Peginterferon lambda-1a for the prevention and treatment of SARS-CoV-2 infection: The PROTECT Study

Sponsor: Johns Hopkins University

Industry collaborator: Eiger BioPharmaceuticals

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Version 5.0 18 September 2020	Current Version

Investigator Signature Page

Trial Title: Peginterferon lambda-1a for the prevention and treatment of SARS-CoV-2 infection
Protocol Version: Version 4.
Protocol Date: July 16, 2020

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Contents

1. Protocol Synopsis

TITLE: Peginterferon lambda-1a for the prevention and early treatment of SARS-CoV-2 infection

DESIGN: A phase 2b prospective, randomized, single-blind, controlled trial of one subcutaneous injection of peginterferon lambda-1a or placebo for non-hospitalized participants at high risk for infection with SARS-CoV-2 due to household exposure to an individual with COVID-19 and one subcutaneous injection of peginterferon lambda-1a or placebo for non-hospitalized participants with asymptomatic SARS-CoV-2 infection detected at study entry. All participants will be followed for an observation period of up to 10 weeks

DURATION: Participants will be on study for a total of 4 weeks (treatment and observation period).

SAMPLE SIZE: Up to 164 participants will be enrolled in the study for a sample of 110 participants at risk for SARS-CoV-2 infection due to household exposure to an individual with COVID-19 (Prevention Cohort). The treatment cohort sample will be determined by the proportion of asymptomatic persons with SARS-CoV-2 detected at study entry constituting an exploratory cohort.

STUDY CENTER: Johns Hopkins Health System.

POPULATION Household contacts of patients confirmed to have COVID-19 based on SARS-CoV-2 RT-PCR. Consented participants will subsequently enter the treatment or prevention cohorts based on the presence or absence of SARS-CoV-2 on the nasopharyngeal sample obtained at study entry.

Group A: Non-hospitalized, household contacts of individuals with confirmed COVID-19 infection who test RT-PCR negative for SARS-CoV-2 infection at study entry (Prevention cohort)

Group B: Non-hospitalized, household contacts of individuals with confirmed COVID-19 infection who test RT-PCR positive for SARS-CoV-2 at study entry (Treatment cohort).

All participants ≥ 18 years of age who are household contacts of individuals with confirmed COVID-19 infection (within 7 days of diagnosis) without self-report of symptoms of acute respiratory illness (fever, cough or shortness of breath).

At the time of enrollment, the SARS-CoV-2 infection status of the participant will not be known and their inclusion in Group A (Prevention cohort) or Group B (Treatment cohort) will be based on the results of upper respiratory tract sampling at study entry. Participants without detection of SARS-CoV-2 RNA at the time of screening/enrollment will constitute Group A (Prevention cohort) whereas as those with detection of SARS-CoV-2 RNA will constitute Group B (Treatment cohort).

At enrollment into Step 1, all participants in both Group A and B will be non-hospitalized and have a normal blood oxygen saturation by pulse oximetry (≥ 95%) on room air and a respiratory rate of fewer than 25 breaths/minute.

REGIMEN
Enrollment occurs in two Steps. After confirming eligibility, participants are enrolled into Step 1.

Prior to knowledge of infection status, participants will be randomized 1:1 to treatment with peginterferon lambda-1a (Lambda) 180 micrograms by subcutaneous injection one dose (Active Arm) or placebo by subcutaneous injection (Placebo Arm).

Duration of treatment is one week with an additional three week observation period.

Based on the results of SARS-CoV-2 RT PCR testing of upper respiratory tract samples at the time of enrollment into Step 1, persons who test RT-PCR negative at Day 0 will constitute group A.

Participants who test RT-PCR positive for SARS-CoV-2 at entry make up Group B, the treatment cohort.

Group A Prevention Cohort	Day 0	Ratio
Active	Active	1
Placebo	Placebo	1

Group B Treatment Cohort	Day 0	Ratio
Active	Active	1
Placebo	Placebo	1

PRIMARY OUTCOMES

- Group A Prevention cohort: To estimate the proportion of participants with no evidence of SARS-CoV-2 infection at or before day 28
  For the purpose of the study endpoint, SARS-CoV-2 infection is defined as any of the following outcomes:
  1. SARS-CoV-2 detected in upper respiratory samples at any of day 7, day 14 or day 21; or
  2. New finding of serum antibodies (IgA or IgG) against the SARS-CoV-2 spike protein according to validated specifications and performance characteristics before or on day 28.

- Group B. Treatment cohort: Proportion of participants with resolved SARS-CoV-2 infection at Day 14 defined as non-detection of SARS-CoV-2 RNA in two respiratory samples before or on day 14

SECONDARY OUTCOMES

Group A Prevention cohort

- Time to onset of signs and symptoms consistent with COVID -19 (Symptoms: Cough, sore throat, generalized body aches and shortness of breath; Signs Fever >100.4 F, RR >25, SpO2 <95% on room air)
- Hospitalization
- Proportion with treatment-emergent adverse events

Group B Treatment cohort

- Time to onset of signs and symptoms consistent with COVID -19 (Symptoms: Cough, sore throat, generalized body aches and shortness of breath; Signs Fever >100.4 F, Respiratory rate >25, SpO2 <95% on room air)

- Incidence of progressive clinical disease at or before 14 days after enrollment assessed by SpO2 (determined by home pulse oximetry, when available).
- Hospitalization
- Time to clinical resolution of signs and symptoms consistent with COVID-19 (Among those that develop symptoms)
- Proportion with treatment emergent adverse events

EXPLORATORY OUTCOMES

- Relationship of outcomes with genetic polymorphism related to interleukin-28b
- Compare the rates, levels and duration of SARS-CoV-2 RNA in upper respiratory samples using RT-PCR

