"A Phase 2 Randomized, Single-Blind Study of a Single Dose of Peginterferon Lambda-1a (Lambda) Compared with Placebo in Outpatients with Mild COVID-19"

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Product Name: Peginterferon Lambda-1a

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Sponsor: Stanford University

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Table of Contents

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1. PROTOCOL SYNOPSIS

Study Title	A Phase 2 Randomized, Single-Blind Study of a Single Dose of Peginterferon Lambda-1a (Lambda) Compared with Placebo in Outpatients with Mild COVID-19
Sponsor	Stanford University
Description	Single-blind randomized controlled trial
Study Objectives	1. To evaluate the efficacy of subcutaneous (SC) injections of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo in reducing the duration of viral shedding of SARS-CoV-2 virus in patients with uncomplicated COVID-19 disease. 2. To evaluate the efficacy of subcutaneous injections of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo, in reducing SARS-CoV-2 viral loads and the duration of symptoms, hospitalizations, or ED visits in patients with uncomplicated COVID-19 disease. 3. To evaluate the safety and tolerability of subcutaneous injections of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo.
Scientific rationale	Recently, a novel corona virus has been identified as the causative pathogen of a rapidly spreading infection associated with pneumonia and severe acute respiratory syndrome. COVID-19, originally identified in Wuhan in the Hubei province of China, has now spread across the globe and has been declared by the WHO as a global pandemic. While the majority of infected patients display mild symptoms if any, death rates of up to 4% due to development of severe acute respiratory syndrome (COVID-19 SARS), have been reported in patients with co-morbid conditions and in the elderly population. With the unprecedented global health and economic threats imposed by COVID-19, development of therapies capable of suppressing or eradicating this emerging pathogen has become an urgent unmet medical need. The interferon (IFN) system represents a major element of the innate immune response against viral infections. Virus-induced IFN is a complex mixture of biologically active molecules, which includes type I and type III IFNs. Binding of type I IFN and type III IFN to their cognate receptor complexes triggers signaling cascades that result in the activation of a large number of genes, many of which encode antiviral proteins. Type III IFN (i.e. IFN-λ) uses a distinct receptor complex (IL28R) for signaling which appears to be expressed on only a few cell types, including epithelial cells in the respiratory and gastrointestinal tract, resulting in demonstrated improved tolerability profile. Based on IFN-λ's more limited receptor distribution and therefore expected improved tolerability profile, a pegylated form of recombinant Peginterferon Lambda-1a (Lambda) has been developed for the treatment of chronic viral hepatitides such as hepatitis C, hepatitis B and recently also hepatitis D. Lambda has so far been administered in over 3000 patients in multiple clinical trials, showing a good safety and tolerability profile with varying degrees of antiviral efficacy. The presence of IL28R in the epithelial cells of the lungs and respiratory tract has also evoked research on the potential role of IFN-λ in

	possible mitigation of viral induced respiratory infections. Indeed, studies in animal models have shown that IFN-λ inhibits replication of respiratory viruses such as influenza as well as the SARS-coronavirus. The use of Lambda for treatment of COVID-19 infection has not yet been explored.
Participants and Sample Size	We will enroll 120 patients ages 18-64 with confirmed COVID-19 infection diagnosed by molecular diagnostic assay.
Clinical Site	The study will be conducted at the Stanford University School of Medicine
Study duration	The total anticipated duration of the study for each patient is up to 28 days, with optional long-term follow-up to 10 months following recruitment. The planned duration of the entire study is 12 months.
Selection Criteria	Inclusion Criteria 1. Age ≥ 18 years and ≤ 75 years at the time of the assessment 2. Able and willing to understand the study, adhere to all study procedures, and provide written informed consent 3. Diagnosis of COVID-19 disease: a. If symptomatic, presence of mild to moderate symptoms without signs of respiratory distress, with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from swab to the time of commencing informed consent: b. If asymptomatic, initial diagnosis of SARS-CoV-2 infection with positive FDA-cleared molecular diagnostic assay obtained no more than 72 hours from initial swab to the time of commencing informed consent Exclusion Criteria: 1. Patients who are hospitalized for inpatient treatment or currently be evaluated for potential hospitalization at the time of initiation of informed consent 2. Patients with a known allergy to Peginterferon Lambda-1a or any component thereof 3. Display symptoms of respiratory distress (Respiratory rate >20, room air oxygen saturation of <94%.) 4. Participation in a clinical trial with or use of any investigational agent within 30 days before screening 5. Treatment with interferons within 12 months before screening 6. Previous use of Peginterferon Lambda-1a 7. History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication. 8. Female patients who are pregnant or breastfeeding. Male patients must confirm that their female sexual partners are not pregnant. 9. Current or previous history of decompensated liver disease (Child-Pugh Class B or C) or hepatocellular carcinoma 10. Co-infection with human immunodeficiency virus (HIV) 11. Any of the following abnormal laboratory test results at screening:

	c. Platelet count <75,000 cells/mm^3 d. Absolute neutrophil count <800 cells/mm^3 e. Hemoglobin <11 g/dL for women and <12 g/dL for men f. Serum creatinine concentration ≥1.5× ULN and creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault 12. History of liver disease other than viral hepatitis 13. Prior history or current evidence of any of the following: a. Immunologically mediated disease that is uncontrolled b. Retinal disorder or clinically relevant ophthalmic disorder c. Any malignancy (excluding non-melanoma skin cancer) within 5 years before screening d. Cardiomyopathy or significant ischemic cardiac or cerebrovascular disease. e. Chronic uncontrolled pulmonary disease f. Pancreatitis g. Severe or uncontrolled psychiatric disorder h. Active seizure disorder i. Bone marrow or solid organ transplantation 14. Other significant medical condition that may require intervention during the study 15. Concurrent use of any of the following medications: a. Therapy with an immunomodulatory agent b. Current use of heparin or Coumadin c. Received blood products within 30 days before study randomization d. Use of hematologic growth factors within 30 days before study randomization e. Systemic antibiotics, antifungals, or antivirals for treatment of active infection within 24 hours before study randomization f. Any prescription or herbal product that is not approved by the investigator g. Long-term treatment (> 2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity unless it is approved by the medical monitor h. Receipt of systemic immunosuppressive therapy within 3 months before screening
Treatment assignment	Study participants will be randomly assigned 1:1 to a single subcutaneous dose of Peginterferon Lambda-1a or normal saline placebo, along with standard of care
Treatment arms	1. Peginterferon Lambda-1a (Lambda), 180 mcg, administered as subcutaneous injection 2. Normal saline, 0.45 ml administered as subcutaneous injection
Dose Justification	A single dose PK of Peginterferon Lambda-1a given subcutaneously has been assessed in four Phase 1 studies in healthy subjects and in two phase 2 studies in subjects with HCV. In these studies, Lambda exhibited dose-proportional PK over the dose range of 80 to 240 mcg.

