts* *Medical history – any pre-existing medical conditions with specific focus on history of diabetes, heart disease, lung disease* *Current prescribed medications and any drug allergies.* *Habits: smoking (none/current/past), recreational drug and alcohol use (none/current/past)* *Physical examination: Cohort A: Vital signs, weight & height* *Cohort B: Full physical examination, weight & height* *Routine blood tests: complete blood count, biochemistry (blood glucose, electrolytes, creatinine, liver enzymes, total and direct bilirubin and albumin) and inflammatory markers including D-Dimers, LDH, ferritin, amylase c-reactive protein, and troponin.*
DATA MANAGEMENT AND ANALYSIS	*The study will be overseen by the study steering committee including PIs, site PIs and statistician. Data will be stored in a secure REDCap database through UHN. Analysis will be carried out by the study team statistician.*

5.0 Abbreviations & Definitions

AE – adverse events
ALT – alanine aminotransferase
AST – aspartate aminotransferase
ASV – asunaprevir
AUC – area under the curve
Beta-hCG – beta human choriogonadotropin
BP – blood pressure
CI – confidence interval
Co-I – co-investigator
COPD – chronic obstructive pulmonary disease
COVID-19 – Coronavirus disease 19
CTN – Clinical Trials Network
CXR – chest x-ray
CYP – cytochrome P-450
DCV – daclatasvir
DSMC – Data Safety Monitoring Committee
eGFR – estimated glomerular filtration rate
ER – emergency room
ESRD – end-stage renal disease
GMR – geometric mean ratio
HBeAg – hepatitis B e antigen
HBV – hepatitis B virus
HCV – hepatitis C virus
HDV – hepatitis D virus
HIV – human immunodeficiency virus
IFN - Interferon
IFN-λ - interferon lambda
IFNL4 – interferon lambda 4
Mcg – micrograms
MGH – Michael Garron Hospital
NOAEL – no-observed-adverse-event-level
NP – nasopharyngeal
PBMC - peripheral blood mononuclear cells
PCR – polymerase chain reaction
pDILI – presumed drug-induced liver injury
PEG – polyethylene glycol
PegIFN-λ - peginterferon lambda
PI – principal investigator
PK - pharmacokinetic
RBV – ribavirin
RNA – ribonucleic acid
SAE – serious adverse events
SARS-CoV-2 – Severe Acute Respiratory Syndrome – Coronavirus 2
SC – steering committee
SMH – St. Michael's Hospital

Sub-I – sub-investigator
SVR – sustained virologic response
TCLD – Toronto Centre for Liver Disease
UHN – University Health Network
ULN – upper limit of normal
WBC – white blood cell count

6.0 Background/Rationale

SARS-CoV-2 is a novel coronavirus that has led to a global pandemic due to its relatively high transmissibility and potential to cause severe acute respiratory disease[1]. There are currently no approved therapies for coronavirus disease-19 (COVID-19) and although various antiviral strategies are under evaluation, none has shown significant benefits in early phase trials[2].

The cornerstone of the innate antiviral immune response is the interferon (IFN) system. Sensing of viral infection leads to production of Type I (alpha, beta) and Type III (lambda) IFNs, which drive a potent antiviral response through the induction of a wide array of genes, collectively known as IFN-stimulated genes (ISGs)[3]. Both Type I and Type III IFNs signal through the JAK-STAT pathway to drive ISG induction with comparable antiviral activity, however their systemic effects differ markedly due to the use of distinct receptors with different tissue distributions[3]. The Type I IFN receptor is highly expressed on all cells in the body, whereas the IFN-λ (lambda) receptor is primarily expressed on epithelial cells with high expression in lung, intestine and liver and very limited expression in hematopoietic and central nervous system cells[4]. As a result, production of or treatment with Type I IFNs leads to significant off-target effects, which have limited the safety, tolerability and ultimately clinical use of this class of agents. Interferon-alpha was used with some evidence of clinical efficacy in a pilot trial during the first SARS outbreak[5], however, concerns have been raised of the toxicity of a Type I IFN for COVID. IFN-λ was developed as a therapeutic to overcome the toxicity seen with IFN alpha and beta. Conjugation of IFN-λ to polyethylene glycol increases the half-life and allows for once weekly dosing. PegIFN-λ has been studied in Phase 1, 2 and 3 clinical trials in over 3000 patients for the treatment of hepatitis C virus[6], hepatitis B virus[7] and most recently hepatitis delta virus[8] infections, showing comparable antiviral activity to IFN-α, but with a much better safety and tolerability profile.

IFN-λ is particularly attractive for acute respiratory disease due to the high expression of the IFN-λ receptor in lung epithelia. In vitro and mouse studies have shown that IFN-λ is strongly induced in influenza, SARS-CoV-1 and other respiratory virus infections[9]. More importantly, IFN-λ treatment has been shown to be highly effective in a mouse model of severe influenza A infection. In mice challenged with influenza A, pre-treatment with either IFN-α or IFN-λ prevented mortality[10]. However, when the IFNs were given after infection, IFN-α worsened outcome, whereas IFN-λ treatment improved survival[10]. IFN-λ is particularly attractive as a treatment strategy for SARS-CoV-2 infection because in addition to its anticipated effect in the lung, the IFN-λ receptor is highly expressed in intestine and liver[11], which would address intestinal and hepatic involvement documented in patients with COVID-19[1,12]. Furthermore, the lack of the lambda receptor on hematopoietic cells limits concerns about the potential to worsen cytokine storm syndrome[13].

Based on extensive human safety data using PegIFN-λ and strong mouse data supporting the use of IFN-λ in acute respiratory infection, this study will evaluate PegIFN-λ in patients with mild to moderate COVID-19.

7.0 Study Outline

7.1 Hypothesis: Treatment with peginterferon lambda 180μg SC in patients with mild to moderate COVID-19 will accelerate viral clearance compared to best supportive care.

7.2 Objectives

Cohort A - Ambulatory

1. To evaluate the safety and tolerability of immediate treatment with Peginterferon Lambda 180 mcg in patients with mild to moderate COVID-19 discharged to home isolation.
2. To compare the proportion of individuals with a nasopharyngeal swab negative for SARS-CoV-2 RNA at day 7 post-treatment in those treated with peginterferon lambda 180 mcg vs. those who receive placebo.

Cohort B - Hospitalized

1. To evaluate the safety and tolerability of immediate treatment with peginterferon-lambda 180 mcg in patients hospitalized with moderate COVID-19 admitted to hospital.
2. To compare the time until the first negative mid-turbinate swab for SARS-CoV-2 RNA by day 28 in those treated with peginterferon lambda 180 mcg on Days 0 and 5 vs. those receiving placebo.

7.3 Study Populations

The study population will include 2 cohorts and will follow an adaptive design with initial safety data in Cohort A guiding the initiation of Cohort B.

7.4 Study Design

Cohort A – Ambulatory

Individuals who are seen at the assessment centre who are swabbed for possible COVID-19 and deemed well enough for home isolation will be informed about the study. They will be provided with contact information for the study team (email and phone number) and will contact the study team if interested in learning more about the study. Interested participants who contact study staff will be confirmed to be COVID-19 positive by research staff as soon as results are available (turnaround time ~12 hours) and if confirmed will be further screened for eligibility criteria by research study staff. Providers caring for patients with COVID-19 may refer patients to the study after obtaining verbal consent for sharing of contact information with the study time. The study team will contact referred patients by phone to describe the study and assess eligibility. After review, a consent form will be emailed to the participant and informed consent will be obtained

(see 'Consent Process') though witnessed telephone consent. Consenting individuals will be provided with instructions for follow-up. Participants who consent will come to the outpatient office and be randomized to receive a single dose of peginterferon lambda 180µg SC or placebo (see 'Study Procedures').

Cohort B – Hospitalized
Patients with confirmed SARS-CoV-2 infection admitted to hospital will be screened for inclusion and exclusion criteria and if eligible will be offered study enrolment. Written informed consent will be obtained (see 'Consent Process'). Consenting eligible patients will be randomized to receive peginterferon lambda 180µg SC or placebo and a second dose on day 5.

Study procedures, eligibility criteria and outcomes will be described for the 2 cohorts separately.

8.0 Study Medication

8.1 Peginterferon lambda overview

- Administered subcutaneously in the lower abdomen

- Dose 180 µg SC weekly (in ambulatory arm of the study only 1 dose is given, which may last up to 1 week)

- Composition: according to the manufacturer's specifications.

- Expiry date: mentioned on the label or package.

8.2 Composition: Peginterferon lambda Injection is a sterile, nonpyrogenic, ready-to-use solution (0.4 mg/mL) that is clear to opalescent, colorless to pale yellow, and essentially free of particles. Lambda Injection is provided in a 1-mL long Type I glass syringe (0.18 mg/syringe) with a staked 29-gauge, 1/2- inch, thin-walled needle. The syringe has a rigid needle shield and is stoppered with a plunger stopper. Syringes are prefilled with a solution of Peginterferon lambda Injection, mannitol, L-histidine, polysorbate 80, hydrochloric acid, and water for injection; they are intended for a single use at adjustable doses. The syringe is marked with dose indicator lines, which are used as a reference point for administering the correct dose.

The coordinator will expel the air bubble from the syringe and set the dose by aligning the front edge of the stopper with the correct dose indicator line. A sufficient overfill is included in each syringe for needle/syringe, dose adjustment, and bubble expulsion losses, leaving a sufficient amount of Peginterferon lambda Injection for delivery of up to 180 µg. Peginterferon lambda Injection should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from long-term (> 24 hours) exposure to light. Peginterferon lambda injection should not be frozen.

8.3 Use

Peginterferon lambda is currently not approved for clinical use in Canada. Eiger BioPharmaceuticals, Inc (manufacturer) is providing the drug for study purposes. The syringes will be covered and dispensed from the study pharmacy at UHN to the participating hospitals and offsite clinic.

8.4 Mechanism of Action

- Peginterferon lambda is a covalent conjugate of human recombinant non-pegylated IFN lambda (IFN L) and a 20-kDa linear PEG chain.

- Peginterferon lambda binds to the interferon lambda receptor expressed on epithelial cells in the lung, intestine, liver and skin and activates a signaling pathway leading to the production of a variety of genes with antiviral and anti-proliferative effects, collectively known as interferon-stimulated genes (ISGs).

8.5 Contraindications

- Hypersensitivity to peginterferon lambda

8.6 Summary

As of 11-May-2018, approximately 3,743 subjects (including 237 healthy subjects; 3,276 subjects with HCV; and 197 subjects with HBV; and 33 subjects with HDV) have received peginterferon lambda or comparator in 19 Phase 1, 2, or 3 studies.