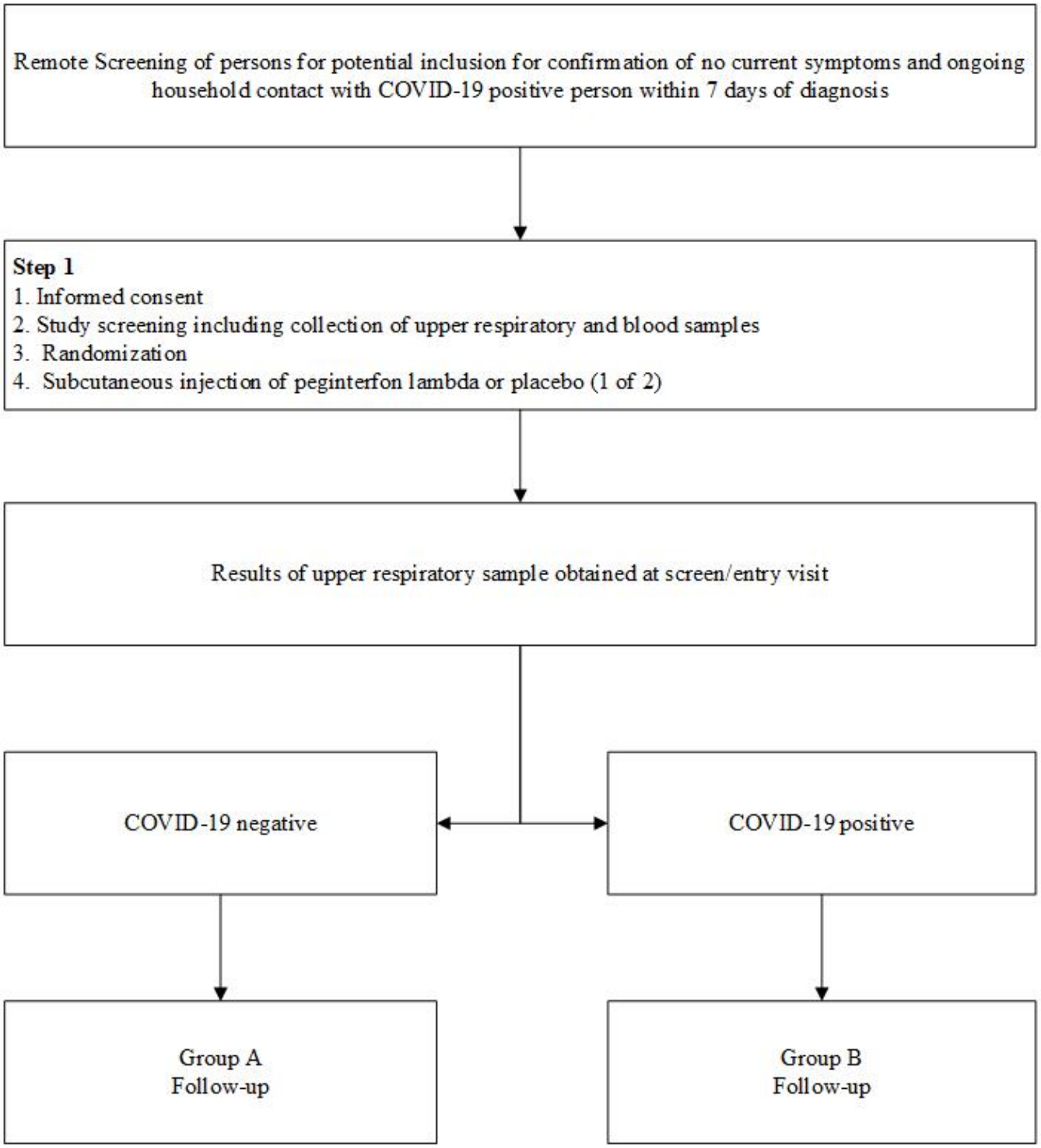
KEY INCLUSION

- Willing and able to provide written informed consent
- Peripheral capillary oxygen saturation (SpO2) ≥ 95% on room air at screening
- Age ≥18 years to ≤ 80 years

KEY EXCLUSION

- Hospitalized or impending hospitalization at the time of screening
- Symptoms of cough, fever or shortness of breath within 72 hours
- Prior or current treatment with other experimental or approved agents targeting SARS-CoV-2 or SARS-CoV-1
- Positive pregnancy test
- Active autoimmune disease or sarcoidosis (with the exception of controlled thyroid disease)
- Active decompensated liver disease (ascites, encephalopathy)
- Active congestive heart failure
- Hemodialysis or peritoneal dialysis

2. Study Schema



3. Hypothesis and study objective

3.1. Hypothesis

3.1 Prevention Cohort.

Peginterferon lambda-1a will result in a greater proportion of household contacts of persons with SARS-CoV-2 infection with no evidence of infection over a 4-week period compared to placebo

3.1.2 Treatment Cohort

Peginterferon lambda-1a will result in a higher proportion of participants with resolved SARS-CoV-2 infection at Day 14.

3.2 Primary objective

3.2.1 Prevention cohort.

To estimate the proportion of participants with no evidence of SARS-CoV-2 infection at or before study day 28

3.2.2 Treatment cohort

To estimate the proportion of participants with resolved SARS-CoV-2 at day 14

3.3 Secondary objective

3.3.1 Prevention cohort

3.3.1.1 To estimate time to onset of signs and symptoms consistent with COVID -19 (e.g., fever, generalized body aches, cough, and shortness of breath)
3.3.1.2 To estimate time to SpO2 < 95% on room air
3.3.1.3 To summarize the occurrence of treatment emergent adverse events

3.3.2 Treatment cohort

3.3.2.1 To estimate time to hospitalization with progressive COVID-19
3.3.2.2 To estimate time to SpO2 < 95% on room air
3.3.2.3 To summarize the occurrence of treatment emergent adverse events
3.3.2.4 To estimate the time to resolution of SARS CoV-2 infection

3.4 Exploratory objectives

3.4.1 To assess the relationship of primary outcomes to genetic polymorphism in the region of the gene interleukin-28B
3.4.2 To compare the rates, levels and duration of SARS-CoV-2 RNA in respiratory samples using RT-PCR

4 Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a major cause of upper and lower respiratory tract infection which progresses to severe pneumonia in approximately 15% of infected persons with potential progression to adult respiratory distress syndrome (ARDS) and, death in 1 to 3% of persons infected [1]. However, SARS-CoV-2 infection also manifests with relatively mild respiratory tract infection symptoms such as cough, sore throat and fever, or with no symptoms (asymptomatic infection) [2]. Collectively, respiratory illness due to SARS-CoV-2 is referred to as Coronavirus Disease 2019 (COVID-19). Antiviral treatments are urgently needed to prevent transmission and treat persons with early infection to prevent clinical progression to severe pneumonia and ARDS. While studies are underway, there are no approved treatments for persons with COVID-19 [3]. Similarly, early antiviral treatment may limit the transmission of SARS-CoV-2. While several host risk factors, like age and chronic comorbid diseases, have been associated with severe COVID-19, transmission of the virus from persons with minimal or no symptoms is estimated to account for as much as 78% of infections in the pandemic [4]. While studies of prophylactic vaccination are underway, medications to prevent person-to-person transmission are urgently needed.

In humans, the innate immune response to viral infections involves type I and type III interferons. Interferon alpha is a type 1 interferon that binds to broadly-expressed cell surface co-receptors which activates the JAK-STAT signal transduction pathway and upregulates numerous interferon-stimulated genes. Interferon lambda is a Type III interferon which binds to a receptor complex which is distinct from those used by type I interferons but appears to activate the same signaling cascade and stimulates cell-mediated immune responses that are critical for the development of host protection during viral infections [5].

Interleukin (IL)-29 is a member of the Type III interferon (IFN) family. Lambda targets type III IFN receptors which are distinct from the type I IFN receptors targeted by interferon alfa. Lambda type III receptors are highly expressed in epithelial cells within the lungs, intestine, and liver with limited expression on hematopoietic, muscle, and central nervous system cells, which may reduce the off-target effects associated with other interferons and has demonstrated improved tolerability with Lambda treatment [6]. Peginterferon lambda-1a (Lambda) is a conjugate of recombinant human interleukin 29 (rIL-29) and a linear polyethylene glycol (PEG) chain, which enables once a week dosing. Lambda has been evaluated in Phase 1, 2 and 3 clinical trials in over 3,000 healthy volunteers and patients infected with chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) [7]. In randomized controlled trials of interferon lambda-1a and interferon alfa-2a for the treatment of chronic HCV and HBV infection, interferon lambda-1a demonstrated similar antiviral efficacy and improved tolerability compared to interferon alfa-2 with lower frequency of hematologic suppression. However, in August 2014, the development of interferon lambda-1a was terminated due to the advent of HCV direct acting antiviral therapy and remains under investigation for treatment of hepatitis D virus (HDV) infection [8].