	Phase 2 studies established the optimal dose for virologic suppression and minimizing treatment-related adverse events for hepatitis C at 180 mcg; this dose is also currently being used in hepatitis D trials.
Screening, enrolment, randomization, and follow-up of participants	Patients will be screened, and a baseline physical examination and laboratory assessment performed. Eligible patients will be randomized 1:1 to receive Lambda 180 mcg SC (intervention arm) or normal saline placebo (control arm) (Day 0). Patients will complete an at-home symptom questionnaire on each day of follow-up, including in-home assessments of temperature and O2 saturation and collection of anterior nare swabs and stool. Patients will then be seen at follow-up visits at Day 1±1, 3±1, 5±1, 7±1, 10±1, 14±1, 21±1, and 28±1. At each visit, vital signs (temperature, blood pressure, pulse rate per minute, breath rate per minute and oxygen saturation), will be performed. Efficacy of Lambda will be assessed by analysis of COVID-19 in respiratory secretions obtained by oropharyngeal swabs collected consecutively at each visit, and by anterior nare swabs collected daily at home. Clinical laboratory measurements (CBC, chemistries, LFTs) will be performed at enrollment and Days 5±1, and 14±1. Additionally, ~25 mL peripheral blood will be collected from study participants at enrollment and at Days 5±1, 14±1, and 28±1 for processing and cryopreservation into a specimen biobank. Safety and tolerability of Lambda will be assessed by adverse event (AE) monitoring, vital signs assessment and clinical laboratory tests. Patients will reach the end of study at day 28±1 of follow-up.
Primary Outcome	Duration of viral shedding of SARS-CoV-2 virus
Safety monitoring	Frequency of adverse events and serious adverse events will be analyzed in all study participants.
Planned interim analysis	An interim analysis will be performed and analyzed by a data and safety and monitoring board after 50% of study participants are enrolled and have completed 1 day of follow-up following study drug administration.
Statistical Analysis and Sample Size Considerations	We will evaluate the intention-to-treat (ITT) population, defined as the original treatment assignment groups after randomization, for the primary efficacy analysis. We will analyze the per-protocol group as supportive evidence for the primary efficacy analysis. Approximately 120 patients with COVID-19 infection are planned to be enrolled and randomized, and we conservatively assume that 90% of participants will complete follow-up. The primary endpoint will be assessed in all patients. We assume that the mean duration of virologic shedding is 14 days in individuals receiving placebo, with a standard deviation of 4 days (Zhou et al, Lancet 2020). With 60 patients randomized per arm, we will have 80% power to detect a minimum 50% reduction in virologic shedding in participants receiving Lambda.

2 BACKGROUND

2.1 SCIENTIFIC RATIONALE

2.1.1 COVID-19, a novel coronavirus with an urgent need for novel therapeutics to decrease viral shedding and transmission

Recently, a novel coronavirus has been identified as the causative pathogen of a rapidly spreading infection associated with pneumonia and severe acute respiratory syndrome. COVID-19, originally identified in Wuhan, in the Hubei province of China[1], has now spread across the globe and has been declared by the WHO as a global pandemic. While the majority of infected patients display mild symptoms if any, death rates of up to 4% due to development of severe acute respiratory syndrome (COVID-19 SARS), have been reported in patients with co-morbid conditions and in the elderly population[2]. With the unprecedented global health and economic threats imposed by COVID-19, development of therapies capable of suppressing or eradicating this emerging pathogen has become an urgent unmet medical need.

In a recent report, COVID-19+ patients presenting with mild symptoms had a median viral load of 1 X 10^6 copies in oropharyngeal specimens at diagnosis (an average of 2-4 days post symptom onset), and this declined in the subsequent period and correlated with resolution of symptoms[3]. All patients had evidence of viral shedding in the oropharynx 7 days following symptom onset; by day 14, 22% of patients had evidence of oropharyngeal shedding. In contrast, nearly 80% of subjects had evidence of viral shedding in both sputum and stool specimens at 14 days, in many patients outlasting the resolution of symptoms and despite the development of IgM and IgG seroconversion to the spike protein of SARS-CoV-2. These tissue-specific differences in the duration of viral shedding suggest prolonged transmissibility of SARS CoV-2 in recovered individuals. Novel therapeutics that can shorten this duration of viral shedding could be critically important in reducing transmission.

2.1.2 Peginterferon Lambda-1a, a broad-spectrum antiviral

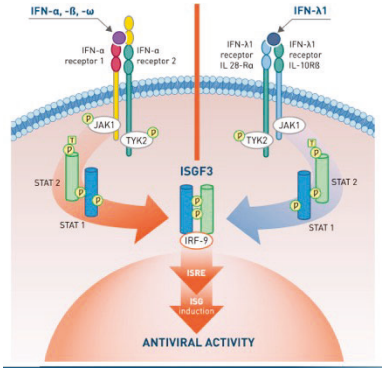

Fig. 1. Interferon lambda and type 1 interferons induce similar antiviral response

Peginterferon Lambda-1a (hereafter referred to as Lambda) is a covalent conjugate of human recombinant non-pegylated interferon lambda and a 20-kDa linear PEG chain. Lambda is a type III interferon (i.e. IFN-λ) that stimulates innate immune responses that are critical for the development of host protection during viral infections[4]. Similar to type 1 interferons (including IFN-a), binding of IFN-λ to its cognate receptor complexes triggers signaling cascades, including those mediated by the JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway, that result in the activation of a large number of genes, many of which encode antiviral proteins (Fig 1)[5]. However, IFN-λ uses a distinct receptor complex (IL28R) for signaling which appears to be expressed on only a few cell types, including epithelial cells in the respiratory and gastrointestinal tract[4]. Based on IFN-λ's comparable antiviral activity, more limited receptor distribution, and improved tolerability profile in comparison to IFN-a, a pegylated form of

recombinant interferon lambda (Lambda) was developed for the treatment of chronic viral hepatitides[6, 7].

Lambda was previously investigated by Bristol-Myers Squibb (BMS) for the treatment of chronic hepatitis B (HBV) and C (HCV) virus infection. This development was discontinued in 2014 based on the rapidly evolving landscape of chronic HBV and HCV treatment using non-interferon-based regimens, and not due to any new safety or efficacy findings in clinical studies. Because of the broad-spectrum antiviral activities of Lambda and fewer side effects of Lambda compared with pegylated IFN alfa-2a in HCV and HBV clinical studies, Eiger BioPharmaceuticals is investigating Lambda in the treatment of hepatitis D virus (HDV) infection, licensing worldwide rights to Lambda from BMS. Lambda has so far been administered to over 3743 patients in Phase 1, 2, and 3 clinical trials.

2.1.3 Interferons, including Lambda, for the Treatment of Respiratory Viruses including SARS-CoV

Type 1 interferons have been shown to induce inhibition of respiratory coronavirus infection[8-10]. In *in vitro* experiments, type 1 interferons were also effective in inhibiting severe acute respiratory syndrome-coronavirus (SARS-CoV)[11]. In a study of patients with SARS-CoV, a synthetic formulation of IFN-a, when given with corticosteroids, was associated with reduced disease-associated impaired oxygen saturation and resolution of radiographic lung abnormalities, in comparison with a group receiving corticosteroids alone (Figure 2)[12]. These data suggest that therapeutic use of interferon may be efficacious in the treatment of SARS-CoV.