Identified risks associated with treatment with peginterferon lambda based on nonclinical and/or clinical data, as well as potential class effects, include hepatobiliary toxicity (transaminase elevations with or without hyperbilirubinemia) and injection site reactions. Potential risks include neuropsychiatric disorders (including depression), cardiovascular events, immunogenicity/hypersensitivity reactions, autoimmune disorders, elevated amylase/lipase, dermatitis, reproductive risk, and pediatric growth inhibition. Overall, peginterferon lambda was well tolerated at single SC doses of up to 5 µg/kg and multiple SC doses of up to 180 µg administered weekly for 48 weeks. The primary safety finding observed has been dose-dependent and reversible elevations in serum transaminases, with the majority of events observed across studies in the highest (240 µg) dose group, which were accompanied, in some cases, by increases in total and conjugated (direct) bilirubin. The dose of 240 µg has been discontinued from further development. Increases in total and direct bilirubin have also been noted with doses of 180 µg that may be accompanied by mild increases in transaminases. These increases were not accompanied by evidence of loss of synthetic function of the liver and were readily reversible with dose withholding and/or dose reduction. Currently available data from peginterferon lambda clinical

studies indicate that cirrhotic patients with portal hypertension are at greater risk for hepatic decompensation.

8.7 Special Populations

Renal Impairment: The PK of peginterferon lambda in subjects with normal renal function or impaired renal function (IR) was measured in a total of 43 subjects (age 18–75 years, BMI 18–35 kg m–2) enrolled into one of 5 renal function groups: normal (n = 12), mild RI (n = 8), moderate RI (n = 8), severe RI (n = 7), end-stage renal disease (ESRD, n = 8 (Study AI452019, Hruska 2015). Subjects received a single dose of peginterferon lambda (180 µg) subcutaneously on day 1 followed by PK serum sample collections through day 29. Safety, tolerability and immunogenicity data were collected through day 43. PK parameters were estimated and summarized by group. Geometric mean ratios (GMR) and 90% confidence intervals (CIs) were calculated between normal and RI groups. With decreasing eGFR, peginterferon lambda exposure (Cmax, AUC) increased while apparent clearance (CL/F) and apparent volume of distribution (V/F) decreased. Relative to subjects with normal renal function (geometric mean AUC= 99.5 ng ml–1 h), peginterferon lambda exposure estimates (AUC) were slightly increased in the mild RI group (geometric mean [90% CI]: 1.20 [0.82, 1.77]) and greater in the moderate (1.95 [1.35, 2.83]), severe RI (1.95 [1.30, 2.93]) and ESRD (1.88 [1.30, 2.73]) groups. Peginterferon lambda was generally well tolerated.

In conclusion, the data show that following single dose peginterferon lambda administration, mild renal impairment appears to slightly increase exposure, but may not be clinically significant, while subjects with moderate and severe renal insufficiency and ESRD had approximately two-fold increases in exposures. These results suggest that subjects with mild renal impairment could use the same dosing regimen as subjects with normal renal function.
Similar to the other pegylated interferons, patients with moderate to severe renal impairment and ESRD most likely would require dose modifications of peginterferon lambda.

Hepatic Insufficiency: No data are available for comparative PK in subjects with hepatic insufficiency.

8.8 Drug-Drug Interactions: The effect of a single dose of peginterferon lambda on a cocktail of CYP substrates was assessed in healthy subjects. The activity of select CYP enzymes were evaluated using the following probe substrates: caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A4). Subjects received the cocktail on Day 1 followed by PK sample collection for 5 days; the subjects then received a single dose of peginterferon lambda 180 µg on Day 8, followed by a second dose of the cocktail on Day 15 with subsequent PK sample collection for 5 days. Peginterferon lambda increased the AUC of the probe drugs as follows: caffeine ~73%, warfarin ~40%, omeprazole ~2-fold, dextromethorphan ~2- fold, and midazolam ~75%. These results suggest that following a single 180µg dose, peginterferon lambda is a mild inhibitor of CYP1A2, CYP2C9, and CYP3A4

and a moderate inhibitor of CYP2C19 and CYP2D6. Because the effects on these sensitive CYP substrates are mild or moderate, dose adjustments for other concomitant CYP substrates may not be necessary, but such agents should be used with caution. Given that only a single or two doses will be used in this trial, concern about drug interactions is limited compared to other settings in which peginterferon lambda is given weekly for long durations.

8.9 Clinical Trial Data

Clinical Activity in Chronic HCV and HBV Infection

The clinical activity of peginterferon lambda in combinations with direct-acting anti-viral agents is summarized in Table 8 The antiviral activity of peginterferon lambda against HCV was demonstrated in 2 Phase 2 studies investigating peginterferon lambda regimens in treatment-naive subjects with chronic HCV. The regimens included peginterferon lambda/ribavirin (RBV) in EMERGE Phase 2a/2b (526H04, N = 624) and peginterferon lambda/RBV/DCV (daclatasvir) and Lambda/RBV/ASV (asunaprevir) in D-LITE (AI452008, N = 140). Initial doses tested in the Phase 2a/2b study EMERGE were 80, 120, 180 or 240 µg per week for 24 weeks (GT 2/4) or 48 weeks (GT 1/4). Pharmacodynamic modeling to derive the optimal dose and duration of peginterferon lambda treatment for Phase 3 studies has been described in 2 publications (Wang 2014, Hruska 2014). Wang et al (2014) derived a population model of peginterferon lambda exposure; adapting a previously published viral dynamic model for peginterferon lambda treatment and host genotype and using it to simulate sustained virologic responses (SVR). peginterferon lambda population pharmacokinetics were described by a one compartment model with first-order absorption, and 33.0 L per day clearance with 47% interindividual (36% intra-individual) variability. Weight explained a negligible proportion of the variability. Based on SVR predictions, optimum treatment durations were 48 weeks for HCV genotypes 1 or 4 (SVR estimates for 120, 180, and 240 µg peginterferon lambda: 58%, 54%, 47%, respectively) and 24 weeks for genotypes 2 or 3 (75%, 72%, 67%). SVR predictions for 240 mg were lower due to dropout predictions. The SVR model established the optimum treatment duration for Phase 3 studies but did not differentiate between 120 and 180 mg dosing. Hruska et al (2014) described the derivation of regression models for 12-week on-treatment virologic response and safety outcomes at 120, 180, and 240 µg peginterferon lambda with ribavirin. In patients with HCV genotypes 1 or 4, there was a significant (P=0.024) relationship between undetectable HCV-RNA at Week 4 and peginterferon lambda exposure (AUC or Cmax), with the largest difference between adjacent dose levels between the 180 and 120 µg exposure ranges. The risk of Grade 3-4 aminotransferase or bilirubin elevations relative to a peginterferon alfa-2a/ribavirin control were related to peginterferon lambda exposure for all patients, and the largest increase between adjacent dose levels was seen for 240 versus 180 µg. Anemia and neutropenia events were lower than control across all doses and exposures.

Based on these finding, the Phase 3 studies for HCV were designed to evaluate fixed 180 µg doses of peginterferon lambda in combination with ribavirin and a direct-acting antiviral for 24–48 weeks in HCV genotypes 1 or 4 or 12–24 weeks in genotypes 2 or 3.

The antiviral activity of peginterferon lambda as a monotherapy against HBV was investigated in 1 dose-ranging study in IFN-naïve patients (LIRA-B). Initial treatment groups received weekly peginterferon lambda 180 µg or 240 µg, or IFN-alfa at 180 µg for 48 weeks. The 240 µg dose was discontinued for development during the study and only 13 patients received this dose. The primary endpoint was HBeAg seroconversion at week 24. HBeAg seroconversion rates were comparable for peginterferon lambda and alfa at week 48 (17.5% vs. 16.9%, respectively); however, lambda non-inferiority was not met at week 24 posttreatment (13.8% vs. 30.1%, respectively; lambda vs. alfa 80% CI).

8.10 Summary of Safety

Peginterferon lambda has been generally well tolerated in clinical studies. A lower frequency of musculoskeletal (myalgia, arthralgia, and back pain) and flu-like symptoms (chills, pyrexia, and pain) was observed across Phase 2 studies in subjects receiving interferon regimens peginterferon lambda compared with alfa. In addition, there was a notable lack of hematologic toxicity in the WBC or platelet lineages in subjects receiving peginterferon lambda regimens.

Laboratory abnormalities have generally been of low grade and self-limited. When study regimens included concomitant RBV administration, decreases in hemoglobin levels were observed as expected; however, anemia was less frequent and milder with peginterferon lambda /RBV than with alfa/RBV. Hematologic toxicity was also reported less frequently in groups treated with Lambda compared with alfa.

The main safety finding associated with peginterferon lambda treatment has been the higher frequency of transaminase elevations, accompanied, in some cases, by increases in total and conjugated (direct) bilirubin, but without evidence for impaired liver synthetic function such as decreased albumin or increased INR. The hyperbilirubinemia cases resolved with no laboratory evidence of sustained hepatic dysfunction following dose reduction or discontinuation of study drug. In EIGLMD-001 study, the frequency of liver related SAEs (jaundice) was 7/15 (46.7%) at the Pakistan site compared to 0/18 (0.0%) at the other three sites, and 2.7% to the rate described in PEDESTAL study. Further evaluation of the potential pharmacogenomic or environmental basis for the higher frequency of these events in Pakistani patients is warranted. In one study, 3 cases of concurrent ALT and TBILI elevations in patients with HCV treated with peginterferon lambda/RBV/asunaprevir (ASV) met program-defined criteria for pDILI; this led to discontinuation of this regimen in future development plans. Frequencies of concurrent ALT/AST and TBILI elevations across studies were as follows: 18.2% for peginterferon lambda /RBV/ASV, 3.6% for peginterferon lambda/RBV, 2.3% for alfa-2a/RBV/ASV, and 3.5% for alfa-2a/RBV. In another study in patients with HBV, 4 subjects (5.0%) in the peginterferon lambda 180-µg group and 1 subject (7.7%) in the 240 µg group, and 1 subject (1.2%) in the alfa group met the laboratory criteria for pDILI. In 5 of the 6 cases, an alternative explanation (early, on-treatment, host-mediated ALT flare) was identified. In vitro data did not suggest a hypothesis-driven metabolism- or transporter-related rationale for the clinically observed differences in rates of

hyperbilirubinemia between subjects treated with alfa-2a or peginterferon lambda, but retrospective analysis of safety data from the EMERGE study (Zwirtes 2016) found that hyperbilirubinemia events occurred within the first 12 weeks of treatment, and the temporal pattern of mean total bilirubin level in the Alfa/RBV group was similar to that observed in the peginterferon lambda 120 and 180 mg groups (although with lower quantitative values for Alfa), suggesting a similar underlying mechanism of hyperbilirubinemia, probably RBV-induced hemolysis, for peginterferon lambda and Alfa treatments during the first 4–6 weeks of therapy. For the peginterferon lambda 240 mg group, however, a second peak occurred after week 12 suggesting additional reasons for increases in bilirubin levels, probably as a result of direct toxicity to hepatocytes with that dose.