Interferon alfa has been evaluated in a study of 22 patients with the 2002-2003 SARS-CoV infection who received corticosteroids alone or in combination with interferon alfa. Interferon alfa was associated with more rapid resolution of lung radiographic abnormalities, less need for supplemental oxygen, and lower levels of creatine kinase [9]. In animal models, interferon lambda inhibits replication of respiratory viruses such as influenza as well as the SARS-CoV and may induce resistance of the respiratory epithelium to viral infections. Lambda interferons are a major

component of the innate immune defense to viruses, bacteria, and fungi. Lambda has been shown to protect against pulmonary influenza and human metapneumovirus (HMPV), gastrointestinal rotavirus and norovirus, and hepatic HBV, HCV and HDV [10]. Studies in mice have shown potent antiviral effects of Lambda against influenza and SARS coronavirus, rotavirus, norovirus, and reovirus [11].

Virus-infected cells secrete a broad range of IFNs which confer resistance to yet uninfected cells by triggering the synthesis of antiviral factors. The relative contributions of the various IFN subtypes to innate immunity against viral pathogens that infect the respiratory and gastrointestinal tract was determined using mice lacking functional receptors for type I IFN, type III IFN, or both. Results found that Lambda plays an important role in the defense against several human pathogens that infect the respiratory tract, such as influenza A virus, influenza B virus, respiratory syncytial virus, human metapneumovirus, and SARS-CoV [12]. These viruses were more pathogenic and replicated to higher titers in the lungs of mice lacking both IFN receptors than in mice with single IFN receptor defects. Interestingly, SARS-CoV was present in feces from infected mice lacking receptors for both type I and type III IFN but not in those from mice lacking single receptors, supporting the view that Lambda contributes to the control of viral infections in epithelial cells of both respiratory and gastrointestinal tracts (Mordstein et al 2010). Based on this preliminary data, the WHO has recently included peginterferon lambda in its landscape analysis of potential therapeutics for COVID-19 [13].

5 Study Design

This is a Phase 2b, single-center, randomized, single-blind, dummy-placebo controlled study to evaluate the efficacy and safety of one dose of peginterferon-lambda-1a administered by injection (Lambda) for the prevention of COVID-19 in persons with high-risk exposure.

This study will enroll 164 participants with household high risk exposure to an individual with laboratory confirmed COVID 19 infection who will be followed using the PROTECT protocol for a duration of 4 weeks. Males and females aged greater than 18 years will be randomized in a 1:1 ratio to active: placebo arms and evaluated in two groups based on RT-PCR testing for SARS-CoV-2 infection at study entry.

Group A Prevention cohort: Non-hosptialized household contacts of individuals with confirmed COVID -19 infection who test RT-PCR negative for SARS-CoV-2 at study entry

Group B Treatment cohort: Non-hospitalized household contacts of individuals with confirmed COVID-19 infection who test RT-PCR positive for SARS-CoV-2 at study entry.

Enrollment will occur in two Steps.

Step 1: All participants will be ≥ 18 years of age and will be determined on remote telephonic screening to be household contacts of individuals with confirmed COVID-19 infection. Household contacts are individuals who have lived in the same household for at least 24 hours preceding COVID-19 infection diagnosis in the index patient and who intend to continue to live in the same household for the next 14 days after diagnosis. At the time of enrollment, the SARS-CoV-2

infection status of the participant will not be known. Participants will be enrolled in a 1:1 ratio into Active or Placebo Arms

Step 2: Based on the results of SARS-CoV-2 RT PCR testing of upper respiratory tract samples at the time of enrollment into Step 1, persons who were found to be RT-PCR negative for SARS-CoV-2 at screening/entry will form the study population for the Group A Prevention Cohort.

Step 2 Groups A COVID-19 negative	Day 0		Ratio
Active	Active		1
Placebo	Placebo		1

Participants who test RT-PCR positive for SARS-CoV-2 at Day 0 will not be eligible for Step 2 and will proceed to a follow-up Schedule of Events. These participants make up Group B, the treatment cohort.

Step 2 Group B COVID-19 positive	Day 0		Ratio
Active	Active		1
Placebo	Placebo		1

The primary study population is the participants in the Group A Prevention cohort. However, since the infection status of persons enrolled in Step 1 is not known, there is an opportunity to study the effect of a single dose of lambda or placebo in a population of participants with mild SARS-COV-2 infection (Group B Treatment Cohort).

All participants will have interval follow-up visits until the end of week 4.

6 Selection of Participants

The following criteria must be met at the time of study entry/ Day 0 in order for participants to be enrolled in this study.

6.1. Step 1 Criteria

6.1.1 Step 1 Inclusion Criteria

The following criteria must be present and documented at Day 0 for enrollment into Step 1:

6.1.1.1 Willing and able to comply with study procedures and provide written informed consent.
6.1.1.2 Able to read and understand a language in which an informed consent form and other patient study documents are available.
6.1.1.3 Males and Females Age ≥18 to ≤ 80 years
6.1.1.4 Participants at high risk for infection with SARS-CoV-2 infection due to household exposure to an individual with confirmed COVID-19 (diagnosed in the preceding 7 days) for more than 24 hours
6.1.1.5 Peripheral capillary oxygen saturation (SpO2) ≥ 95% on room air and respiratory rate < 22 breaths/minute after 3 minutes of rest
6.1.1.6 Females of childbearing potential and males with partners of childbearing potential must agree to use adequate methods of contraception during the study and through day 84. Females of childbearing potential are all those except women who are surgically sterile, who have medically documented ovarian failure, or who are at least 1 year postmenopausal.

For females: 2 of the following contraceptive methods are required:

- Hormonal contraceptives for ≥ 27 days before dosing
- Intrauterine device (IUD) in place ≥ 27 days before dosing
- Double-barrier methods (use of condom [male partner] with either diaphragm with spermicide or cervical cap with spermicide) from screening
- Surgical sterilization of the partner (vasectomy ≥ 1 month before screening)

For males, the following are considered acceptable options:

- Surgical sterilization (vasectomy ≥ 1 month before screening) **or**
- Use of both of the following contraceptive methods from screening:
  - Consistent and correct use of a male condom
  - Partner must use a hormonal contraceptive or a nonhormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide).

Males must agree not to donate sperm from Day 0 through Day 84 of this study.

6.1.1.7 Ability to be contacted remotely via telephone, text message, email or other modality.
6.1.1.8 Access to a smart device that can run Emocha software or secure computer device capable of video contact with internet access; willing and able to use the software for this study.