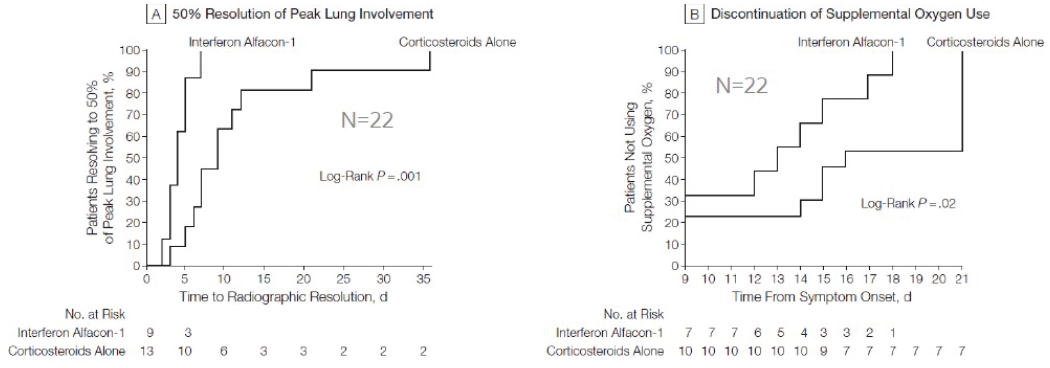

Fig. 2 In a study of patients with SARS-CoV, patients given IFN-α and corticosteroids had improved clinical outcomes compared with patients given corticosteroids alone.

The presence of IL28R in the epithelial cells of the lungs and respiratory tract has spurred research on the potential role of IFN-λ in possible mitigation of viral induced respiratory infections. In a murine model of influenza infection, IFN-λ treatment post-infection was associated with significantly lower mortality compared to mice treated with IFN-a, and this was associated with lower influenza viral loads[13]. Furthermore, studies in animal models have shown that IFN-λ may play an important role in restricting viral replication of SARS-coronavirus (Figure 3)[14]. The use of Lambda for treatment of COVID-19 infection has to our knowledge not yet been explored.

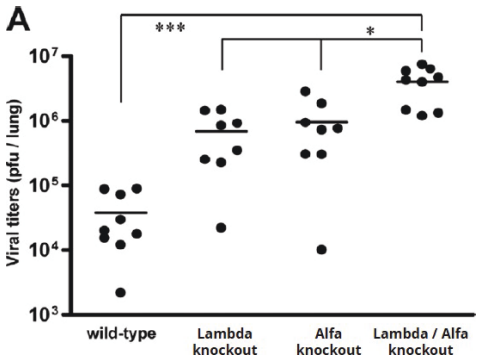

Fig. 3 In comparison to wild-type mice, mice lacking IFN-λ or IFN-α had impaired viral restriction against SARS-CoV.

2.2. SAFETY AND TOLERABILITY OF LAMBDA

Approximately 3,743 subjects (including 237 healthy subjects; 3,276 subjects with HCV; 197 subjects with HBV; and 50 subjects with HDV) have received Lambda to date.

In a study of healthy volunteers administered a single s.c dose of lambda up to 7.5ug/kg, reversible dose-related increases in liver transaminases (ALT and AST) were seen in 5/17 (29.4%) subjects. One of the 2 subjects treated with Lambda 7.5 µg/kg experienced reversible Grade 3 elevation of ALT. Transaminase elevations were not associated with increases in bilirubin. Mild dose-proportional decreases in serum fibrinogen were reported for 7 subjects.

In a second healthy volunteer study, the most common AEs associated with s.c administration of lambda were abdominal pain and venous puncture site hematoma. All AEs were mild in intensity. One (3.3%) subject in the 180-µg group had reversible Grade 1 elevations of AST and ALT not associated with clinical symptoms or bilirubin elevations.

In a recently completed 48-week study of patients with chronic hepatitis delta virus infection, treatment with 180ug lambda, 7/14 (50.0%) patients reported a Grade 3 or 4 treatment-related AE with the following frequencies: injection site reaction 1 (7.1%), ALT or AST increase 5 (35.7%), bilirubin increase 2 (14.3%), decreased neutrophil count 1 (7.1%), flu-like symptoms including fever/chills 9 (64.3%), arthralgia or myalgia 7 (50.0%) and fatigue 8 (57.1%). At the end-of-treatment ALT or AST >5xULN <10ULN was reported in a single patient. There were no increases in bilirubin >2xULN concurrent with increases in ALT or AST at the end-of-treatment. In other studies of lambda as a combination therapy for hepatitis B or C, clinically meaningful increases in total bilirubin occurred in 7.6% and 2.6% of patients dosed with Lambda/Ribavirin (RBV) and Lambda/RBV/Daclatasvir (DCV), respectively. Similarly, increases in serum ALT were noted in 6.2% and 3.7% of subjects on Lambda/RBV and Lambda/RBV/DCV, respectively. All increases were manageable with dose withholding, reduction, or discontinuation. Lymphopenia was not seen with any significance in prior Lambda studies of 48 weeks. Pyrexia occurred at a frequency of 9.9% of patients treated with the 180ug lambda + RBV.

IFN-based treatment induces a variety of psychiatric adverse effects, including depression, manic condition, acute and chronic cognitive dysfunction, suicidal behavior, and relapse of

substance abuse. These effects are observed with a much lower frequency than seen with interferon alpha.

Injection site reactions including erythema, irritation, inflammation, rash, eczema, pruritus, dryness, swelling, and hematoma have been reported (range: 2–15%).

2.3 DOSAGE JUSTIFICATION

The single dose PK of Peginterferon Lambda-1a given subcutaneously has been assessed in four Phase 1 studies in healthy subjects and in two phase 2 studies in subjects with HCV. In these studies, Lambda exhibited dose-proportional PK over the dose range of 80 to 240 mcg. Phase 2 studies established the optimal dose for virologic suppression and minimizing treatment-related adverse events for hepatitis C at 180 mcg; this dose is also currently being used in hepatitis D trials.

2.4 RISK/BENEFIT ASSESSMENT

As no known effective treatment is available for COVID-19, participants may have access to effective therapy in the trial. They may have the added benefit of reducing household and community transmission of the virus

3. STUDY OBJECTIVES

3.1 Primary objective

- To evaluate the efficacy of subcutaneous injections of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo in reducing the duration of viral shedding of SARS-CoV-2 virus in patients with uncomplicated COVID-19 disease.

3.2. Secondary objectives

- To evaluate the efficacy of subcutaneous injection of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo, in reducing the duration of symptoms, hospitalizations, or ED visits in patients with uncomplicated COVID-19 disease.
- To evaluate the safety and tolerability of subcutaneous injection of a single dose of 180 mcg of Peginterferon Lambda-1a compared with placebo.

4. STUDY DESIGN

4.1 Study overview

This is a single center, open-label randomized controlled trial. Each subject will be administered either a single subcutaneous dose of study drug or placebo.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study

The following treatment regimens will be used:

- Experimental treatment: Peginterferon Lambda-1a, 180 mcg subcutaneous
- Control treatment: Normal saline, 0.45 mL subcutaneous

The duration of participation for each individual will be up to 28 days, with optional follow-up to 10 months following randomization. The planned duration for the entire study is 12 months.

5. CRITERIA FOR EVALUATION

5.1. Primary efficacy endpoint

- Time to first of two consecutive negative oropharyngeal tests for SARS-CoV-2 by qRT-PCR.