Decompensation of cirrhosis has been observed with peginterferon lambda, as with alfa interferons. A total of 4 cases have been reported. One subject with baseline cirrhosis and Gilbert's disease developed Grade 1 hepatic decompensation and ascites while receiving peginterferon lambda 120 μg in the EMERGE Phase 2b study. The events resolved with drug interruption, and the subject subsequently resumed therapy at a lower dose. In the Phase 3 study (AI452017) in GT-2, -3 HCV-infected subjects, 3 of approximately 70 randomized subjects with pre-existing compensated cirrhosis developed decompensated cirrhosis while on treatment with peginterferon lambda. All 3 subjects were Child-Pugh Class A at entry and had evidence of portal hypertension. Two of these subjects subsequently recovered; however, 1 subject died of infectious complications. No cases of acute liver failure or hepatic decompensation in the absence of pre-existing cirrhosis with portal hypertension have been reported with use of peginterferon lambda. Based on these data, peginterferon lambda appears to be associated with decompensation of cirrhosis especially in the context of portal hypertension. Enrollment of cirrhotic subjects in current studies is restricted to compensated cirrhotic subjects (Child-Pugh Class A) without evidence of portal hypertension.

Prior studies of peginterferon lambda included patients with ALT values up to 5 times the upper limit of normal (HCV) and 10 times the upper limit of normal (HBV) and excluded patients with evidence of cirrhosis and with current or past hepatic decompensation.

In analyses of the cardiac effects of peginterferon lambda, no evidence of a clinically meaningful impact on QT/QTc interval or other key ECG parameters was detected in 32 healthy subjects given a single dose of peginterferon lambda 80 to 240 μg or in 176 patients with HBV treated with peginterferon lambda 180 μg for 24 weeks. A slight increase in mean ΔQTcF was seen in the HBV patients. Peginterferon lambda was not associated with AEs of ventricular arrhythmias or QT/QTc prolongation.

8.11 Pregnancy

Reproductive Risk Potential
Peginterferon lambda has not been tested in pregnant or lactating women; however, in the embryo-fetal development study in pregnant mice, peginterferon lambda was determined to be a selective developmental toxicant with increased embryo mortality when administered at ≥ 0.02 mg/kg/day (maternal AUC0-24h = 0.232 µg×h/mL) during the period of organogenesis. There was no identified maternal toxicity. The NOAEL for female reproductive toxicity was 0.01 mg/kg/day (AUC0-24 h = 18 ng×h/mL), which is approximately 0.9′ the maximum AUC of 143 ng×h/mL in humans following a weekly dose of 180 µg peginterferon lambda.

Female subjects should not be pregnant or lactating at the time of exposure to peginterferon-lambda. Female and male subjects should use appropriate measures to avoid pregnancy during the administration of peginterferon lambda and for up to 3 months after the last dose of peginterferon lambda.

8.12 Placebo
The placebo will be 0.9% sodium chloride (normal saline) solution. A plastic 1 mL syringe will be prefilled by the study pharmacy. Each syringe will contain 0.5 mL (0.45 mL to match the volume of the Interferon plus 0.05 mL overfill) to allow for needle priming by the unblinded study nurse.

The syringes will be stored in a refrigerator at 2 to 8 degrees Celsius (36 to 46 Fahrenheit) after preparation and should not be frozen. The study nurse will attach a staked 25-gauge needle and needle shield at the time of administration. It will be handled and administered by the study coordinator in a fashion analogous to Peginterferon lambda injection.

9.0 A. Cohort A – Ambulatory

9. 1 Inclusion/Exclusion Criteria

Inclusion Criteria
1. Adult patients between the ages of 18 and 75 years.
2. Confirmed COVID-19 infection by PCR within 7 days of symptom onset (fever, respiratory symptoms, sore throat).
3. Discharged to home isolation.
4. Willing and able to sign informed consent.
5. Willing and able to follow-up by daily phone or videoconference.
6. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication. Female patients of childbearing potential are

all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least 1 year postmenopausal. Adequate methods of contraception are:

a. For female patients
    i. Hormonal contraceptives including progestogen injection (eg, Depo-Provera®), combined oral contraceptive pill or vaginal ring for ≥ 3 months before screening AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
    ii. Intrauterine device (IUD) or intrauterine system (IUS) in place ≥ 3 months before screening AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
    iii. Surgical sterilization of the partner (vasectomy ≥ 1 month before screening) AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
    iv. Double-barrier methods (use of condom [male partner] with either diaphragm with spermicide or cervical cap with spermicide) from screening.
b. For male patients
    i. Surgical sterilization (vasectomy ≥ 1 month before screening) AND a barrier method (use of condom or diaphragm with spermicide or cervical cap with spermicide) from screening, or
    ii. Consistently and correctly use a condom from screening AND female partner must agree to use a hormonal contraceptive, a nonhormonal nonbarrier method (eg, copper IUD), or a nonhormonal barrier method (eg, diaphragm with spermicide or cervical cap with spermicide).

Exclusion Criteria

1. Requirement for hospital admission
2. Current immunosuppression due to medication (steroids, biologics, chemotherapy) or underlying condition such as organ/bone marrow transplant or untreated HIV or HIV infection with detectable HIV RNA and/or CD4 count of <500.
3. Pregnancy (or positive urine pregnancy test) or lactating
4. The following pre-existing medical conditions:
    a. Known seizure disorder
    b. Known retinal disease requiring therapy
    c. Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (rheumatoid arthritis, lupus, inflammatory bowel disease)
    d. Known history of chronic obstructive pulmonary disease (COPD) or asthma associated with functional impairment
    e. Known cirrhosis with any history of decompensation (ascites, variceal bleeding or hepatic encephalopathy)

f. Known chronic kidney disease with estimated creatinine clearance < 50 mL/minute or need for dialysis
g. Severe psychiatric disorder – schizophrenia, bipolar disorder, depression with prior suicidality
h. Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of peginterferon lambda

5. Advanced cancer or other illness with life expectancy of < 1 year
6. Known alcohol or drug dependence that in the opinion of the investigator would impair study participation
7. Known prior intolerance to interferon treatment
8. Enrolment in another clinical trial with use of any investigational agent in the prior 30 days
9. Use of off-label therapy for COVID-19

9.2 Study Procedures (Cohort A)

9.2.1 Consent Process

Individuals at the COVID-19 assessment centres or emergency departments will be provided with information related to the study through study recruitment materials (posters) and instructed to contact study staff by email or telephone if they are interested in study participation. The study will also be advertised on social media with contact information of the study team. Providers caring for patients with COVID-19 may also refer patients to the study after obtaining verbal consent to share contact information with the study team. Those interested in the study who contact or are contacted by study staff will be confirmed to be COVID-19 positive based on nasopharyngeal swab results and screened by study staff for other inclusion/exclusion criteria and will be provided a consent form electronically for review. The study coordinator will explain the rationale and the risks and benefits of the study. A sub-investigator/principal investigator will be available to answer any questions by phone. In addition to the consent to the trial, participants will be offered an additional optional consent for genetic testing (see 'Genetic Testing') and a second optional consent for collection of peripheral blood mononuclear cells (PBMCs) (see 'PBMCs'). In keeping with REB adapted consenting process, the study coordinator will read the consent form verbatim while the patient reads along. When the patient consents, the study coordinator will sign his/her copy of the document and this will be witnessed and signed by an impartial witness. This document will stay in the patient's study file. Upon coming to the clinic, the study team will provide the patient a paper copy to keep and not return to the study team. Those with a positive test for SARS-CoV-2 and who meet all inclusion/exclusion criteria and have signed consent will be asked to come to the outpatient office at a designated time (see 'Standard Operating Procedures for Outpatient Visits').

9.2.2 Enrolment and randomization

Those who test positive will be invited to attend the outpatient clinic for completion of screening, enrolment and randomization (see Standard Operating Procedures for Clinic Visits). Consenting individuals will undergo a medical history including current medication use and complete a symptom survey to be recorded on the Baseline Case Report Form (Appendix A). Women of

childbearing potential will take a urine pregnancy test to confirm eligibility. Female participants who are concerned they may be pregnant will not be enrolled even if the test is negative (in case it is too early for a positive result). Female and male subjects will be advised to use appropriate measures to avoid pregnancy during the week following administration of peginterferon lambda and for up to 3 months after the dose of peginterferon lambda.

Vital signs, including blood pressure, temperature, pulse, respiratory rate and oxygen saturation in ambient air will be recorded. The eligibility checklist will be reviewed by a site sub-investigator/principal investigator and if deemed to be necessary, a history and physical examination will be performed by the sub-I/PI. Potential participants meeting all inclusion and no exclusion criteria will be offered study enrolment. Eligible participants will have blood drawn for routine laboratory (CBC, creatinine, liver profile) and inflammatory markers (LDH, ferritin, D-Dimers, c-reactive protein, amylase), a research sample for plasma to be stored for future use, as well as optional blood for genetic and PBMC sub-studies for those who consent. The genetic and/or PBMC sample will replace the research plasma sample, as plasma can be used after PBMC isolation or preparation for extraction of genetic material. Patients will also provide a baseline saliva sample and self-collected mid-turbinate nasal swab.

Randomization will be centralized at TCLD (at UHN) and eligible patients included in the study will be assigned to one of the 2 treatment arms according to a standard computer-generated randomization schedule 1:1 in blocks of 4, stratified by site.

To randomize a subject into the study, after completion of the above procedures, the coordinator will send the completed eligibility checklist to the TCLD (at UHN) by e-mail/fax. Once reviewed and approved by the PI or designate sub-I, the coordinator will be contacted by SMS to randomize the patient. Numbered opaque envelopes with treatment arm allocation will be stored at the outpatient site. Upon instruction to randomize from the PI or designate sub-I, the coordinator will open the envelope to reveal the treatment allocation. The study ID, month and year of birth and initials will be recorded on the randomization form as a unique identifier and emailed/faxed to the TCLD. The treatment codes will be maintained by the trial statistician in a password-protected file which cannot be accessed by other study personnel or subjects. In future study materials and analyses, the subject will be referred to only by the study identification number.

9.2.3 Study Interventions (See Schedule of Events – Ambulatory)

Those randomized to the peginterferon lambda arm will receive a single SC injection in the lower abdomen of peginterferon lambda 180µg and those randomized to placebo will receive a single SC injection of saline (and this will count as Day 0 of the study for the Schedule of Events). After the injection, participants will be observed for 30 minutes to ensure there are no immediate complications from the medication. After 30 minutes of observation, participants will be discharged. Prior to discharge, patients in both arms will be taught self-collection technique of mid-turbinate nasal swabs and how to properly collect saliva specimens with observation by the coordinator of a collection of each specimen. Participants will be provided with 5 additional swabs for mid-turbinate nasal swabs and 5 sterile specimen containers (see 'Nasal Swabs and Saliva Collection') to be collected by self-collection as well as a sealable cooler for home swab storage until collection. The coordinator will confirm contact information for the participant with the number of an emergency contact as well, and the participants will be provided with the contact

information to reach the study team. A detailed daily schedule for follow-up will be provided to the participant. If participants do not own a digital thermometer, they will be given one by the study team.

After discharge, participants will follow the standard-of-care advice given to all individuals with presumed/confirmed COVID-19 at the Assessment Centre/ER. Participants will return home and remain in home isolation for at minimum 14 days from symptom onset according to current Toronto Public Health recommendations. The exception to home isolation will be for study visits, as permitted by Public Health (for example, people with COVID-19 may attend medical appointments provided proper precautions are taken including wearing a mask at all times).

A study coordinator will contact the participant by phone/videoconference 4-6 hours post-injection to record symptoms and potential adverse events (AEs) related to the treatment because of the known early side effects reported in previous trials with initial dosing of peginterferon lambda[6]. Symptoms/AEs will be recorded using the Symptom Assessment form (below) - the questions will be asked by the study coordinator and recorded in REDCap.