6.1.2. Step 1 Exclusion criteria

The following criteria must be absent and documented on Day 0 for entry into Step 1:

6.1.2.1 Women who are pregnant or lactating
6.1.2.2 Fever or cough or shortness of breath within 72 hours of the screening visit
6.1.2.3 Hospitalization or the need for hospitalization for any reason at the time of screening
6.1.2.4 Prior or current treatment with other experimental or approved agents targeting SARS-CoV-2 or SARS-CoV-1
6.1.2.5 Active autoimmune disease or sarcoidosis (with the exception of controlled thyroid disease)
6.1.2.6 Active decompensated liver disease (ascites, encephalopathy)
6.1.2.7 Active congestive heart failure
6.1.2.8 Current hemodialysis or peritoneal dialysis
6.1.2.9 History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication.
6.1.2.10 Participation in a clinical trial with or use of any investigational agent within 30 days before screening.

6.2 Step 2 Criteria

6.2.1 Step 2 Inclusion Criteria

The following criterion must be present and documented on Day 7 for entry into Step 2:

6.2.1.1 Absence of SARS-CoV-2 infection at screening/entry visit

7 Schedule of Events

7.1 Step 1 Schedule of Events (All participants)

Evaluation	Prescreen Day -2 to Day 0	Screen/Enroll Day 0	Days 1- 6
Evaluation location	Remote	Site	Remote
COVID-19 symptom screen (8.1) (Phone, Video, or In-Person)	X	X	X
Informed consent(8.2)		X	
Demographic and Medical history(8.3)		X	
Household survey(8.16)		X[a]	
Administration of Flu-PRO Questionnaire(8.4)		X	X
Concomitant medications(8.5)		X	X
Pregnancy test(8.6)		X	
Complete Vital signs(8.7) (T, P, BP, RR, Pox)		X	
Limited Vital Signs(8.7) (T, RR, Pox)			X
Physical examination(8.8)		X	
Randomization(8.9)		X	
Drug/Placebo administration(8.10)		X	
Upper respiratory specimens for SARS-CoV-2 assessment (8.11)		X	X[b]
Serology for SARS-CoV-2(8.12)		X	
CBC and CMP(8.13)		X	
Blood for Exploratory Testing (8.14)		X	
Adverse Event Monitoring(8.15)			X

[a] If unable to conduct household survey at Day 0, it may be conducted by phone anytime before Day 14 evaluation.
[b] Home sampling for Group B participants Days 2, 4, and 6 if available. Frequency of collection is limited by shortages and infection control considerations. No upper respiratory specimens for Group A until Day 7.

7.2 Step 2 Schedule of Events (Prevention Cohort)

Evaluation	Day 7	Day 8- 13	Day 14 ± 4 Days	Day 28 ± 4 Days	Day 84 ± 4 Days
Evaluation location	Site or Remote	Remote	Site or Remote		Remote
COVID-19 symptom screen (8.1) (Phone, Emocha, or In-Person)	X	X	X		
Household survey(8.16)			X		
Administration of Flu-PRO Questionnaire(8.4)	X	X	X		
Concomitant medications(8.5)	X	X	X		
Limited Vital Signs(8.7) (T, RR, Pox)	X	X	X		
Drug/ Placebo administration(8.10)					
Upper respiratory specimens for SARS-CoV-2 assessment (8.11)	X		X		
Serology for SARS-CoV-2(8.12)				X	
CBC and CMP(8.13)					
Blood for Exploratory Testing (8.14)					
Adverse Event Monitoring(8.15)	X	X	X		
Contraception remote follow-up(8.17)					X[a]

[a] For participants who, at screening, are females of childbearing potential or males with female partners of childbearing potential.

7.3 Group B Follow-Up Schedule of Events (Treatment)

Evaluation	Day 7	Day 8- 13	Day 14 ± 4 Days	Day 28 ± 4 Days	Day 84 ± 4 Days
Evaluation location	Remote	Remote	Remote		Remote
COVID-19 symptom screen (8.1) (Phone, Emocha, or In-Person)	X	X	X		
Household survey(8.16)			X		
Administration of Flu-PRO Questionnaire(8.4)	X	X	X		
Concomitant medications(8.5)	X	X	X		
Limited Vital Signs(8.7) (T, RR, Pox)	X	X	X		
Upper respiratory specimens for SARS-CoV-2 assessment (8.11)	X	X[a]	X		
Serology for SARS-CoV-2(8.12)					
Blood for Exploratory Testing (8.14)					
Adverse Event Monitoring(8.15)	X	X	X		
Contraception Remote Follow-Up (8.17)					X[b]

[a] Home sampling for Group B participants Days 9, 11, and 13 if available. Frequency of collection is limited by shortages and infection control considerations.

[b] For participants who, at screening, are females of childbearing potential or males with female partners of childbearing potential

8. Study Procedures

8.1. COVID-19 Symptom Screen

The spectrum of clinical presentation for SARS-CoV2 can range from asymptomatic infection, mild symptomatic infection, or severe symptomatic infection with an acute respiratory distress syndrome. Presenting symptoms compiled from hospitalized patients include fever (44-99%), cough (59-82%), myalgias (11-44%), fatigue (>35%), sore throat (<20%), nausea/vomiting/diarrhea (3-10%), headache (<10%), and rhinorrhea (<5%) [14-17]. The symptoms screen will incorporate the CDC recommendations including: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat.

Participants will be contacted by telephone and screened for these symptoms consistent with COVID-19 at prescreening. Individuals who do not endorse symptoms will be instructed to present to the ambulatory testing facility with appropriate precautions including physical distancing and masking. Persons who are not able to travel to/from the site in a manner consistent with recommendations will not be enrolled. At subsequent visits, participants will complete this symptom screen electronically using Emocha Mobile Health or other HIPAA-compliant means of remote contact.

Emocha Mobile Health (https://www.emocha.com) is a pioneering mobile health company with experience in clinical trials, population health management, and customized clinical applications with a proven track record for remote and mobile health research data collection. Emocha is a HIPAA compliant commercial mobile health software platform for remote patient monitoring. If the participant is not able to use this techonology, the study team will use alternative communication include telephone and secure video connection such as Doximity or other compliant platform.

8.1.1 Participants who Develop Symptoms

COVID-19 symptom reporting by participants will be tracked in real time. Participants who develop symptoms will undergo testing and medical management according to the standard of care protocol at Johns Hopkins Medicine. Symptomatic participants will have testing ordered through the electronic medical record, EPIC and an appointment scheduled at one the testing facilities (tents). Participants who are found to have SARS-CoV-2 infection will be managed according to established protocols. Johns Hopkins Medicine Standard operating procedure for the study will include facilitation of testing for SARS Co-V-2 infection through standard testing protocols at the closest Johns Hopkins Medicine testing facility.

8.2. Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related

activity. The ICF that is used must be approved by the IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, Johns Hopkins Medicine IRB (JHMIRB) policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. This may be done in person or over secure video or phone utilizing the Emocha platform, Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant. Due to the infectious nature of the population under investigation, paper original copies of the ICFs will not be retained. All ICFs will be scanned into the EMR and then destroyed.

Participants who do not speak English will be enrolled, as questionnaires are validated for languages other than English.

8.3. Demographic and Medical History

Participant’s name, date of birth, age (calculated), sex, primary and secondary forms of contact, address, race, and ethnicity will be collected at screening.