5.2. Secondary efficacy endpoints

- SARS-CoV-2 RNA levels during follow-up
- SARS-CoV-2 viral load area under the curve
- Time to alleviation of all symptoms (fever, chills, cough, nasal congestion, muscle pains), defined as the time from initiation of treatment until all symptoms are rated as absent or mild in symptomatic patients
- Incidence of emergency department visits or hospitalizations within 28 days of initiation of treatment

5.3. Safety evaluations

- Frequency of adverse events and serious adverse events by standardized DAIDS AE grading criteria (see appendix)

6. SELECTION AND ENROLLMENT OF SUBJECTS

6.1 Study Population

Healthy adults ages 18-64 with molecularly confirmed SARS-CoV-2 infection (COVID-19 disease) who are not currently admitted to a hospital will be eligible for participation in this study.

6.2 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria to be eligible for the study:

1. Age ≥ 18 years and ≤ 75 years at the time of the assessment
2. Able and willing to understand the study, adhere to all study procedures, and provide written informed consent
3. Diagnosis of COVID-19 disease:
    a. If symptomatic, presence of mild to moderate symptoms without signs of respiratory distress, with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from swab to the time of commencing informed consent:
    b. If asymptomatic, initial diagnosis of SARS-CoV-2 infection with positive FDA-cleared molecular diagnostic assay obtained no more than 72 hours from initial swab to the time of commencing informed consent

6.3 Exclusion Criteria

1. Patients who are hospitalized for inpatient treatment or currently being evaluated for potential hospitalization at the time of initiation of informed consent
2. Patients with a known allergy to Peginterferon Lambda-1a or any component thereof

3. Display symptoms of respiratory distress (Respiratory rate >20, room air oxygen saturation of <94%.)
4. Participation in a clinical trial with or use of any investigational agent within 30 days before screening
5. Treatment with interferons (IFN) within 12 months before screening
6. Previous use of Peginterferon Lambda-1a
7. History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication.
8. Female patients who are pregnant or breastfeeding. Male patients must confirm that their female sexual partners are not pregnant.
9. Current or previous history of decompensated liver disease (Child-Pugh Class B or C) or hepatocellular carcinoma
10. Co-infected with human immunodeficiency virus (HIV)
11. Any of the following abnormal laboratory test results at screening:
    a. Platelet count <75,000 cells/mm^3
    b. Absolute neutrophil count <800 cells/mm^3
    c. Hemoglobin <11 g/dL for women and <12 g/dL for men
    d. Serum creatinine concentration ≥1.5× ULN and creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault
12. History of liver disease other than viral hepatitis
13. Prior history or current evidence of any of the following:
    a. Immunologically mediated disease that is uncontrolled
    b. Retinal disorder or clinically relevant ophthalmic disorder
    c. Any malignancy (excluding non-melanoma skin cancer) within 5 years before screening
    d. Cardiomyopathy or significant ischemic cardiac or cerebrovascular disease.
    e. Chronic uncontrolled pulmonary disease
    f. Pancreatitis
    g. Severe or uncontrolled psychiatric disorder
    h. Active seizure disorder
    i. Bone marrow or solid organ transplantation
14. Other significant medical condition that may require intervention during the study
15. Concurrent use of any of the following medications:
    a. Therapy with an immunomodulatory agent
    b. Current use of heparin or Coumadin
    c. Received blood products within 30 days before study randomization
    d. Use of hematologic growth factors within 30 days before study randomization
    e. Systemic antibiotics, antifungals, or antivirals for treatment of active infection within 24 hours before study randomization
    f. Any prescription or herbal product that is not approved by the investigator
    g. Long-term treatment (> 2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity unless it is approved by the medical monitor
    h. Receipt of systemic immunosuppressive therapy within 3 months before screening

6.4. Identification and Recruitment of Participants

Flyers will be handed out to anyone being tested at Stanford testing sites (ER, drive-through tent, and occupational health), inviting them to call us should their test turn positive. We plan to have personnel at the testing site handing out the flyers. Currently, Stanford's blood testing sites are identifying 30-50 newly diagnosed patients per day, the great majority of whom are not admitted. We are hoping to identify two COVID patients per day. If recruitment is slow in the first week, we will also advertise for newly diagnosed COVID cases on social media and hand out flyers at other screening sites as possible. We are also exploring the possibility of calling all COVID positive patients directly; this recruitment approach will be added to an amended protocol if we find it is possible.

6.5. Phone Screening Interview

Individuals who provide informed consent to be contacted after testing COVID-19 positive via the emergency department or occupational health will be contacted by phone. At the initial phone call, we will screen for inclusion and exclusion criteria; the clinical research coordinator (CRC) will fill out the RedCap screening form and determine if the subject is eligible and interested in participating. If the patient meets the criteria in the phone interview, we will invite them to the clinical research site (Stanford University) where we will review inclusion criteria again at the first patient visit. The subject will also be asked to bring in their proof of infection with them or to have it accessible in on-line form.

6.6. Study Enrollment Procedures and Baseline Evaluation

At the initial intake visit, screening eligibility criteria will be reviewed and confirmed. Subjects will undergo a standardized history, including time since symptom onset, and physical examination and have blood collected by phlebotomy. We will conduct the laboratory screening with complete blood count (CBC), comprehensive metabolic panel (CMP) and, in premenopausal women, beta HCG. Additional blood will be collected for biobanking. Inclusion/exclusion labs will be performed stat in the clinical lab. Participants will be asked whether they are enrolled in another study; they cannot be enrolled in other studies of investigational agents. After initial screening, the participant will then provide written informed consent to participate in the study and for the future use of biological specimens.

6.6. Potential Limitations on Recruitment and Mitigation Strategies

Given the fast-changing landscape during the COVID-19 pandemic, potential alterations are considered to mitigate the impact of newly identified therapies that change the standard of care and/or slower than planned enrollment. The study team plans to evaluate the rate of enrollment two weeks after enrollment opens. If fewer than 10 patients have been enrolled within the first two weeks, a potential solution to increase enrollment is to change the randomization ratio to be 2:1 on treatment:control. We have selected a 1:1 ratio under the assumption of equipoise; however, we anticipate that participants may not want to have a 50% chance of being randomized to placebo. To address this concern, we could increase the ratio in order to reduce the chance of being randomized to placebo to 33%. Under the assumptions described in our sample size estimates (Section 12.6 below), the change in the randomization ratio will not require a larger sample size.

7. CONCURRENT MEDICATIONS

7.1 Allowed medications and treatments

a. Acetaminophen
b. Ibuprofen or other non-steroidal anti-inflammatory medications
c. Symptomatic care for cough/URI (e.g., decongestants/cough syrups)

7.2 Prohibited medications and treatments

a. Other investigational and/or immunomodulatory agents for treatment of COVID-19, including but not limited to chloroquine or hydroxychloroquine.
b. Heparin or coumadin

8. STUDY TREATMENTS

8.1 Method of assigning subjects to treatment groups

Up to 120 eligible patients will be randomly assigned to Lambda or placebo in a 1:1 ratio to the treatment and control arms using a REDCAP-based computer-generated randomization scheme developed by the study data management provider. Randomization will be stratified by age (>=50 and <50 years old) and sex. The investigator or designee will complete a password-protected electronic spreadsheet containing the randomization allocation, along with the code used to generate the allocation along with the seed used in the random number generation, will be stored on secure servers at Stanford.