Participants will be contacted at a pre-specified time on days 1, 2, 3, 5, 7, 10 and 14 by a study coordinator by phone/videoconference to review the same symptom and AE survey, concomitant medications and to record the digital oral temperature. During the call, results will be recorded onto case report forms by the study coordinator and entered into the secure REDCap electronic case report form (eCRF) database. Participants will collect a mid-turbinate nasal swab and saliva specimen on Days 1 and 2 after speaking to the study coordinator and, wherever possible, collection will be observed by the study coordinator using videoconferencing (see 'Nasal Swabs and Saliva Collection'). The viral media with the swab and the sterile specimen containers will be stored in a plastic container inside a cooler that will be provided to the participant and stored until collection.

On Day 3, the participant will return to the outpatient clinic for symptom, AE, concomitant medications and temperature recording. The participant will bring the self-collected nasal swabs and saliva specimens to the clinic in the sealed cooler following the written instructions for transport (see 'Nasal Swabs and Saliva Collection'). During the visit, the participant will self-collect a mid-turbinate nasal swab and the study coordinator will perform a nasopharyngeal swab as well as collect a saliva specimen. Blood will be drawn for routine laboratory and inflammatory markers, a research sample to be stored for future use and additional samples for those who consented to PBMC collection. The coordinator will bring the Day 3 swabs as well as the stored swabs from Days 1 and 2 and return them to the Mount Sinai Hospital Microbiology laboratory (T. Mazzulli) for processing. The samples will be labeled and transported in 2 sealed clean biospecimen bags inside a sealed plastic container, in line with Infection Protection and Control recommendations.

On Day 5, a coordinator will contact the participant by phone/videoconference for symptom, AE, concomitant medications and temperature recording. A self-collected mid-turbinate nasal swab and saliva specimen will be taken and stored as above.

On Day 7, the participant will return to the outpatient clinic and similar to the Day 3 visit, a self-

collected mid-turbinate nasal swab, a coordinator-collected nasopharyngeal swab and a saliva specimen will be collected. Blood will be drawn for routine laboratory and inflammatory markers, a research sample to be stored for future use and additional samples for those who consented to PBMC collection.

On Days 10, a coordinator will contact the participant by phone/videoconference for symptom, AE, concomitant medications and temperature recording. Self-collected mid-turbinate nasal swabs and saliva specimens will be collected on Days 10 and stored as above.

On Day 14, the participant will return to the outpatient clinic and similar to the Day 3 visit, a self-collected mid-turbinate nasal swab, a coordinator-collected nasopharyngeal swab and a saliva specimen will be collected. Blood will be drawn for routine laboratory and inflammatory markers, a research sample to be stored for future use and additional samples for those who consented to PBMC collection.

On Day 90+ (up to one year), participants who consented to a final symptom survey and PBMC collection (even if they did not consent to PBMC collection during the treatment phase of the study) will return to the outpatient clinic for a final blood draw and to complete the symptom survey. Up to 8 tubes of blood will be collected.

For participants who cannot travel to the clinic, the option of home visits by the study team will be discussed for the Day 3, 7, 14 and 90+ visits (See 'Home Visits').

9.2.4 Nasal Swabs and Saliva Collection

The rationale for self-collection of mid-turbinate nasal swabs and saliva is to allow for more frequent sampling to determine the time of viral clearance and quantitative viral kinetics. Understanding how quickly individuals clear SARS-CoV-2 is very important for determining when people could potentially return to work/public. It is possible that peginterferon lambda will be highly effective and lead to rapid clearance, which can only be recognized if frequent early sampling is conducted. In addition, viral kinetics using quantitative PCR may provide insights into the mechanisms of clearance, as has been successfully done with other viral infections[14,15]. A previous study done by our group has shown that mid-turbinate nasal swabs can be reliably self-collected with only marginally lower sensitivity (69/71 91% concordance) for influenza, rhinovirus and respiratory syncytial virus detection than standard nasopharyngeal swab[16]. Because nasopharyngeal swabs are considered the gold standard for SARS-CoV-2 diagnosis, we will collect these on days 3, 7 and 14 for the primary (day 7) and key secondary (day 3 and 14) endpoints. Self-collection of nasopharyngeal swabs is not feasible[16]. To directly compare the methods for SARS-CoV-2 recovery, on Day 3, 7 and 14, a self-collected mid-turbinate nasal swab, a coordinator-collected nasopharyngeal swab and saliva will be tested.

Detecting SARS-CoV-2 using saliva specimens may be equivalent to detection rates of nasopharyngeal swab early in the course of the disease. Our group has recently shown that by day 14 of symptom onset saliva specimens were positive in 17/24 individuals with COVID-19 as compared to 18/24 by nasopharyngeal swab (Jamal A et al, unpublished data). A preprint report from Wyllie et al at Yale found that saliva was actually marginally superior to nasopharyngeal swab with higher sensitivity and higher SARS CoV-2 RNA levels on a quantitative assay from

samples taken on the same day[17]. Additional benefits from using saliva for SARS-CoV-2 detection includes the ease of self-collection while lowering potential patient discomfort and, more importantly, a microbiological swab is not required, which are currently in limited supply during the COVID-19 pandemic.

Participants will be instructed and observed at the first visit on the collection of mid-turbinate nasal swabs and saliva and if possible, the subsequent self-collection samples will be observed by the coordinator during the daily videoconferencing visits. Participants will be given written instructions on how to store the swabs and saliva. After putting the swab into the viral culture media, the swab will be placed into two clear biohazard bags inside the provided sealed cooler. Saliva will be collected in sterile collection containers and placed into two clear biohazard bags inside the provided sealed cooler. At the day 3, 7 and 14 clinic visits, the participant will place the cooler into 2 provided clear biohazard bags and bring the bags to the clinic. Upon receipt of the bags in the clinic, the outer bag will be decontaminated and then the specimens will be taken to Toronto General Hospital for storage at -80C in the laboratory of the PI (J Feld). PCR for SARS-CoV-2 will be performed in the future when there is no longer concern for reagent use at the microbiology laboratory.

9.2.5 Home Visits

For participants unable to travel to clinic visits, home visits by study staff will be provided as an alternative, provided participants live within a 30-minute drive of the site from which they were recruited and are agreeable to having study staff visit their home. Prior to home visits, study staff will review and follow UHN standard operating procedures for 'Working safely while alone at KITE or Offsite' (SOP Number: SRRL0008 version 3.0). They will also complete the UHN Occupational Health and Safety ***Off-Site Work PRE-VISIT ASSESSMENT CHECKLIST*** for each specific visit and review with the PI to determine if risks to staff safety have been identified. If risks cannot be mitigated, the visit will not be undertaken and will be recorded as a missed visit in the trial documents. If the staff member and PI agree with proceeding with the visit, the precautions outlined will be taken to ensure staff safety including: maintain and provide schedule of visits to PI/site PI, verbally check in and check out with PI/site PI, wear a hospital identification at all times during the visit as required by UHN, ensure that cellular phone is charged for the home visit. Staff will be advised not continue a home visit if situations and/or conditions become unsafe and to report all work related incidents immediately to the PI/site PI and submit an online Employee Incident Report (EIR) within 24 hours. For home visits, the study coordinator will drive to the participant home at an agreed up pre-specified time. Upon arrival, the coordinator will call the participant as notification. The coordinator will don personal protective equipment (mask, gown, gloves and face shield) and enter the home to carry out the study visit. Upon completion of the study visit, the coordinator will doff personal protective equipment and place it in a clear plastic bag. It will then be transported back to the hospital/clinic for appropriate disposal.

9.2.6 Household contacts

For participants with household contacts, the coordinator will ask the participant to report a confirmed diagnosis of COVID-19 in any household contacts. Participants will be contacted at Days 14 and 30 to specifically ask if any household contacts have been diagnosed with COVID-19.

9.2.7 Participant Compensation

Participants will be reimbursed $50 CAD for each of the study clinic visits (Day 0, 3, 7 and 14) for transportation and parking expenses. For the day 90+ visit, participants will be reimbursed $100 for their time and costs associated with the visit. Any extra expenses incurred related to attending study visits will be paid upon invoice.

9.2.8 Standard Operating Procedures for Clinic Visits

To ensure that clinic visits are carried out safely minimizing exposure to the public and study staff, the following procedures will be followed. Participants will be provided with hospital masks for themselves and their chauffeurs (if applicable) to be worn during travel to and from the clinic. Participants will be encouraged to attend clinic visits by car, if possible. If arriving by car, a parking spot outside the clinic will be reserved in advance. Upon arrival, the participant will call the study coordinator from the car. The coordinator will advise the participant when to come into the clinic. Entry will only occur when there are no other study participants or other individuals in the pharmacy to avoid interaction between infected and potentially uninfected individuals. Upon entry into the clinic, the participant will perform hand hygiene (hand sanitizer) and the study staff in appropriate personal protective equipment will guide the participant to one of the clinic rooms where the participant will wait to be seen. For participants who are unable to drive to clinic visits, a chauffeur will be arranged (and costs covered through taxi chit or mailed reimbursement) by the study team. The chauffeur/taxi company will be informed that the individual is known to have COVID-19 and the individual driver will be informed of this prior to the trip. A surgical mask will be provided for the driver. The participant will wear a mask during the drive to and from the clinic visits. The study staff will wipe the seat of the taxi with disinfectant after the participant leaves the car.

The study staff will wear masks, gloves, gowns and face shields for all visits and will follow directions of Infection Protection and Control from UHN in the event that guidance changes. (https://intranet.remote.uhn.ca/cvpn/tlJTnOjlDlsJLjHQDzsvAj6HOjg8ig/departments/infection_control/covid-19/IPAC.asp).

9.2.9 Safety Assessment

Peginterferon lambda has been given to >3,000 patients with chronic viral hepatitis for up to 48 weeks duration without major safety concerns, however, it has not been used in COVID-19 previously. We do not expect major safety concerns however, we will follow patients in the ambulatory arm closely to document adverse events during treatment. Blood work will be collected prior to the peginterferon lambda injection but will not be used to determine eligibility in the ambulatory cohort. Hepatotoxicity has been noted in studies of peginterferon lambda in patients with chronic viral hepatitis. Transaminase elevations were reported, and hepatic decompensation has been reported but only in people with a prior history of decompensation prior to dosing. The study team has extensive experience managing patients with underlying liver disease (3 investigators are hepatologists) and multiple investigators have experience with peginterferon lambda use as well. If baseline laboratory results are suggestive of cirrhosis (unlikely), patients will be informed of this and followed carefully for signs of hepatic

decompensation (ascites, hepatic encephalopathy, variceal hemorrhage) during follow-up, with prompt referral to the hospital should these signs/symptoms occur.

The most relevant other concern would be unrecognized renal impairment. Dosing advice is unclear for patients with estimated glomerular filtration rate (eGFR) below 50 mL/min. Participants found to have a reduced eGFR (<50 mL/min) after dosing will be advised of the test result and the need for follow-up. The consequences of dosing during renal impairment are not well understood but may lead to increased concentrations of systemic interferon lambda. Participants will be followed virtually frequently with in-person visits at day 3, 7 and 14 with repeat blood tests on those days. Those with unexpected renal impairment will be followed according to the standard follow-up in the protocol, however, additional investigations may be performed at the discretion of the treating physician.