Medical history will be collected by participant interview. Participants will be asked to provide all medical history to the best of their recollection, and then will be asked specifically about the following medical history items that impact eligibility: Presence or absence of liver cirrhosis, Active autoimmune disease or sarcoidosis, hemodialysis and/or peritoneal dialysis and congestive heart failure.

8.4. Administration of Flu-PRO Questionnaire

Participants will be assessed to determine the presence or absence of symptoms consistent with COVID-19 using the CDC defined COVID-19 symptom check list daily. In addition, Flu-PRO, a validated, standardized patient-reported outcome (PRO) symptom scale that comprehensively assesses the symptom experience in acute respiratory symptoms across multiple body systems will be used at enrollment and days 1-14 and 28. This will provide an opportunity to assess for potential symptoms related to Lambda as well as COVID-19.

For remote visits, FLU-PRO will be collected directly in REDCap though a link embedded in the

eMocha app. Participants will include their eMocha app username and cell phone number on the survey. For participants who are unable to access or use eMocha, surveys will be interviewer administered over the phone by trained research staff.

A validated, standardized patient-reported outcome (PRO) symptom scale that comprehensively assesses the symptom experience in influenza across multiple body systems was reported in 2016 by Powers and colleagues at the National Institute of Allergy and Infectious Diseases [18]. The purpose of the InFLUenza Patient-Reported Outcome (FLU-PRO©) measure is to comprehensively assess the presence and severity of influenza symptoms across body systems often affected by these viruses. The instrument was created in accordance with drug development recommendations of the US Food and Drug Administration (FDA) [19]. This new instrument yields a profile of scores across six body systems with a total score reflecting overall symptom severity. The questionnaire instructs respondents to rate the severity of 37 influenza symptoms over the past 24 hours, including those related to the nose, throat, eye, chest, head, stomach, fatigue, and body aches/pains. Six items measured the same symptom using different wording in order to select the best performing item for the final instrument. For 32 of 37 items, respondents rated the severity of each symptom on 5-point Likert-type scales from 0 (“Not at all), 1 (“A little bit”), 2 (“Somewhat”), 3 (“Quite a bit”), to 4 (“Very much”). For the five remaining items, severity is expressed as frequency of occurrence: vomiting or diarrhea (0 times, 1 time, 2 times, 3 times, or 4 or more times), and sneezing, coughing, and coughed up mucus or phlegm on a scale from 0 (“Never”) to 4 (“Always”), with higher scores indicating more severe symptoms.

8.5. Concomitant medication documentation

All concomitant medications and supplements will be recorded from the time of informed consent through protocol Day 28. There are no known drug-drug interactions.

Concomitant medications will be collected directly in REDCap though a link embedded in the eMocha app. Participants will include their eMocha app username and cell phone number on the survey. For participants who are unable to access or use eMocha, surveys will be interviewer administered over the phone by trained research staff.

8.6. Pregnancy Test

All participants will be asked to provide information determining childbearing status. Females who are post-menopausal (absence of menses for 12 months or greater) or who have had a hysterectomy are considered not to be of childbearing potential. Any females not meeting these criteria are considered to be of childbearing potential and will have a dipstick urine HCG test performed at the point of care at screening. Pregnant women will not be enrolled in this study.

Females of childbearing potential will be cautioned against getting pregnant or attempting to get pregnant during this study. Requirements for ongoing contraception are noted in protocol section 6.1.1.6.

8.7. Vital Signs

Complete Vital Signs: Temperature, Pulse, Respiratory Rate, Blood Pressure and Pulse Oximetry will be collected at the study site after at least 3 minutes of rest.

Limited vital signs (Temperature, Respiratory Rate, and Pulse Oximetry [when available]) will be performed after 3 minutes of rest at the participant's home using study supplies and documented by Emocha software, or other HIPAA-compliant method of remote contact. Readings will be taken at least once a day. Participants who have a SpO2 reading of <95% or respiratory rate >25 breaths per minute after at least 3 minutes of rest will be asked to take a confirmatory measurement and instructed to visit an emergency room.

8.8. Physical Examination

A limited physical examination will be performed to examine the following body systems: Constitutional; HEENT; Cardiovascular; Pulmonary; Gastrointestinal; Skin; and Musculoskeletal. Abnormal findings will be evaluated for clinical significance toward an assessment of eligibility, treatment-emergent adverse events, and assessment of COVID-19 signs and symptoms.

8.9. Randomization

Randomization will take place on day 0 after screening activities have been performed and the Investigator or designee has determined that the participant is eligible. Day 0 laboratory tests including blood SARS-CoV-2 RT-PCR results are not part of the eligibility criteria and participants will be randomized without this information. Randomization will be built into the study REDCap database. It will not be known at entry/screening whether participants are part of Group A or Group B since their COVID-19 infection status will not be known until entry/screening specimens are processed. All participants will be randomized in a 1:1 ratio to receive Lambda/Lambda (Arm 1) or Placebo/Placebo (Arm 2). Participants who are not eligible for enrollment into Step 2 (will be removed from protocol therapy Single dose of Lambda or placebo) respectively.

8.10. Drug/Placebo Administration

Peginterferon-Lambda-1a 180 mcg or dummy placebo injection will be administered subcutaneously by personnel on Day 0. Participants will be sent home for self-monitoring and will communicate with study staff between in-person visits to communicate any adverse events.

Details on drug/ placebo interventionand storage are in Protocol Section 9.

8.11. Upper respiratory specimens for SARS-CoV-2 assessment

All participants in Group A Prevention cohort with onset of symptoms consistent with COVID-19 will be referred for clinical testing of upper respiratory samples for evidence of SARS-CoV-2.

All persons who remain asymptomatic will have study testing with upper respiratory samples for evidence of SARS-CoV-2 at study day 7, 14, and 28. When onsite visit for Day 28 is not on the exact Day 28, the study team will make every effort to have the upper respiratory specimens self-collected Day 28 at the participant's residence.

Specimens obtained will depend on site of collection and availability of swabs. Mid turbinate samples will be collected using a nylon flocked swab using the following steps: 1) inserting the swab into the nose in the horizontal position until gentile resistance is met, 2) leaving the swab in for 10-15 seconds then, rotating the swab, 3) repeating in the other nostril with the same swab. Specimens collected with nasopharyngeal swabs will be done according to standard instructions. The swab will be inserted into the nostril parallel to the palate. The swab should reach a depth equal to the distance from nostrils to outer opening of the ear. The swab will be left in place for several seconds to absorb secretions. The swab will be slowly removed from the nostril while rotating it.

8.12. Serology for SARS-CoV-2

At entry and day 28, all participants will have blood sampled to detect antibodies against the SARS-CoV-2 spike protein (S1 subunit). Testing will be performed at the Johns Hopkins Pathology Laboratory using the commercial Euroimmun antibody assay according to the manufacturer's recommendation. This assay has been validated by the Johns Hopkins laboratory. 6 mL of blood will be collected for each timepoint.

8.13. CBC and CMP

Complete blood count and comprehensive metabolic panel will be collected and tested for safety assessment at day 0. 12 mL of blood will be collected at each timepoint.