8.2 Blinding

Administration of all study drugs will be single-blind (blinded to the study participant). All doses of study drugs will be prepackaged by the investigational pharmacist and administered by a study nurse not involved in data analysis. The study biostatisticians will be blinded to subject randomization, with the exception of an unblinded subgroup who will generate the randomization scheme and perform unblinded interim analyses. The subgroup will not discuss the unblinded data or interim results with the blinded biostatisticians and will save their materials on a server that is inaccessible to the blinded members. This study blind will be broken on completion of the clinical study and after the study database has been locked. During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the data safety and monitoring board prior to unblinding.

8.3 Formulation of test and control products

8.3.1 Formulation of test product

Peginterferon Lambda-1a (Lambda), 180 mcg, administered as a single subcutaneous injection

8.3.2 Formulation of control

A 0.45mL normal saline in 1 mL syringe sealed with red cap (prevent leaking during transport) The placebo syringe product will not match the test product.

8.3.3 Packaging and labeling

Lambda Injection is a sterile, nonpyrogenic, ready-to-use (RTU) 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-1a drug substance, L-histidine, mannitol, polysorbate 80, hydrochloric acid, and water for injection and for a single use only.

Normal saline injection is a sterile, nonpyrogenic solution that is clear and will be provided in a 1 ml BD plastic syringe with a ½ inch, thin-walled needle with safety shield. Syringes are prefilled with a 0.9% sodium chloride solution and for a single use only. The injection will be prepared by the Stanford Investigational Pharmacy.

8.4 Study drug supply, dosage, administration, and storage

8.4.1 Supply of study drug at the site
Lambda will be shipped by the manufacturer (Eiger BioPharmaceuticals) and stored at the Stanford Health Care Investigational Pharmacy. Normal saline injection will be prepared by the Stanford Health Care Investigational Pharmacy

8.4.2 Dosage
Each participant randomized to receive Lambda will receive a single subcutaneous dose of either 180 mcg Peginterferon Lambda-1a or 0.45 mL normal saline.

8.4.3 Dispensing
Study drug will be dispensed daily by the Stanford Investigational Pharmacy and brought in a cooler to the study clinic for administration.

8.4.4 Administration instructions
Lambda syringes are marked with dose indicator lines, which are used as a reference point for administering the correct dose. The clinician 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 Lambda Injection for delivery of up to 180 mcg.

Both lambda and normal saline will be administered subcutaneously in either the lateral or posterior aspect of the upper arm or thigh. Injection sites should be clean and free of infection, skin lesions, scars, birthmarks, bony prominences, and large underlying muscles, blood vessels, and nerves. A lifted skinfold technique (pinching or bunching the skin) will be used to lift the subcutaneous layer away from underlying muscle, and the skin will be cleaned with an alcohol-impregnated swab before injection at a 90° angle.

Following study drug administration, participants will be observed in the study clinic for thirty minutes to assess for any adverse events.

8.4.5 Storage
Lambda Injection will 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. Lambda injection should not be frozen.

Normal saline injection will be stored in a refrigerator at 2°C to 8°C.

8.4.6 Study drug accountability

Study drug accountability and monitoring will be performed by the Stanford Health Care Investigational Pharmacy. The Investigational Pharmacy will maintain accurate, complete, and current records of receipt, use, or disposition of study drugs, including: 1) dates of receipt, 2) dates of dispensing, 3) quantities currently maintained for dispensing, 4) name of participant and amount dispensed, and 4) amounts remaining at the end of trial and method of disposition. Medications will 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; refrigerators will have temperature logged.

9 SUBJECT MANAGEMENT

9.1 Subject Follow-up

9.1.1. In home assessments.

Participants will complete an at-home symptom questionnaire by REDcap on each day of follow-up through day 28, including in-home assessments of temperature and O2 saturation. These assessments will be reviewed daily by a clinical research coordinator, and patients will be telephoned by a physician if they report an elevated temperature, diminished O2 sat (<94%), or signs/symptoms of respiratory or cardiopulmonary distress (e.g. shortness of breath, dyspnea on exertion). On each day through day 28, patients will also be instructed to collect an anterior nare swab in a pre-labeled container and to store these specimens in a refrigerator at 2°C to 8°C, and to bring these in to their next scheduled appointment. Prior to the optional follow up visits at months 4, 7 and 10, participants will complete an at-home symptom questionnaire and will be asked to collect a stool specimen to bring to their next scheduled appointment.

9.1.2. Follow-up in-clinic assessments.

Participants will be seen at follow-up visits at Day 1±1, 3±1, 5±1, 7±1, 10±1, 14±1, 21±1, and 28±1. At each visit, a subjective medical history will be performed, including assessments for use of any concomitant medications. Vital signs will be obtained (temperature, blood pressure, pulse rate per minute, breath rate per minute and oxygen saturation), and oropharyngeal and anterior nare swabs will be collected. Participants will also submit at-home collected anterior nare swab specimens for evaluation. Clinical laboratory measurements will be performed at days 5±1 and 14±1 to assess for safety, with additional clinical laboratory assessments performed as needed for clinical follow-up and/or patient management. Additionally, ~25 mL peripheral blood will be collected from study participants at enrollment and at Days 5±1, 14±1, and 28±1 for processing and cryopreservation into a specimen biobank. Safety and tolerability of Lambda will be assessed by adverse event (AE) monitoring, vital signs assessment and clinical laboratory tests. Patients will reach the end of study at day 28±1 of follow-up. Optional long-term follow up visits will be scheduled 4,7, and 10 months post-enrollment. The window of ±3 weeks is allowed for these long term follow up visits.

At these long-term follow up visits, patients will undergo a detailed medical history, physical exam and psychosocial assessment, as well as specimen collection for biobank, a 6-minute walk test, and an olfactory assessment using the NIH toolbox. All patients will receive standard supportive care for management of COVID, as defined by clinical practice guidelines: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

9.2 Clinical laboratory measurements

All clinical laboratory measurements (CBC and CMP) at enrolment and during follow-up will be performed using point-of-care CLIA-waived devices or in the Stanford Hospital clinical laboratory. Follow-up clinical laboratory assessments will be performed at Day 5±1 and Day 14±1 post randomization, with additional clinical laboratory assessments performed as needed for clinical follow-up and/or patient management. (Fig 4).