9.3 Outcomes (Cohort A)

Primary efficacy endpoint:

The proportion of participants with negative SARS-CoV-2 RNA on nasopharyngeal swab at day 7.

Primary safety endpoint:

Rate of treatment-emergent and treatment-related serious adverse events (SAEs)

Secondary Endpoints:

Clinical

1. Time to resolution of symptoms (fever, cough, diarrhea)
2. Change in symptom scores (respiratory, gastrointestinal, fever) from day 0 to day 7
3. Need for hospital admission by day 14
4. Adverse events and serious adverse events by day 14

Virologic/Immunological

5. Proportion negative for SARS-CoV-2 RNA by nasopharyngeal swab on day 3
6. Proportion negative for SARS-CoV-2 RNA by nasopharyngeal swab on day 14
7. Time to SARS-CoV-2 RNA negativity on mid-turbinate nasal swab or saliva
8. Proportion with SARS-CoV-2 RNA in blood at day 0 and 7
9. Proportion with SARS-CoV-2 antibodies in blood at day 0, 7 and 14
10. Correlation of response with interferon lambda 4 (IFNL4) genotype

11. Change in laboratory and inflammatory markers (hemoglobin, white blood cell count, lymphocyte count, liver profile, ferritin, lactate dehydrogenase, c-reactive protein, D-dimers, amylase) from day 0 to day 7 and day 7 to 14

Transmission

12. Confirmed diagnosis of COVID-19 in household contacts by day 30

9.4 Sample Size Calculation

Cohort A

Existing data from France and China were used to estimate the effect size. In a recent French study comparing chloroquine to no treatment, 2 of 16 (12.5%) untreated patients were SARS-CoV-2 negative at day 6[18]. Although no studies have been performed with peginterferon lambda a small Chinese study compared interferon-α alone or with chloroquine[19]. By day 7, 14 of 15 (94%) in the IFN-only arm were RNA negative. To be conservative, if we estimate a clearance rate of 40% by day 8 (equivalent to day 7 in the Chinese study) in the placebo arm and 80% in the peginterferon lambda arm, 23 patients are required in each arm for 80% power at alpha 0.05. With potential dropout of 20% due to either logistical problems or loss-to-follow-up, this translates to 30 patients per arm or 60 patients total across 3 sites (UHN, SMH, MGH).

Rationale for Primary Endpoint Selection

The primary endpoint for the study is the proportion of people with a negative nasopharyngeal swab for SARS-CoV-2 at Day 7. This endpoint was selected based on existing data about the natural history of SARS-CoV-2 infection and practical considerations. As noted above in the Sample Size calculations, in the untreated arm of the French chloroquine study by Gautret et al, 2 of 16 (12.5%) patients were SARS-CoV-2 negative at day 6 of follow-up. Similarly, in a study from China of 113 patients with COVID-19 of varying severity, the median time to viral clearance by nasopharyngeal swab was 17 (IQR 13-22) days, with approximately 20% clearing by day 12, 18% clearing by day 10 and 7% by day 7. Notably some patients received treatments in this study, but the data were not presented by treatment regimen making it difficult to discern the time to clearance with no treatment. Time to clearance was calculated from the time of symptom onset whereas in our study we will determine the proportion with negative nasopharyngeal swabs from 7 days after randomization. In our study, patients must be enrolled within 7 days of symptom onset, meaning for our placebo group, patients could be up to 14 days since symptom onset when they reach day 7 post-enrollment. Both studies would suggest that the probability of clearance by that point would be 12-20% and thus our estimate for the sample size calculation of 40% clearance is appropriately conservative. As noted, in patients treated with interferon alpha, ~90% had cleared by day 7, giving us confidence that our estimate of 80% clearance in the treatment arm is realistic.

In addition to the natural history, we took into account practical considerations as well. The purpose of treatment in the ambulatory arm in patients who do not require hospitalization is to

prevent progression of illness but also to accelerate viral clearance to reduce viral shedding and thus onwards transmission. If treatment does not lead to high rates of clearance by day 7, it is unlikely to be of significant clinical or practical value, as patients discharged are advised to remain in home isolation for 10-14 days depending on the jurisdiction. If treatment does not lead to clearance by day 7 in the vast majority of patients, it will be of questionable benefit. We are evaluating the earlier timepoints with self-collected mid-turbinate nasal swabs and saliva specimens (days 1, 2 and 3), and a coordinator-performed nasopharyngeal swab 3 days post-randomization to determine if patients may indeed clear much earlier than study day 7. Self-collected mid-turbinate nasal swabs and saliva specimens will also be collected after day 7 to determine the ultimate time to viral clearance in both groups. The collection of mid-turbinate nasal swabs and saliva specimens is described in detail in the study procedures.

10. B. Cohort B - Hospitalized

10.1 Safety Assessment

Prior to initiating screening for Cohort B, the Data Safety and Monitoring Committee (DSMC) will review data from Cohort A. They will review data after every 10 randomized participants Cohort A complete 7 days of follow-up until 50% of Cohort A has been recruited (n=30). After 50% of Cohort A has been enrolled and completed 7 days of follow-up, the DSMC will review all available safety data and will advise the steering committee whether Cohort A may continue enrolment and whether Cohort B may initiate enrolment (see DSMC). The DSMC will review data from Cohort B after 25% have enrolled and completed 14 days of follow-up and after 50% have enrolled and completed 14 days of follow-up.

Exclusion criteria were selected to ensure that patients with an increased risk of adverse events from peginterferon lambda use are excluded. These included comorbidities that may be worsened by peginterferon lambda and thresholds on screening blood tests. The threshold for transaminase elevation of 5 times the upper limit of normal was selected because of the frequency of liver enzyme elevation in patients with COVID-19. Two recent studies reported that liver enzyme elevation was common, occurring in 43% of 70, and 76% of 417, hospitalized individuals in China[20,21]. Most patients had mild enzyme elevations but 33 (10.4%) in the larger study had ALT above 3 times the upper limit of normal. Enzyme elevation was associated with a more severe disease course, but not with liver failure or hepatic decompensation[20]. Prior studies of peginterferon lambda in chronic viral hepatitis allowed patients with ALT values up to 5 times the upper limit of normal (HCV) and 10 times the upper limit of normal (HBV) with no cases of hepatic toxicity detected in the absence of current or past decompensated cirrhosis[6,7]. To avoid missing patients who may be at risk of more severe COVID-19 and thus might derive greater benefit of antiviral therapy, patients with ALT or AST values up to 5 times the upper limit of normal without a history of decompensated cirrhosis are eligible. Other laboratory values are in line with prior studies of peginterferon lambda.

10.2 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Adult patients over age 18
2. SARS-CoV-2 RNA-positive on nasopharyngeal swab/respiratory specimen within 10 days of symptom onset
3. Admitted to hospital for management of COVID-19
4. Willing and able to provide informed consent
5. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication. Female patients of childbearing potential are all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least 1 year postmenopausal. Adequate methods of contraception are:
    a. For female patients:
        i. Hormonal contraceptives including progestogen injection (eg, Depo-Provera®), combined oral contraceptive pill or vaginal ring for ≥ 3 months before screening AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
        ii. Intrauterine device (IUD) or intrauterine system (IUS) in place ≥ 3 months before screening AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
        iii. Surgical sterilization of the partner (vasectomy ≥ 1 month before screening) AND a barrier method (use of condom [male partner] or diaphragm with spermicide or cervical cap with spermicide) from screening, or
        iv. Double-barrier methods (use of condom [male partner] with either diaphragm with spermicide or cervical cap with spermicide) from screening.
    b. For male patients:
        i. Surgical sterilization (vasectomy ≥ 1 month before screening) AND a barrier method (use of condom or diaphragm with spermicide or cervical cap with spermicide) from screening, or
        ii. Consistently and correctly use a condom from screening AND female partner must agree to use a hormonal contraceptive, a nonhormonal nonbarrier method (eg, copper IUD), or a nonhormonal barrier method (eg, diaphragm with spermicide or cervical cap with spermicide).

Exclusion Criteria

1. Severity of illness
    a. Respiratory failure (requiring>6L O_2 or intubation in the ER)
    b. Shock – systolic BP<90 mmHg or mean arterial BP<60 mmHg after fluid resuscitation

2. Current immunosuppression due to medication (steroids, biologics, chemotherapy) or underlying condition such as organ/bone marrow transplant or untreated HIV or HIV infection with detectable HIV RNA and/or CD4 count of <500.
3. Pregnancy (or positive urine pregnancy test) or lactating
4. The following pre-existing medical conditions:
    a. Known seizure disorder
    b. Known retinal disease requiring therapy
    c. Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (rheumatoid arthritis, lupus, inflammatory bowel disease)
    d. Known cirrhosis with any history of decompensation (ascites, variceal bleeding or hepatic encephalopathy)
    e. Known chronic kidney disease with estimated creatinine clearance < 30 mL/minute or need for dialysis
    f. Severe psychiatric disorder – uncontrolled schizophrenia, bipolar disorder, depression with prior suicidality
    g. Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of peginterferon lambda
5. Known prior intolerance to interferon treatment
6. Enrolment in another clinical trial with use of an antiviral agent in the prior 30 days (co-enrollment with immunomodulatory agents permitted)
7. Use of off-label therapy for COVID-19
8. Any of the following abnormal laboratory indices
    a. Hemoglobin < 100 mg/dL
    b. Platelet count < 75,000 cells/mm^3
    c. Absolute neutrophil count < 1,000 cells/mm^3
    d. Estimated creatinine clearance < 30 cc/mL
    e. Total bilirubin > 2x upper limit of normal (ULN)
    f. Alanine aminotransferase (ALT) > 5x ULN
    g. Aspartate aminotransferase (AST) > 5x ULN
    h. Lipase or amylase > 2x ULN
    i. Random blood glucose > 20 mmol/L

10.3 Study Procedures (Cohort B)

10.3.1 Consent Process

Potential participants meeting all inclusion and no exclusion criteria will be offered study enrolment. The study coordinator will explain the rationale and the risks and benefits of the study. A study investigator will be available to answer any questions related to the study. In addition to the consent to the trial, participants will be offered an additional optional consent for genetic testing

(see 'Genetic Testing' below) and a second optional consent for collection of peripheral blood mononuclear cells (PBMCs) (see 'PBMCs' below). A study coordinator or other team member (except PI) will obtain written informed consent.

10.3.2 Enrolment and randomization

Consenting individuals will undergo a medical history, focused physical examination, complete a symptom survey and have blood drawn for routine laboratory and inflammatory markers (if not already performed as standard of care). Female participants of childbearing potential will have a blood pregnancy test (serum beta hCG). Female and male subjects will be advised to use appropriate measures to avoid pregnancy during the 2 weeks of administration of peginterferon lambda and for up to 3 months after the last dose of peginterferon lambda.