8.14. Blood for Exploratory Testing

At entry, DNA will be collected to evaluate polymorphisms related to IL28B and future evaluation of association with study outcomes including infection. Serum and plasma will also be collected as part of the JHU COVID-19 biorepository. If resources are available, a multiplex cytokine panel will be performed to evaluate for differences in longitudinal peripheral cytokine levels comparing infected individuals that received the study drug compared to those that received placebo. 6 mL of plasma in EDTA tubes and 6 mL of serum in SST tubes will be collected and stored, in addition to the serum collected for IL28B. 30 mL of blood will be collected at each timepoint.

8.15. Adverse Event Evaluation

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All adverse events, both serious and nonserious, will be collected from the time of informed consent through protocol Day 28. Participants will be asked open-ended and non-leading questions to evaluate for adverse events. Participants will also be asked directed questions to evaluate the presence or absence of fever, chills, arthralgia, myalgia, or pain. To monitor for injection site reactions, participants will be asked directed questions regarding pain, erythema, induration, or pruritus. The injection site will be inspected via video check-in on Day 7.

Adverse events will be collected directly in REDCap though a link embedded in the eMocha app. Participants will include their eMocha app username and cell phone number on the survey. For participants who are unable to access or use eMocha, surveys will be interviewer-administered over the phone by trained research staff.

8.15.1 Investigator's Assessment of Adverse Events

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Adverse Events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

8.15.2 Serious Adverse Events

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding

whether expedited reporting is also 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

An exception to expedited reporting is progression of the disease under investigation; worsening of respiratory function due to COVID-19 requiring hospitalization will be reported as an adverse event but will not be reported as a SAE.

Any SAEs will be reported to the JHMIRB within 24 hours of the study team becoming aware of the event.

Initial reporting to the FDA: The Investigator/ designee will report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within 15 calendar days following the Investigator's initial receipt of the information.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the Investigator's initial receipt of the information.

•Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

Any reports submitted to the FDA will also be filed with Eiger Biopharmaceuticals within the same timelines prescribed above.

8.15.3 Pregnancy monitoring and reporting

All participants of childbearing potential must follow the contraception requirements listed in section 6.1.1.6 from Day 0 to Day 84. A pregnancy test will be administered at screening to confirm that pregnant women are not enrolled in this study. Female participants will be asked to confirm ongoing use of required contraception and to report pregnancy through Day 84. Male participants will be asked to confirm ongoing use of required contraception and to report pregnancy of female partners through Day 84.

If a female participant or the female partner of a male participant becomes pregnant while on this study, the investigator/ designee will request to follow the pregnancy to its

outcome. Pregnant partners of male participants will not be required to provide records for themselves or their fetus/child but may do so under a separate HIPAA medical records request form if they choose. Pregnant female participants will be required to provide this information for themselves and the fetus/child unless they withdraw consent from this study.

Pregnancy is not reported as an adverse event, however, it will be reported to Eiger Biopharmaceuticals and the FDA as per voluntary reporting requirements.

8.16 Assessment of exposure to SARS-CoV-2 through household survey.

Dose of exposure to SARS-CoV-2 will be assessed through assessment of household size, household relationships COVID -19 exposure and social distancing measures employed within and outside the home assessed at baseline and day 14. If unable to conduct household survey at Day 0, the survey may be conducted by phone anytime before Day 14 evaluation. We will utilize validated survey items from the NIH Public Health Emergency and Disaster Research Response (DR2) repository (https://dr2.nlm.nih.gov/).

Surveys are adapted from the COVID-19 Household Environment Scale (https://www.phenxtoolkit.org/toolkit_content/PDF/Behar_Zusman_CHES_ENG.pdf) and the WHO Household transmission investigation protocol for 2019-novel coronavirus (COVID-19) infection.

8.17 Contraception Remote Follow-Up

Females who were of childbearing potential at the time of screening and males with female partners who are of childbearing potential will be contacted by phone, text, or other electronic means available to the participant to confirm that study-required contraception has been used per protocol and that neither the participant or female partner has become pregnant between Day 0 and Day 84.

8.18.1 Remote collection of concomitant medication, adverse events and FLU-PRO.

This will be collected directly in REDCap though a link embedded in the eMocha app. Participants will include their eMocha app username and cell phone number on the survey. For participants who are unable to access or use eMocha, surveys will be interviewer administered over the phone by trained research staff.

9. Study Intervention/ Investigational Product

9.1 Investigational Agent

Lambda Injection, 0.18 mg/syringe (0.4 mg/mL) is supplied in BD Hypak syringes for SC administration of 180 µg. Dummy syringes of saline in equivalent volume of 0.45mL will be made and administered for participants receiving placebo.

9.2 Administration

Subcutaneous injection of Lambda/placebo will be administered by licensed study personnel on Day 0.

9.3 Storage of Investigational agent

Investigational product must be stored refrigerated at 2-8ºC and protected from long-term (> 24 hours) exposure to light. Maximum room temperature of 15C-30C permitted up to 8 hrs. Do Not Freeze. Used syringes must be discarded in a biohazard container.

9.4 Blinding of study participants

Participants will be blinded to study intervention. To preserve the blind, participants will be asked to turn away during the first injection. Unblinding will not be permitted in this study.

10. Study Location and Infection Control Considerations

Johns Hopkins Hospital Epidemiology and Infection Control (HEIC) has determined that persons who screen negative for COVID symptoms prior to arrival to an ambulatory setting may be treated with standard precautions. These precautions evolve over time; the study team will follow the precaution requirements in place at the time of each study visit. Current precautions and screening questions can be found on the internal Johns Hopkins website https://intranet.insidehopkinsmedicine.org/heic/novel_coronavirus/clinical_resources.html.

Screening visits and subsequent visits for any participant who is not infected with SARS-CoV-2 and is asymptomatic will take place in the Clinical Research Unit (CRU). Nasal swabs for asymptomatic participants will be performed in the drive-through testing tents, since aerosolizing procedures are not permitted in the CRU. While it is permissible for persons to leave their homes for study visits, this protocol is written to reduce the number of touchpoints for both participants and personnel where possible. Study visits listed in the Schedule of Events as “site or remote” may be performed in the CRU or, in a limited fashion, in the home on a case-by-case basis per investigator judgment.

To support possible remote visits, participants will be sent home on day 0 with the following supplies:

- Eight respiratory sampling test kits to satisfy sampling requirements through Day 14.
- Thermometer
- Pulse oximeter (if available due to limited supply)

On day 0, participants will be instructed on self-sampling for SARS-CoV-2 RT-PCR. For participants who engage in home sampling, these specimens will be picked up by a courier that is

equipped and approved to handle this type of biohazard.

Participants who are found to be infected with SARS-CoV-2 at baseline (Group B) or who become infected during the course of the study (Group A) will not return to the study site until Day 28 or until criteria for discontinuation of infected status is met per HEIC standards, whichever occurs later. In the event that an interim in-person visit is required to evaluate an adverse event, these participants may be seen in an ambulatory setting equipped for encounters with SARS-CoV-2 infected persons. In the event that participants become hospitalized, study evaluations that coincide with clinical care will be abstracted from the medical record. Research-specific evaluations will not continue in the inpatient setting.