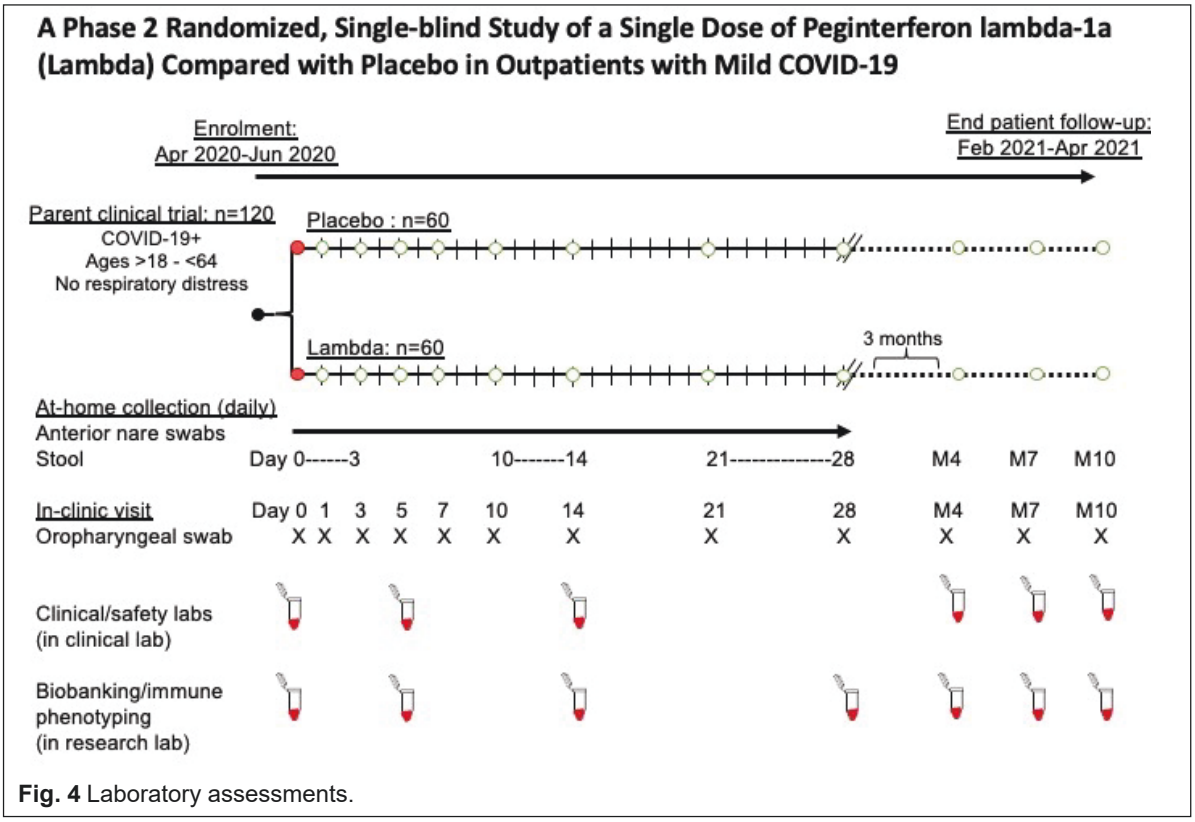

Fig. 4 Laboratory assessments.

9.3 Virologic assessments

Oropharyngeal and anterior nare swabs for SARS-CoV2 RNA will be collected using a standardized technique at all study visits. Additionally, participants will be instructed in collection of anterior nasal swabs at home and asked to collect a swab each day. We will ask participants to collect stool at home (between days 0-3, 10-14, and 21-28; and at 4, 7 and 10 months post-randomization). All swabs will be collected in viral transport media or phosphate buffered saline. Stool will be collected in stabilization tubes, kept at room temperature, and brought to the next study visit. Samples collected in the clinic will be refrigerated and transported the same day to the Stanford clinical virology laboratory for processing. We will ask that swabs collected at home be stored in a 4 degree refrigerator until their study visit, at which point they will be transferred to the study team and transported to the clinical virology laboratory. Fridges will be provided to the participants at enrolment. In the clinical virology laboratory, samples will undergo automated nucleic acid extraction followed by a FDA-cleared quantitative real-time PCR assay for SARS-CoV-2, which will generate both qualitative (positive or negative) and quantitative (estimated viral copies) results. The assay is validated for nasopharyngeal , oropharyngeal, and anterior nare samples. The stool assays have been analytically validated and are undergoing clinical validation.

9.4 Biobanking/Immune phenotyping

We will biobank longitudinal samples collected from patients enrolled in this trial. This will allow for ongoing studies to define the dynamics of the host immune response to COVID-19, with the eventual goal of gaining insight into mechanisms by which control or prevention can be achieved. For biobanking activities, samples will be collected at enrolment, day 5±1, day 14±1, and day 28±1 post-randomization, with optional additional biobanking at 4, 7, and 10 months post-randomization (Fig 4). The window of ±3 weeks is allowed for these long term follow up visits. Stool will be collected as above and biobanked for microbiome assessments.

At the time of blood draw, one 2.5 ml PaxGene tube and two 10 ml CPT (or green-top heparin) tubes will be collected for biobanking and brought to the BSL2+ research lab in Grant S146b. This whole blood then be stored in either stored in specific fixatives, used directly to assess innate immune phenotype and/or the immune response to toll like receptor stimulation, and/or separated into plasma and peripheral blood mononuclear cells (PBMC) using a Ficoll gradient, following standard protocols. All samples will have unique labels with barcodes and unique study identifier. Specimens will be logged into the Stanford Biobank through the OpenSpecimen database tracking system. Plasma will be stored at -80°C for future immunologic and/or pharmacokinetic studies, which may include measurement of levels of cytokines, antibodies, and other features related to the host immune response. PBMCs will be stored in liquid nitrogen to maintain viability, and will be evaluated using flow cytometry, RT-PCR, RNA sequencing, and other assays to assess the host immune response.

In a subset of patients, we will consider a finger stick blood sample at day 14 and/or 28 to collect blood on a dry blood spot to validate performance characteristics of a serologic assay in comparison to venipuncture.

9.5 Reimbursement of subjects

Subjects will receive $40 for each visit to support transportation costs and inconvenience of frequent visits to the clinic for the first 28 days. For the optional visits at months 4, 7 and 10, subjects will receive $100 per visit; this is to encourage study retention. Preferred method of payment is gift card after the completion of each study visit. Subjects will receive a thermometer and a pulse oximeter for study use which they may keep after study completion.

9 ADVERSE EVENT REPORTING AND DOCUMENTATION

10.1. Monitoring and Reporting of Adverse Events

10.1.1. Definitions

An adverse event is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment" (ICH Guidelines E2A). An adverse event can further be broadly defined as any untoward deviation from baseline health, which includes:

- Worsening of conditions present at the onset of the study
- Deterioration due to the primary disease

- Intercurrent illness
- Events related or possibly related to concomitant medications

(International Centers for Tropical Disease Research Network Investigator Manual, Monitoring and Reporting Adverse Events, 2003).

10.1.2. Identification of Adverse Events

At each scheduled and unscheduled visit to the clinic, study clinicians will assess patients according to a standardized case record form. A severity grading scale, based on toxicity grading scales developed by the NIH Divisions of AIDS (DAIDS) Toxicity Tables, will be used to grade severity of all symptoms, physical exam findings, and laboratory results (Appendix 3). All participants, regardless of treatment arm, will be assessed using the same standardized case record form. Adverse event monitoring will occur during the period when study drugs are given and up to 1 month after cessation of study drugs.