Vital signs, including blood pressure, temperature, pulse, respiratory rate and oxygen saturation in ambient air will be recorded. The eligibility checklist will be reviewed by a site sub-investigator/principal investigator and eligible participants will then be randomized 1:1 using centralized randomization in blocks of 4, stratified by country of site and sex, with numbered opaque envelopes to treatment or no treatment.

The participant's study ID, month and year of birth and initials will be recorded on the randomization form and emailed/faxed to the TCLD. The treatment codes will be maintained by the trial statistician in a password-protected file which cannot be accessed by other study personnel or subjects. In future study materials and analyses, the subject will be referred to by the study identification number.

10.3.3 Study Interventions (See Schedule of Events – Hospitalized)

On Day 0, those randomized to the peginterferon-lambda arm will receive a SC injection in the lower abdomen of peginterferon lambda 180µg and those randomized to the placebo arm will receive a SC injection of saline. Participants will be seen on each study day by a study team member to record symptoms, temperature and adverse events, which will be captured on a paper Case Report Form (CRF) before being entered into the REDCap database.

Standard-of-care laboratory results (hematology, chemistry, renal and liver profiles) will be collected at the frequency performed by the admitting team. If these laboratory tests are not performed more frequently by the admitting team, they will be done on days 3, 5 (prior to injection if Day 3 tests are abnormal), 7, 10 (if hospitalized), 14, 21, and 28. Inflammatory markers (ferritin, lactate dehydrogenase, D-Dimers, C reactive protein, amylase, troponin) will be measured on days 3, 7, 10 (if hospitalized), 14, 21, and 28; or more frequently if clinically indicated. A research sample will be collected at baseline and on days 3, 7, 14, 21, 28, and 90 (optional) from which serum will be extracted and stored at -80C for future use.

Self-collected mid-turbinate swabs will be collected daily from Days 0-7 then Day 10, 12, 14, 18,

21, 25, and 28.

On Day 5 (+/- one day), a second dose of peginterferon lambda 180µg SC or placebo (saline) will be given. Day 5 blood will only be collected for dosing eligibility if the dosing eligibility laboratory results from day 3 are abnormal. If all eligibility laboratory results from day 3 are in the normal range, dosing may proceed prior to obtaining Day 5 results. In those with abnormal Day 3 eligibility labs, Day 5 blood and swab should be collected prior to injection of peginterferon lambda or placebo. Results from Day 5 labs will be used to assess eligibility for the second dose with the same thresholds as used for the first dose. For participants with hematology values outside of the accepted thresholds, the second dose may be omitted, or the following dose reductions may be considered, with the final decision made by the investigator:

1. If Day 5 hemoglobin is < 100 mg/dL but ≥ 80 mg/dL, a half dose of peginterferon lambda (90 µg) or placebo (half volume) SC may be given. If Day 5 hemoglobin is < 80 mg/dL, the second dose must be omitted.

2. If the Day 5 platelet count is < 75,000 cells/mm^3 but ≥ 50,000 cells/mm^3, a half dose of peginterferon lambda (90 µg) or placebo (half volume) SC may be given. If the Day 5 platelet count is < 50,000 cells/mm^3, the second dose must be omitted.

3. If the Day 5 absolute neutrophil count is < 1,000 cells/mm^3 but ≥ 750 cells/mm^3, a half dose of peginterferon lambda (90 µg) or placebo (half volume) SC may be given. If the Day 5 absolute neutrophil count is < 750 cells/mm^3, the second dose must be omitted.

4. If the Day 5 creatinine clearance is < 50 but ≥ 30 cc/minute, a half dose of peginterferon lambda (90 µg) or placebo (half volume) SC may be given. If the Day 5 creatinine clearance is < 30 cc/minute, the second dose must be omitted.

If the second dose is omitted at Day 5, a full or reduced dose (half volume - 90 µg SC or half dose placebo) may be given if the laboratory parameters return to within the specified thresholds by Day 9 at the discretion of the investigator. If the laboratory values remain out of the specified ranges at Day 9, the second dose will be omitted. The second dose may be omitted at the discretion of the investigator for reasons other than laboratory value thresholds. If the dose is reduced or omitted, the reason for the change must be documented. For participants who have a dose reduction or dose omission, the primary and secondary endpoints will remain unchanged.

If participants are discharged by the medical team prior to Day 28, follow-up with calls on each study day by phone or videoconference will be arranged for symptom/AE collection, concomitant medications and temperature recording. Participants will be taught to self-collect mid-turbinate nasal swabs (see 'Nasal Swab Collection') and will be given enough swabs to collect a self-swab

for each day remaining in the study. An outpatient office visit will be arranged for collection of swabs and blood on day 3, 5, 7, 14, 21, and 28. Participants discharged before day 5, will receive the second dose of study medication at the day 5 outpatient visit with the same criteria used to determine eligibility for inpatient dosing. Participants will be called at day 21, 28 and 90 to record any persistent symptoms and any additional complications after study completion. All of these visits will have a window of +/- one day.

Participant Compensation
Participants in Cohort B will not receive financial compensation for study participation unless they are discharged before completion. If discharged with ambulatory follow-up, they will receive compensation following the schema for Cohort A.

10.4 Outcomes

Cohort B

Primary efficacy endpoint:

Clinical status on an ordinal scale at Day 14.

Primary safety endpoint:

The rate of treatment-emergent and treatment-related serious adverse events (SAEs)

Secondary Endpoints:

1. Clinical status on an ordinal scale at Day 7, 21 and 28
2. ICU admission during hospitalization
3. Need for intubation by day 14 and day 28
4. Length of hospital stay
5. Change in respiratory symptom on ordinal scale score day 0 to 7 and day 0 to 14 and 0 to 28
6. Readmission to hospital by day 28 and day 90
7. All-cause mortality at day 28 and day 90
8. COVID-19-related mortality at day 28
9. Adverse (AEs) and Serious Adverse Events (SAEs) by day 28
10. Frequency of dose reduction or dose omission for the second dose of peginterferon-lambda

Virologic/Immunological

18. Time to SARS-CoV-2 negativity
19. Proportion negative for SARS-CoV-2 RNA by mid-turbinate swab on days 0-7, 10, 12, 14, 18, 21, 25, 28

20. Change in quantitative SARS-CoV-2 RNA by mid-turbinate swab over time
21. Correlation of clinical and virologic response with interferon lambda 4 (IFNL4) genotype
22. Change in laboratory and inflammatory markers hemoglobin, white blood cell count, lymphocyte count, liver profile, ferritin, lactate dehydrogenase, c-reactive protein, D-dimers, amylase) from day 0 to day 7 and to day 14, 21, and 28
23. Proportion with SARS-CoV-2 antibody at day 7, 14, 21, and 28
24. Proportion with SARS-CoV-2 RNA in blood at day 0, 7 and 14, 21, and 28

10.5 Sample Size Calculation

The sample size was re-calculated based upon a change in the primary outcome to the score on an ordinal scale. Using the outcomes from the ORCHID trial evaluating the utility of hydroxychloroquine in hospitalized patients the following proportions at day 14 were identified; 6% died, 8% on invasive ventilation, 3% non-invasive ventilation or high-flow oxygen, 8% hospitalized with oxygen, 8% hospitalized without oxygen, 36% outpatient without activity limitation and 31% outpatient without activity limitation (https://jamanetwork.com/journals/jama/fullarticle/2772922). Using this distribution of outcome in the study population and an estimated odds ratio of benefit of 2.1, based upon the odds of improvement in an ordinal scale from a trial assessing inhaled interferon-beta the estimated sample size is 190, based on a power of 0.8 (lancet ifn-beta inhaled rct). With an estimate 5% loss to follow up the total sample size is 200.

10.6 Rationale for Primary Endpoint Selection for Cohort B

The clinical manifestations of COVID-19 are myriad, but the main symptom necessitating hospitalization is respiratory distress. An ordinal scale captures the spectrum of the clinical care received by an individual hospitalized with respiratory failure. Furthermore, this scale has been adopted by multiple randomized COVID-19 therapeutic trials for hospitalized patients (ORCHID trial) and is the recommended outcome as outlined by the WHO Research and Development Blueprint for COVID-19 (https://www.who.int/teams/blueprint/covid-19). Adopting this commonly used scale will permit comparisons between this and other treatment trials. Moreover, the use of death or ICU admission will ultimately require a larger sample size that could overlook a beneficial effect of peginterferon-lambda for reasons that contribute to a prolonged hospitalization, which are worthwhile in their own right. Lastly, given that rapidly changing treatment paradigm for COVID-19 the estimates of mortality and ICU admission are sure to change as new treatments, such as dexamethasone, become the standard of care.

11. Optional Consents

11.1 Genetic Testing

A genome-wide association study (GWAS) performed on people treated with interferon-alpha therapy for hepatitis C virus (HCV) infection identified a single nucleotide polymorphism (SNP) near the interleukin 28B (IL28B) gene that was strongly associated with response to treatment[22].

Subsequent studies confirmed the association and found that this SNP was also associated with spontaneous HCV clearance[23]. Although the originally identified SNP was in a non-coding region, a later study identified a novel mRNA transcript induced by viral infection in hepatocytes. The transcript codes for a novel Type III interferon called interferon lambda 4 (IFNL4)[24]. A deletion in the IFNL4 gene prevents production of a functional protein. The lack of the functional IFNL4 is associated with HCV treatment response to interferon-based therapy and with spontaneous HCV clearance. In contrast, production of functional IFNL4 is associated with non-response to interferon-based therapy for HCV[24]. The prevalence of the IFNL4 mutation varies by ethnicity, with 80% of East Asians producing no functional IFNL4 whereas approximately 75% of Africans produce the functional protein[22]. The difference in prevalence explains the bulk of the difference in HCV treatment response by ethnicity. It is unknown whether the IFNL4 genotype affects response to interferon lambda treatment and/or the natural course of COVID-19. Currently no other genes have been identified that modify the course or response to treatment of COVID-19.

Study participants will be asked to sign an optional consent giving permission to study genetic associations between disease outcome and treatment response during COVID-19 infection. Participants in either cohort who agree to genetic testing will have a tube of whole blood taken on Day 0 for DNA extraction and storage. The IFNL4 genotype will be determined in all consenting participants and DNA will be stored for future analysis in case other relevant genes are identified.

11.2 Peripheral Blood Mononuclear Cell (PBMC)

To evaluate SARS-CoV-2-specific immune responses, a subset (~30%) of participants in each cohort will be asked to consent to provide additional blood for PBMC isolation. Those who agree will have 5 tubes collected on Day 0, 3, 7 and 14 in Cohort A and Day 0, 1, and 14 in Cohort B. The magnitude and change in SARS-CoV-2-specific immune responses will be evaluated using standard interferon-gamma ELISPOT assays to over-lapping peptides of SARS-CoV-2. Participants in both Cohorts will be asked to consent to provide additional blood for PBMC isolation at Day 90+ post-dosing (up to 1-year post-dosing). Provision of blood for the Day 90+ PBMCs will be requested of all participants in both cohorts irrespective of whether they agreed to PBMC collection during the course of treatment. The rationale for the late PBMC collection is to assess the degree of T cell immunity and antibodies targeting SARS-CoV2 and to determine whether the PBMC responses are influenced by peginterferon lambda treatment.