11. Risks and Benefits

Potential Risks of Treatment
Identified risks associated with treatment with 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, hypersensitivity reaction, injection site reaction, and reproductive risk. Complete information on preclinical and clinical safety data is located in the Investigator Brochure.

Potential Benefits of Participation
Potential benefits include prevention of infection with SARS-CoV-2 infection or reduction in severity of COVID-19 symptoms. It is not yet known whether Lambda will have any benefit in this population.

Alternatives to Participation
The alternative to participation in this study is routine care and monitoring following close contact with an individual with COVID-19.

12. Outcome measures

12.1 Group A Prevention cohort primary endpoint:

- No evidence of SARS-CoV-2 infection at or before study day 28

For the purpose of the study endpoint, SARS-CoV-2 infection is defined as any of the following outcomes:
1. SARS-CoV-2 detected in upper respiratory samples at any of day 7, day 14 or day 21; or
2. New finding of serum antibodies (IgA or IgG) against the SARS-CoV-2 spike protein according to validated specifications and performance characteristics at or prior to day 28.

12.2 Group B Treatment cohort primary endpoint

- Resolution of SARS-CoV-2 defined as non-detection of SARS-CoV-2 RNA in two

respiratory samples by or on day 14

13. Statistical Considerations

13.1 Sample Size and Power Considerations

The planned sample size for the trial is 164 participants enrolled and randomized in a 1:1 ratio to lambda interferon-1a versus placebo injection. This sample size is based on the expectation that approximately 32.5% of participants who are enrolled have evidence of SARS-CoV-2 at study entry (an intermediate value consistent with the 25 – 40% infection range that we expect for the study outcome in the placebo group), thus around 110 will be will have no evidence of SARS-CoV-2 infection (Prevention Cohort) at enrollment and around 54 participants will have evidence of SARS-CoV-2 infection (Treatment Cohort). The Treatment Cohort represents an exploratory pilot study to provide estimates of antiviral efficacy for early COVID-19. Power estimates for the study are based on the Prevention Cohort and incorporate the following assumptions (multiple credible scenarios are presented):

The primary analysis for the efficacy/prevention of infection with SARS-CoV-2 in the Lambda interferon-1a and the placebo groups using proportional odds model and a two-sided Type I error rate (alpha) of 0.05. Since participants in both the Prevention and Treatment Cohorts will be dosed after entry, we anticipate that few, if any participants will not start treatment and be excluded from the primary analysis. Further, given the nature of COVID-19, we anticipate low rates of loss to follow-up before the primary endpoint (Day 14). We expect the incidence of new COVID-19 in the placebo group to be between 25% to 40%, thus we will perform calculation for these edge-case scenarios. In addition, we will be offering enrollment to all adults in a household (~2 per household), our analysis sample will be clustered-correlated by household. However, there is no preliminary or published data to model within-cluster correlation. Thus we are modeling scenarios where the effective sample size is as high as 110 individuals, or as low as the number of households of 55. In all scenarios, we are expecting that the cumulative infection fraction for the lambda interferon will be 5%.

Table 1 : Power using Fisher Exact Test to Detect 5% Infection Rate in Treated Group		
Cumulative Infection Percentage in Placebo	Effective sample size	
	N= 110 individuals	N = 55 family clusters
25%	80.1%	36.1%
40%	99.6%	84.0%

We note that we have 80% or greater power (and Type II error rate beta of 0.2 or smaller) in a large range of scenarios.

13.2 Statistical Analysis

13.2.1 Analyses will include all randomized participants Our primary analysis for both the prevention and treatment cohorts (outcomes of non-infection and resolution, respectively) will be mixed model logistic regression correcting for within-household correlation as a random effect. In addition to the placebo cumulative infectivity and odds ratios, we will express the overall

cumulative incidence of infection and the difference between lambda interferon vs. placebo using nonlinear combination (i.e., inverse logit of the placebo and active treatment groups and the difference of these after the inverse logit transformation). Statistical inference will use a two-sided Type 1 error rate of 0.05 and 95% confidence intervals.
For the exploratory treatment cohort, we will similarly examine clearance of infection.

In addition, we will perform survival analysis for time to infection in the prevention cohort and time to infection clearance in the treatment cohort, modeling within cluster correlation of hazard as a random effect (frailty).

13.2.2 Analysis of Secondary outcomes including adverse events
For secondary time to event outcomes, we will perform survival analysis for time to infection in the prevention cohort and time to infection clearance in the treatment cohort, modeling within cluster correlation of hazard as a random effect (frailty).

Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of participants experiencing an SAE and the proportion experiencing a Grade 3 or higher. AE will be compared between randomized arms using Fisher's Exact Test. Statistical analyses for the InFLUenza Patient-Reported Outcome (FLU-PRO©) measure of ordinal data of independent groups with more than three samples will utilize the Kruskal-Walis H method.

13.2.3 Sensitivity analysis for missing data
We expect very low missingness of data in our results. We will explore the demographic and clinical characteristics comparing persons with full and incomplete follow-up, and try to define the mechanism of missingness with the input of study staff about clinical operations. This experiential input is necessary, because there is no data-driven mechanism to decide on non-ignorability of missing data. For Missing Completely At Random (MCAR) or Missing At Random (MAR) data mechanisms, as sensitivity analysis, we will use multiple imputation methods to test the robustness of our results.

14. Safety Oversight

14.1 Monitoring Plan

All AE and SAE will be reviewed by the protocol team twice monthly, or more if needed.

The Principal Investigator will be responsible for safety oversight of the clinical study.

A data safety monitoring board (DSMB), composed of independent experts without conflict of interests will be established. The Board will review the study before initiation and after 50% of planned enrolled participants have reached the primary endpoint. The Board will review study data to evaluate the safety, efficacy, study progress, and conduct of the study.

14.2 Study monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately

monitored by the study Sponsor/Investigator. Monitors will verify that:

- There is documentation of the informed consent process and signed informed consent documents for each participant.
- There is compliance with recording requirements for data points
- All SAEs are reported as required
- Individual participants' study records and source documents align
- Investigators are in compliance with the protocol.
- Regulatory requirements as per Office for Human Research Protections-OHRP, FDA, and applicable guidelines (ICH-GCP) are being followed.

14.3 Withdrawal criteria

Participants will be withdrawn from the study if they withdraw consent or if the study is cancelled.

14.4 Study stopping rules

We will pause enrollment after 50% of participants have reached study end point and wait until the DSMB has completed their planed review prior to resuming enrollment

We will use O'Brien and Fleming limits as the stopping rule based on efficicacy (threshold p-values of 0.0054 at mid-planned sample and 0.0492 for the final analysis). For the futility stopping rule, we will use a conditional power of < 10% at the time of mid-sample accrual, assuming that the remaining sample will have the same treatment success as the sample accrued so far.