Data will be captured on the incidence of all adverse events, regardless of severity. For each adverse event identified and graded as severe or life threatening and felt to be possibly, probably or definitely related to study drugs, an adverse event report form will be completed. In addition, an adverse event form will be completed for all serious adverse events and unexpected events, regardless of severity. An adverse event report form will not be completed for events classified as mild or moderate (unless they are serious or unexpected), as mild and moderate symptoms are common and difficult to distinguish from signs and symptoms due to COVID and other common illnesses. The following information will be recorded for all adverse experiences that are reported:

1) Description of event
2) Date of event onset
3) Date event reported
4) Maximum severity of the event
5) Maximum suspected relationship of the event to study drugs (either SP or DP)
6) Whether the event is a serious adverse event
7) Initials of the person reporting the event
8) Outcome
9) Date event resolved

10.1.3. Reporting of Adverse Events

Guidelines for reporting of adverse events provided by the Stanford Institutional Review Board and the Food and Drug Administration (FDA) in the U.S. will be followed as summarized in Table 1 below.

Table 1. Guidelines for reporting adverse events

Institution	Type of Adverse Events	When to Report
Stanford IRB	Adverse event that Stanford PI determines: • changes the study risks or benefits,	• Within 10 working days of PI's awareness

	OR necessitates modification to the IRB-approved consent document(s) and/or the IRB-approved application/protocol	
FDA	• Definitely, Probably or Possibly related **AND BOTH** Serious* AND Unexpected±	• For fatal or life-threatening events, by telephone or fax within 7 calendar days of first awareness • All other reportable events within 15 calendar days of first awareness

Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience.
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that **may require medical or surgical intervention** to prevent one of the outcomes listed above,
- Event occurring in a gene therapy study
- Event that changes the risk/benefit ratio of the study.

Unexpected Adverse Event An adverse event is defined as being unexpected if the event exceeds the nature, severity, or frequency described in the protocol, consent form and investigator brochure (when applicable). An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the study protocol

10 WITHDRAWAL OF SUBJECTS AND MANAGEMENT OF PROTOCOL VIOLATIONS

10.1 Withdrawal of subjects from the study

Participants will be followed until they reach 28 days post-randomization, with optional follow-up for up to 10 months. Study participants will be prematurely withdrawn from the study for: 1) inability to be located for >7 consecutive days, 2) withdrawal of informed consent, 3) inability to comply with the study schedule and procedures (e.g., missing 3 of the first 6 in-person visits), 4) at the discretion of the site investigator if the study is not in the best interest of the participant, 5) subject judged by the site investigator to be at significant risk of failing to comply with the study protocol as to cause them harm or seriously interfere with the validity of study results. If a subject is withdrawn for reasons # 1 or 2, we will be unable to perform any additional study procedures. If a subject is withdrawn for reasons # 3-5, plans to obtain appropriate follow-up tests outside of the study will be individualized for each subject depending on the health status of the subject at the time of withdrawal and the willingness of the participant and his or her parent/guardian to proceed with additional testing.

10.2 Protocol Violations

All protocol violations will be noted and reported to the Stanford Institutional Review Board within 5 days of the protocol violation report. The PI will develop a corrective action plan to present to the IRB for review and approval.

11 DATA SAFETY MONITORING

The proposed study will conform to rigorous standard monitoring procedures, standardized reporting of adverse events (Adverse Event Report Forms are completed by study coordinators and sent immediately to the investigators), and review of the study by a Data and Safety Monitoring Board (DSMB) at both an interim and final analysis. The PI has primary responsibility for the overall conduct of the study, including the safety of human subjects. The PI will ensure appropriate (1) conduct of the informed consent process (e.g. that informed consent is obtained before proceeding with study procedures); (2) enrollment of study subjects; (3) collection and analysis of data; (4) implementation of study procedures to ensure consistent monitoring of subjects for possible adverse events; (5) review of adverse events and reporting to the DSMB and the IRBs; and (6) maintenance of the privacy and confidentiality of study subjects. The PI maintains ultimate responsibility for the project and for the safety of study participants. The PI will be in contact with the research team on a regular basis to review the progress of the study and address any human subject issues that occur. These discussions may involve adverse event prevention measures, recruiting of appropriate study subjects, research staff training on protection of human subjects, as well as occurrence of adverse events, unexpected incidents, or protocol problems.

11.1. Data and Safety Monitoring Board

A DSMB will be established by the study team in cooperation with the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate the trial. The DSMB will operate according to guidelines documented in a DSMB charter. Minutes will be taken to provide a written record of the DSMB meetings, including interim results; these will be available for review when the trial is complete. The DSMB will be a separate entity from the Institutional Review Board (IRB). The independence of the DSMB is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. DSMB members will not participate in the study as investigators and will not have conflicts of interest regarding the study or the investigational product. The composition of the DSMB will include at minimum:

DSMB Chair, having experience and expertise in clinical trials
Scientist with expertise in viral infectious diseases.
Scientist with expertise in pharmacology
Biostatistician with expertise in clinical trials.

The DSMB will meet before the study, during an interim analysis, and at the conclusion of the trial to review progress of the clinical trial and safety data.

The DSMB will review the study for progress and safety. The PI will provide information that will allow the DSMB to review and assess the following:

· The research protocol, informed consent documents and plans for data safety and monitoring;
· Periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
· Factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the ethics of the trial;
· Study performance to make recommendations and assist in the resolution of problems;
· The safety of the study participants;
· The safety and scientific progress of the trial;
· The continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
· The confidentiality of the data and the results of monitoring; and
· Any problems with study conduct, enrollment, sample size and/or data collection.

The first meeting of the DSMB will take place prior to the initiation of the study to discuss the protocol and the Data Safety Monitoring Plan. Meetings of the DSMB shall be held according to the plan outlined above. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings may be convened as conference calls as well as in person. An emergency meeting of the Board may be called at any time should questions of patient safety arise. The DSMB may request the presence of study investigators at such meetings.

The study PI will distribute study information to the DSMB prior to a scheduled meeting. The DSMB may request additions and other modifications to this information on a one-time or continuing basis. This information will consist of two parts: (1) information on study progress such as accrual, baseline characteristics, and other general information on study status and (2) any confidential data on study outcomes, including safety data. A formal report from the DSMB should be supplied to the PI within 3 days of each meeting. Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A recommendation to terminate the study should be transmitted to the PI and IRBs as rapidly as possible, by immediate telephone and fax if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. At the conclusion of the DSMB meeting for the interim safety review planned at 50% enrollment, the DSMB chair will convey the DSMB’s recommendation to the study PI in order to minimize the amount of time enrollment is paused.

11.2. Interim analysis

An interim analysis for safety and overwhelming efficacy will be performed once 50% of patients have 24 hours of follow-up complete. Enrollment will pause once 50% of patients have received treatment and will remain paused until the DSMB makes their recommendation after their safety review. The DSMB will meet one or two days after enrollment is paused to review the safety data collected within the first 24 hours of follow-up on all enrolled patients. We additionally

expect blood count labs collected at day 5 to be available in approximately 25% of patients at the time of the DSMB review.

The DSMB will also review the efficacy data on all randomized participants at this meeting. The interim efficacy analysis will use the same methods as are planned for the final analysis using the ITT analysis. Based on the results of the interim analysis, the DSMB will either recommend to the sponsor to terminate the study for overwhelming efficacy ($p<0.00001$ at the interim analysis), terminate the study for safety concerns, modify the study, or continue the study as planned. No formal stopping rules for futility are planned.