11.3 Antibody Testing

Currently there are three Health Canada approved testing platforms for antibodies against COVID-19. Although the clinical significance of the presence of IgM/IgG antibodies is not fully understood, the presence and quantity of anti-COVID-19 antibodies up to day 28 of the study to day 90+ visits will be compared; including assessing whether the administration of Interferon-Lambda may affect expression. In addition to collecting plasma, the utility of collecting blood by finger-prick onto a dried blood spot card will be assessed. The sample would be eluted from the

card and will also be analyzed on one of the three Health Canada approved platforms. Dried blood spots have been widely used in resource limited countries for the presence of hepatitis B and C antibodies, and several countries are also implementing this collection method for seroprevalence studies of COVID-19. However, to date, there are few head-to-head comparisons of venipuncture to finger-prick collection for COVID-19 antibodies; and the ability to collect by both methods in this study will provide data as to whether this method is feasible and comparable to testing from plasma.

12. Sample Processing

12.1 Swabs and Saliva

Collection of nasopharyngeal and mid-turbinate nasal will follow the instructions on the label of each specific swab. Immediately after the swab is completed, the swab should be placed in viral culture media. Saliva will be collected by filling one-third of sterile specimen container with spit. Self-collected samples should be stored in the sealed cooler provided to the participants until pick-up.

The swabs in viral culture media and saliva in specimen collection containers will be transported in a sealed plastic container to the Mount Sinai microbiology lab for SARS-CoV-2 testing using the Seegene Allplex SARS-CoV-2 PCR (limit of detection 100 copies/mL), which is Health Canada approved.

12.2 PBMC Collection

Samples for PBMCs will be transported to the laboratory of Dr. Adam Gehring for PBMC isolation, storage and downstream analysis using standard Ficoll PBMC isolation techniques following specific handling laid out by Infection Prevention and Control for UHN.

13. Study Withdrawal

Study Discontinuation

The investigator may advise the participant to withdraw from the study if there are concerns for participant safety. In Cohort B, if there are concerns that the participant's condition worsened after the first injection and it would not be safe to give a second injection, the day 5 dose may be withheld. This decision will be made at the discretion of the treating physician. Data from participants who discontinue for safety will still be collected unless the participant withdraws consent. Participants who discontinue prematurely before assessment of the primary endpoint will be counted as treatment failures for analysis. Participants who discontinue prematurely due to safety concerns will not be replaced.

Participant Withdrawal from the Study

Participants may withdraw from the study at any time. The reason for withdrawal must be documented. Participants who discontinue prematurely will be included in the analysis of results

(as appropriate) and may be replaced in the enrollment. If agreeable, participants who choose to discontinue the study prematurely, will be asked to have a final study visit to document final virologic results. Participants may decline the final study visit at the time of withdrawal.

14. Data Safety and Monitoring Committee (DSMC)

To evaluate safety of this investigational agent, the Data Safety and Monitoring Committee (DSMC) of the Canadian HIV Clinical Trials Network (CTN) will be used. The DSMC consists of 6 members including a community member and follows an established charter.

The DSMC will review safety data after the first 10 randomized participants complete 7 days of follow-up after treatment. They will review after every 10 randomized participants in Cohort A until 50% of the cohort has been enrolled. Once 50% of Cohort A have completed 7 days of follow-up, the entire safety dataset will be reviewed by the DSMC. After review, the DSMC will notify the sponsor/steering committee to indicate whether the trial may proceed. The DSMC will specifically evaluate any change in liver enzymes from Day 0 to 7, given the known association of peginterferon lambda with mild hepatotoxicity. The trial will be stopped for safety if the DSMC notes >1 treatment-related SAE or apparent worsening of the disease course based on increased symptoms in at least 5 individuals in the treatment arm or based on other unexpected safety concerns identified by the DSMC. If approved for continuation, recruitment will continue in Cohort A and in parallel, recruitment will begin in Cohort B.

The DSMC will review after 25% of randomized patients in Cohort B have completed 14 days of follow-up. They will again review at 50% enrollment in Cohort B or more frequently at their discretion based on AE/SAEs reported. The treatment will be halted if >1 treatment-related SAE is reported or based on other unexpected safety concerns identified by the DSMC

15. Trial Oversight

A Steering Committee (SC) will consist of the overall study PIs, the site PI at each site, as well as study statistician. The SC will meet once weekly by teleconference for the first 4 weeks and then will adjust the frequency of meetings based on need. The DSMC will instruct the SC about continuation of the trial in both Cohorts and initiation of enrolment in Cohort B after their evaluations of safety and efficacy.

Eiger Biosciences will provide adequate study medication for all enrolled participants to complete the study dosing according to the Study Contract with UHN. Eiger Biosciences will be provided with aggregate study data, but not individual patient-level data. They will have the right to review study publications 30 days prior to submission.

16. Data Analysis

The assessment of endpoints – both safety and efficacy – will be determined by study staff blinded to the treatment assignment of the participant. Descriptive statistics will be used to summarize demographic and clinical baseline characteristics of enrolled participants in Cohorts A and B.

Continuous variables will be summarized with mean, median, SD, quartiles, and minimum and maximum values, as appropriate. Categorical variables will be summarized using counts and proportions. The primary outcome in cohort A will be assessed using Chi-squared with 95% confidence intervals (CI) on the intention-to-treat (ITT) population. Once Day 14 information has been collected for the last participant in cohort A, the study will be unblinded and the data will be made available for analysis to allow for prompt dissemination of the results. Day 30 information will still be collected thereafter for the remaining participants, but this only pertains to outcomes of potential home transmission so will not influence the primary or key secondary outcomes. The primary outcome for cohort B will be analyzed with a global odds ratio comparing the peginterferon-lambda arm to the control arm. RNA negativity for determination of the key secondary endpoint will require two consecutive negative mid-turbinate swab specimens. Patients who die before reaching RNA negativity will be counted as never reaching negativity. Patients who withdraw from the study prior to reaching RNA negativity will be counted as never reaching negativity for the ITT analysis.

A secondary analysis will be performed on the modified ITT population, including anyone who took at least a single dose of peginterferon lambda or placebo. Factors associated with severity of disease and clinical course will be evaluated by uni- and multivariable logistic regression for cohort A and with Cox regression for cohort B. Secondary endpoints will be described and analysed depending on the outcome with chi-2 test for proportions, log-rank test for time to event and repeated measurement modelling for multiple outcomes per patient over time. Viral kinetics will be determined using quantitative SARS-CoV-2 RNA and correlated with inflammatory and cytokine profiles. If feasible, quantitative results will be plotted to develop a model of peginterferon lambda activity against SARS-CoV-2. A complete statistical analysis plan will be created prior to data analysis.

17. Symptoms and AE/SAE Reporting

Symptom Score

Symptoms will be collected by phone/videoconference. Participants will be asked about specific symptoms known to be common in COVID-19 or to be reported with interferon use. Symptoms will be rated as: none, mild, moderate or severe and will be compared to the day prior as: better, unchanged or worse. They will also be asked an open-ended question about additional symptoms and again rate them by severity and change over time. The following symptoms will be specifically explored:

1. Respiratory symptoms
    - Cough
    - Shortness of breath
    - Chest pain
    - Sore throat

- Runny nose/congestion

2. Fever
    - Objective temperature measurement
    - Chills
    - Rigors
3. Gastrointestinal side effects
    - Loss of appetite
    - Nausea
    - Vomiting
    - Diarrhea
    - Abdominal pain
4. Sensory
    - Loss of sense of taste
    - Lose of sense of smell
5. Dermatological
    - Rash
    - Pruritus (itch)
    - Injection site reaction
6. Headache
7. Depression
8. Muscle pain/aches
9. Confusion
10. Fatigue/weakness
11. Changes in the colour of fingers/toes
12. Light-headedness/dizziness
13.. Other symptoms (open-ended)

18. Adverse Events and Serious Adverse Events

An adverse event (AE) is any adverse change from the participant's baseline (pre-treatment) condition, including intercurrent illness which occurs during the course of the trial, after the consent form has been signed, whether the event is considered related to treatment or not.

The Common Terminology Criteria for Adverse Events CTCAE v 5.0 will be used for grading severity of AEs.

A serious adverse event (SAE) is any adverse event that at any dose:

- results in death (grade 5 event)
- is life-threatening (grade 4 event)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity

- is a congenital anomaly/birth defect

Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure or product monograph.

Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.

All serious adverse events which are unexpected and related to protocol treatment must be considered reportable, and therefore be reported in an expedited manner.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above. These should also be considered serious.

All SAEs meeting the above criteria must be reported to the sponsor site to either Dr. Jordan Feld or the TCLD research coordinator in an expedited fashion. The completed SAE form should be faxed to TCLD at 416-340-4533. The TCLD research coordinator or Dr. Feld (416-340-3155 and ask hospital operator to page Dr. Feld) should be notified by telephone. SAEs should be reported to the sponsor within 24 hours. In many instances, complete clinical information may not be available. Whatever information is available on the SAE should be provided to the sponsor within 24 hours. As new information becomes available, it should be forwarded to the sponsor. Each site will report unexpected AEs or SAEs to their REB as per their local site regulations.

A serious adverse event, which is unexpected and is related, will require expedited reporting to the appropriate oversight committees or entities, as per local site regulations.

19. Ethical and Regulatory Considerations

Confidentiality

Participant confidentiality will be maintained by generating a unique participant identification code that will be stored separately from the anonymized study database.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the participant's privacy is guaranteed.

Sources of Materials

Research material obtained from study participants includes medical information, blood specimens and swab samples obtained for laboratory analysis.

All of the data obtained for this study will be obtained prospectively.

Copies of data obtained as part of the study will be retained by the clinical research centre, with appropriate source documentation, on all patients that sign informed consent. The data utilized in this study are described above and consist of information from medical records, or study-specified measures and interventions.

Maintaining Records

The principal investigator will maintain copies of all study-related correspondence, regulatory documents, data, shipment of supplement accountability logs, adverse supplement effects and other records related to the clinical study. The principal investigator will maintain records related to the signed Investigator Agreements.

Site Record Retention Policy

All core laboratories and clinical sites will maintain study records until the principal investigator notifies them and the reviewing regulatory authorities that research is completed or terminated under the clinical investigation in compliance with national law. Record retention dates will be provided to study sites by the principal investigator at the onsite closeout visit.

Informed Consent and Ethics Committee

All participants must provide written informed consent in accordance with the local clinical site's REB. A signed Informed Consent must be obtained from each participant prior to commencing screening evaluations. One copy of the Informed Consent document will be given to the participant and another retained by the Investigator.

Protocol Deviation

Any incident in which the investigator or site personnel did not conduct the study according to the clinical protocol or the investigator agreement. Protocol deviations are classified into three categories:

- Major deviation: Any deviation from participant inclusion and exclusion criteria or participant-informed consent procedures.
- Critical finding: any deviation that can affect the wellbeing of the participant, or the reliability of the data collected is compromised.
- Minor deviation: Deviation from a clinical protocol requirement such as incomplete/inadequate testing procedures, follow-ups performed outside specified time windows, etc.