15. Protection of Human Subjects

15.1 Ethical Standard

The JHU is committed to the integrity and quality of the clinical studies it coordinates and implements. JHU will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all JHU sites participating in this research study

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, JHU will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, JHU has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for JHU is FWA00005834.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

15.2 Institutional Review Board

The JHU IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before participant enrollment. The JHU IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

15.3 Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The participant will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the participant for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the participants in understandable language. Adequate time will be provided to ensure that the participant has time to consider and discuss participation in the protocol.
The consent will describe in detail the study interventions/products/procedures and risks/benefits associated with participation in the study. The rights and welfare of the participants will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

The Johns Hopkins Medicine IRB has developed a Standard Operating Procedure for consenting persons in isolation for SARS-CoV-2 infection. While this is not expected to apply during screening, since all candidates will receive a phone screen for symptoms prior to the visit, the event may occur that reconsent is required for a participant who is infected. The below procedure applies in such cases:

Each participant must be provided with a copy of the IRB-approved consent form to aid in the consent conversation before the consent process begins. The consent form may be provided to a participant in isolation in one of the following ways:

- Authorized clinical or research personnel provides an unsigned hard-copy consent form; or
- An electronic copy of the consent is presented to the participant on a mobile device [examples: tablet used for clinical interactions, participant's personal phone, or a phone provided by the study-team.].

Informed Consent procedures for study participants:

- The IRB-approved consent designee, and, if required, physician/mid-level provider (MLP) may participate in the consent process remotely via phone or other communication platform [see options in the resource section below].
- A third-party witness must participate in the entire consent conversation. Wherever possible a witness from the trained JH witness pool should be used.
- All parties must introduce themselves and their role in the consenting process.
- The consent form is provided to the participant and is reviewed in detail. The participant is next invited to ask any questions and to have them addressed by the study team.
- The physician/MLP discusses the studies risks and alternatives per the physician/mid-level provider consent policy.

- If the participant is interested in joining the research study, the participant should be asked to sign the consent document
    - Signature may occur by signing the physical document or if the consent is delivered electronically by the participant clicking "I agree" to participate.
- The consent designee and witness must verify the participant physically signed the consent document
    - By viewing via video conference; or
    - Obtaining a photo of the signed consent document; or
    - Obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically.
- To reduce any transmission risks, the hard-copy consent, if signed by the isolated participant, cannot be removed from the participant's space. In order to obtain the other required signatures a separate copy of the informed consent form is to be used to secure the following:
    - The signature and date of the consent designee
    - The signature and date of physician/MLP ("mid-level provider") on the appropriate signature page
    - The signature and date of the witness on the COVID-19 witness attestation page
- The consent designee should return all signed components as one combined document to a study team member with EPIC access.
    - A study team member with EPIC access completes the documentation in EPIC
- The study team must retain the completed consent document in its entirety (i.e., all pages of the consent form) in the study record or participant binder.

15.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsors and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The results of the research study may be published, but participants' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with participants' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded. Participants' records will be available to the FDA, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

16. Data Management and Monitoring

16.1 Source Documents

The primary source documents for this study will be the participants' medical records, Emocha records (if used), and direct entry into REDCap. If the investigators maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study. The investigator will retain a copy of source documents. Due to the infectious nature of the population under investigation, paper original copies of the ICFs will

not be retained. All ICFs will be scanned into the EMR and then destroyed. The investigator will permit monitoring and auditing of these data, and will allow the FDA, IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected and entered in to the study database/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from participants during study visits or will be abstracted from participants' medical records. The participants' medical records must record their participation in the clinical trial and what medications (with doses and frequency) or other medical interventions or treatments were administered, as well as any AEs experienced during the trial.

Pregnant partners of male participants will not be required to provide records for themselves or their fetus/child but may do so under a separate HIPAA medical records request form if they choose. Pregnant female participants will be required to provide this information for themselves and the fetus/child unless they withdraw consent from this study.

16.2 Data Management Plan

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study. A study Data Manager will assure the quality of data entered into the CRFs for this study.

16.3 Data Capture Methods

Data will be entered into a 21 CFR 11-compliant REDCap database. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

16.4 Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents until receipt of written notification to Eiger Pharmaceuticals.

No study document should be destroyed without prior written agreement between the sponsor and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission

must be received by the site prior to destruction or relocation of research records.

17. References

1. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020 Mar 16. pii: ciaa270.
2. Lai CC, Liu YH, Wang CY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect. 2020 Mar 4. pii: S1684-1182(20)30040-2.
3. Lai CC, Shih TP, Ko WC et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirusdisease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020 Mar;55(3):105924.
4. Hemann EA, Gale M Jr, Savan R. Interferon Lambda Genetics and Biology in Regulation of Viral Control. Front Immunol. 2017 Dec 6;8:1707. doi: 10.3389/fimmu.2017.01707. eCollection 2017.
5. Laidlaw SM, Dustin LB. Interferon lambda: opportunities, risks, and uncertainties in the fight against HCV. Front Immunol. 2014 Oct 31;5:545.
6. Syedbasha M, Egli A. Interferon Lambda: Modulating Immunity in Infectious Diseases. *Front Immunol*. 2017;8:119. Published 2017 Feb 28. doi:10.3389/fimmu.2017.00119
7. Chan HLY, Ahn SH, Chang. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B).J Hepatol. 2016 May;64(5):1011-1019.
8. Etzion, O.; Hamid, S.S.; Lurie, Y, et al. End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. J. Hepatol. 2019, 70, e32.
9. *Loutfy et.al* Interferon Alfacon-1 Plus Corticosteroids in Severe Acute Respiratory Syndrome *JAMA.* 2003;290(24):3222-3228. doi:10.1001/jama.290.24.3222
10. Davidson S, McCabe TM, Crotta S et al. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of of IFNα treatment.
11. Lee S, Baldridge MT. Interferon-Lambda: A Potent Regulator of Intestinal Viral Infections. *Front Immunol*. 2017;8:749. Published 2017 Jun 30. doi:10.3389/fimmu.2017.00749
12. Mordstein M, Neugebauer E, Ditt V, et al. Lambda Interferon Renders Epithelial Cells of the Respiratory and Gastrointestinal Tracts Resistant to Viral Infections. Journal of virology, June 2010, p. 5670–5677.
13. WHO COVID-19 landscape analysis of therapeutics. Feb 20, 2020. https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/
14. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032.
15. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513.
16. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi:

10.1001/jama.2020.1585.

18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
19. Powers JH, Guerrero ML, Leidy NK, et al. Development of the Flu-PRO: a patient-reported outcome (PRO) instrument to evaluate symptoms of influenza. BMC Infect Dis. 2016 Jan 5;16: 1.
20. Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. Fed Regis. 2009;74(235):65132–65133.
21. Osborne RH, Norquist JM, Elsworth GR, et al. Development and validation of the influenza intensity and impact questionnaire (FluiiQ™). Value in health. 2011; 14: 687–699.
22. Jacobs B, Young NL, Dick PT, et al. Canadian Acute Respiratory Illness and Flu Scale (CARIFS): development of a valid measure for childhood respiratory infections. J Clin Epidemiol. 2000 53: 793–799.
23. Powers JH, Bacci ED, Leidy NK, et al. Performance of the inFLUenza Patient-Reported Outcome (FLU-PRO) diary in patients with influenza-like illness (ILI). PLoS One. 2018 Mar 22;13(3): e0194180.