20. Schedule of Events

20.1 Cohort A – Ambulatory

Group A - Ambulatory Cohort	Screening	Day 0	Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 14	Day 30	Day 90+
Informed Consent	X										
Medical History		X[2]									
Determine Eligibility (Inclusion/Exclusion Criteria)	X	X[2]									
Nasopharyngeal Swab	X[1]				X		X		X		
Urine Pregnancy Test*		X[2]									
Randomization		X[2]									
Study Drug Administration		X									
Symptom/Temperature Survey** (video/teleconference)		X[2,3]	X	X	X	X	X	X	X		X[4]
Midturbinate Nasal Swab		X[2]	X	X	X	X	X	X	X		
Saliva Collection		X[2]	X	X	X	X	X	X	X		
Adverse Event/Serious Adverse Event assessment		X[2,3]	X	X	X	X	X	X	X		
Concomitant Medications		X	X	X	X	X	X	X	X		
Lab Tests***		X[2]			X		X		X		
Inflammatory Markers****		X[2]			X		X		X		
Research Plasma Sample		X[2]			X		X		X		
Peripheral Blood Mononuclear Cell collection*****		X[2]			X		X		X		X[4]
Genetic Sample*****		X[2]									
Finger-prick blood test											X[4]
Household diagnoses of COVID-19									X	X	

* for women of childbearing potential

**hematology, chemistry, renal and liver profiles

*** ferritin, lactate dehydrogenase, D-Dimers, C reactive protein, amylase

**** Peripheral Blood Mononuclear Cell (PBMC) and genetic samples are optional for those who agree

1. Collected if not already performed by the assessment centre
2. To be performed prior to randomization and dosing
3. To be performed 4-6 hours after study drug administration
4. Can be performed up to 1 year post enrollement.

20.2 Cohort B – Hospitalized

Group B - Hospitalized Cohort	Screening	Day 0	Day 1	Day 2	Day 3[2]	Day 4	Day 5[2]	Day 6	Day 7[2]	Day 10	Day 12	Day 14[2]	Day 18	Day 21[2]	Day 25	Day 28[2]	Day 90
Informed Consent	X																
Medical History	X																
Determine Eligibility (Inclusion/Exclusion Criteria)	X																
Blood Pregnancy Test (Beta HCG)*	X																
Physcial Exam		X															
Randomization		X															
Study Drug Administration		X[1]					X[3]										
Clinical Status									X			X		X		X	
Mid-turbunate Nasal Swab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Symptom/Temperature Survey		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6]
AE/SAE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6]
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lab Tests**		X			X		X[4]		X	X[5]		X		X		X	
Inflammatory Makers***		X			X				X	X[5]		X		X		X	
Research Plasma Sample		X			X				X			X		X		X	X[6]
PBMC Sample****		X	X						X			X					X[6]
Genetic Sample******		X															
Mortality Assessment																X	X

* for women of childbearing potential

**hematology, chemistry, electrolytes, renal and liver profiles (can be performed more frequently at the discretion of treating team)

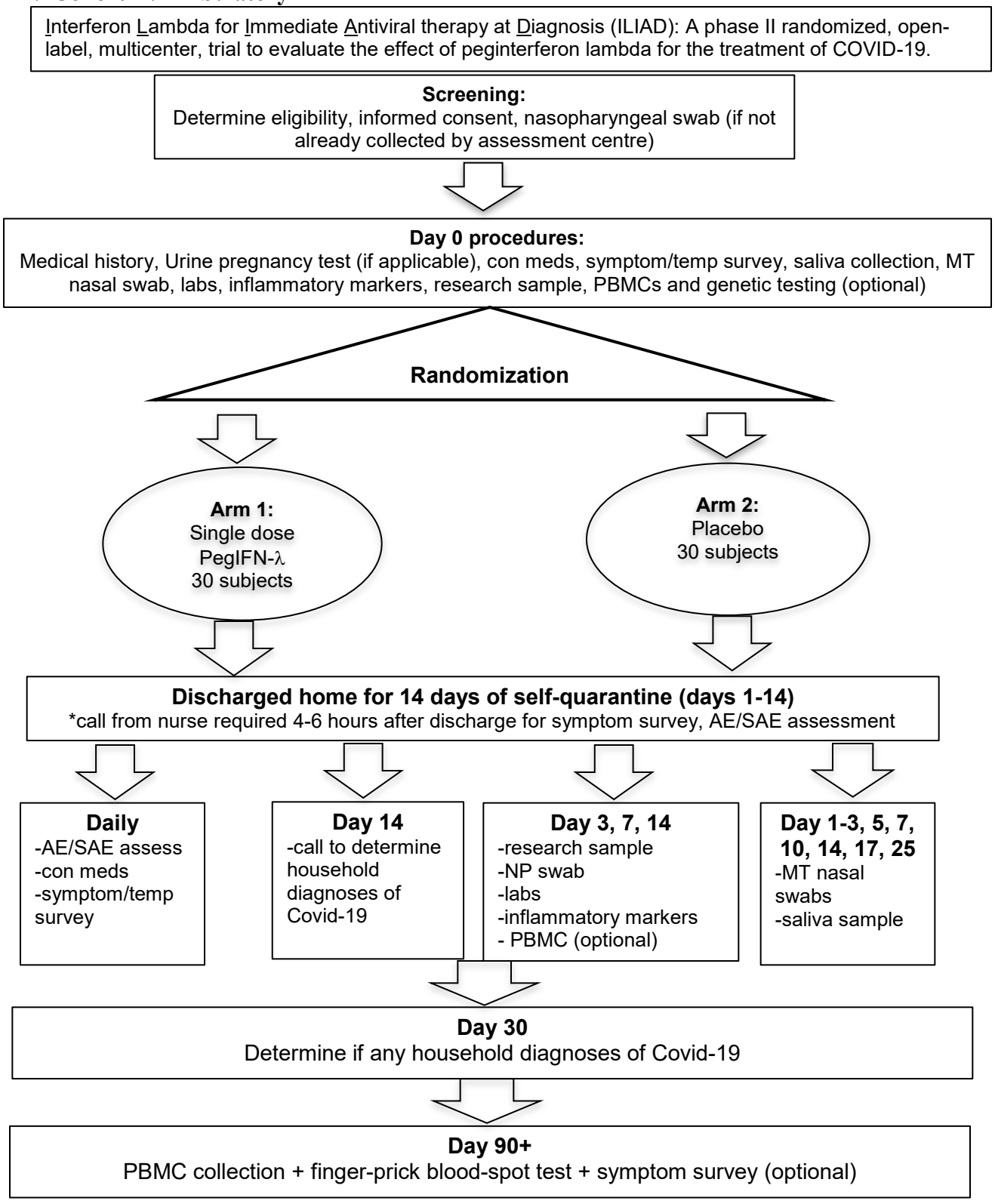
*** ferritin, lactate dehydrogenase, D-Dimers, C reactive protein, amylase, troponin (will be measured more frequently if clinically indicated).

**** PBMC and genetic samples are optional for those who agree

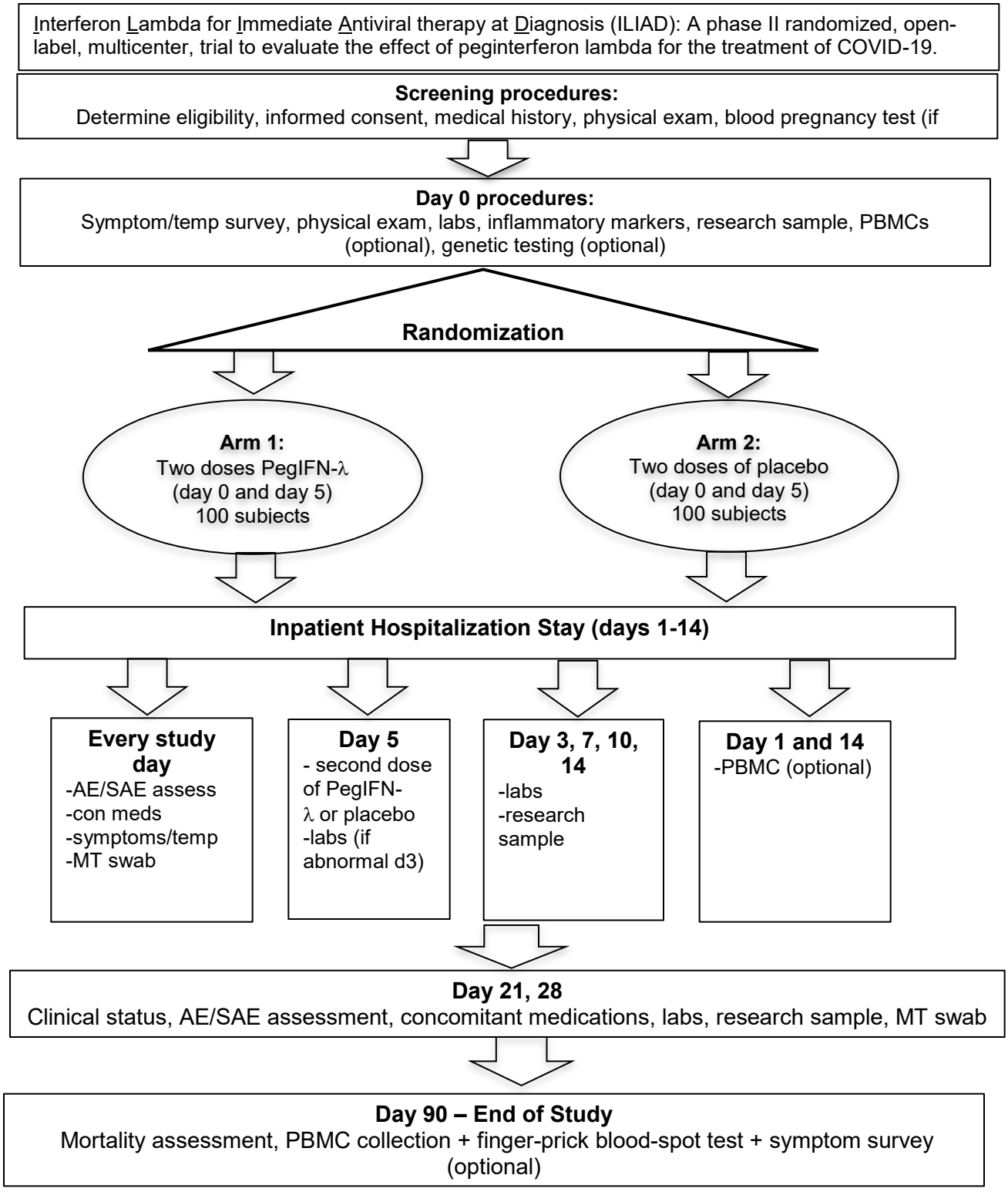
1. To be administered after all baseline procedures.
2. If discharged from hospital, these visits may be done +/- one day
3. Dosing can be delayed out to day 9 depending on lab values (see protocol).
4. Only required if abnormal labs on day 3
5. Not required if discharged from hospital
6. Can be performed up to 1 year post-enrollment

21. Flow Diagram

21.1Cohort A: Ambulatory



21.2 Cohort B: Hospitalized



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