12 STATISTICAL METHODS AND CONSIDERATIONS

12.1 Analysis population

We will evaluate the intention-to-treat (ITT) population. The intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed according to their assigned treatment arm. All efficacy analyses will be completed in the ITT population. The per-protocol (PP) population will include all randomized patients who completed follow-up and adhered to study procedures. All efficacy analyses will be also be completed in the PP population as supportive evidence for the primary efficacy analysis. The safety population will include all patients who receive study treatment. Patients will be analyzed according to actual treatment received. All safety analyses will be completed in the safety population.

12.2 Descriptive analyses

Descriptive statistics (proportions for categorical variables, means, medians, standard deviations and interquartile ranges for continuous variables) will be reported for all key patient variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status. Data that are missing on key patient characteristics and the outcome will be fully described, including any patterns of missingness (i.e., any relationships between missingness of a variable and patient characteristics).

A CONSORT diagram displaying the number of patients screened, eligible, and consented along with reasons for ineligibility will be provided. Graphical tools such as histograms, boxplots, and scatterplots will be created to assess quality of data and to display patterns over time.

12.3 Analysis of primary endpoint

Time until shedding cessation will be compared between the two treatment arms using a two-sided Cox proportional hazards model adjusted for age and sex. The test will be performed at the alpha = 0.05 level of significance. The hazard ratio for shedding cessation will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption.

The distribution of shedding cessation will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to shedding cessation at the end of the study period along with 95% confidence intervals will be presented for each treatment arm.

In a subgroup analyses, the time until shedding cessation analyses will be performed separately in the symptomatic and asymptomatic participants.

12.4 Analysis of secondary endpoints

SARS-CoV2 Log_{10} viral loads at follow-up timepoints will be compared between groups using the Wilcoxon rank-sum test and/or generalized estimating equations with robust standard errors. The area-under-the-curve (AUC) SARS-CoV2 viral RNA levels during follow-up will be estimated using the linear trapezoidal method, and mean AUC levels compared between groups using the Wilcoxon rank-sum test.

The distribution of cessation of symptoms will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to cessation of symptoms at the end of the study period along with 95% confidence intervals will be presented for each treatment arm. The hazard ratio for cessation of symptoms will be estimated, along with its 95% confidence intervals, from a Cox proportional hazards model. Time to cessation of symptoms will be estimated in the subgroup of patients who are symptomatic at baseline.

The incidence of hospitalizations and emergency department visits will be compared between groups using negative binomial regression models, which will account for differing follow-up times through an offset term.

12.5 Analysis of safety endpoints

The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

12.6 Sample size and randomization

For the primary comparison, the following will be tested:

- Null hypothesis: time to cessation of oral shedding is equal in control and treatment;
- Alternative hypothesis: time to cessation of oral shedding differs between control and treatment.

Hypothesis tests will be two sided and conducted at an overall alpha = 0.05 level of significance.

We assume that the mean duration of virologic shedding in individuals receiving standard of care is 14 days, with a standard deviation of 4 days[1].

Assuming 1:1 randomization and the use of a two-sided log rank test at the alpha=0.04999 level of significance for the final analysis, 79 events will provide 80% power to detect a hazard ratio of 2.03. This leaves alpha=0.00001 to check for overwhelming efficacy after 50% of participants have completed 24 hours of follow-up. Assuming the control and treatment arm median cessation of shedding is 14 and 7 days, respectively, a two-month accrual period, a two-week follow-up period after randomization of the last patient, and a drop out of 10% in the control arm, it is estimated that the total sample size required to achieve 79 events is 120 (60 patients in each arm).

As described in section 6.6 above, we provide the following power calculations showing how potential study alterations due to slow enrolment would impact the study's operating characteristics. If fewer than 10 patients have been enrolled within the first two weeks, a potential solution to increase enrollment is to change the randomization ratio to be 2:1 on treatment:control, which would reduce the chance of being randomized to placebo to 33%. Under the assumptions described above, the change in the randomization ratio will not require a larger sample size.

We also consider how a change in the standard of care could impact our study's power. If the standard of care changes and our expected effect size decreases, our expected power would decrease to 61%, 41%, or 22% under an assumed hazard ratio of 1.8, 1.6, or 1.4, respectively. The impact of the change to the standard of care will depend on what proportion of patients have been enrolled. If the standard of care changes before enrollment is 90% complete, we will estimate the conditional power based on the current enrollment and the expected decrease in the effect size; we would not look at the blinded study data or outcome data to estimate the conditional power. If the conditional power is < 70%, the study will be modified by increasing the sample size such that the conditional power reaches 80%. If the total required sample size to reach 80% conditional power is greater than 180, the study will be stopped for futility.

13. DATA COLLECTION, RETENTION AND MONITORING

13.1 Data collection instruments

Paper data (informed consent documents, screening and contact information) will be maintained in a research chart. The remaining clinical data-- daily questionnaires, case record forms (CRFs), and laboratory results--will be entered and maintained in Stanford's RedCap database using the minimum number of personal identifiers (DOB, dates of visit). Physical copies of laboratory data from point of care devices will be stored in a file. Specimen containers and blood tubes will be labeled by the clinical research coordinator only with study ID and date. Virologic measurements will be entered into a database stored on secured servers and provided from the clinical laboratory to the study team. Biobanked specimens (e.g. PaxGene, plasma, PBMC) will be entered into the Stanford Biobank database stored on secure servers.

13.2 Data management procedures

All subjects will be given a study ID. Symptom questionnaires and CRFs used at clinic visits will be completed by subjects and or study personnel using only study ID. Specimen containers will be labeled by the CRC only with study ID and date, time of collection. Virologic measurements will be provided back to the study team electronically once available, and entered into a RedCap database by a CRC.

13.3 Data quality control and reporting

In order to ensure data quality, the study CRC will perform a nightly data quality audit. For this audit all study forms entered into the data management system from that date will be assessed for accuracy with source documents. In addition, the study Data Manager will perform monthly reviews of the data management system audit trail log to identify potential data quality issues. The data will be owned by Stanford University.

13.4 Archival of data

Electronic data including all study databases and supporting electronic documentation will be archived to cloud-based servers on a daily basis.

13.5 Availability and retention of investigational records

All data will be kept in secured RedCap and Box servers. Only the research team will have access to the data.

13.6 Subject confidentiality

Participants will be asked at screening (after the consent is signed) if it is permissible for the study staff to contact them via telephone. If so, the participant's preferred telephone number will be documented in the research record. Subject identification by phone will require two pieces of personal identification (DOB and subject ID#). Computerized questionnaires via redcap are password protected, encrypted and monitored by Stanford IT.

Participant interactions (interviews, data collection, PEs, blood draws, etc.) will be completed in a private clinic room. The following health information related to this study may be used or disclosed in connection with this research study, including, but not limited to, name and initials, address, email, phone number(s), date of birth, age, sex, race, ethnicity, medical record number, information related to COVID-19 disease, symptoms, physical exams, symptoms that might relate to medication side effects, vital signs including temperature and oxygen saturation levels laboratory tests, radioimaging results, pregnancy test and tests of viral shedding of Covid-19 and other viruses, medications received including study drug, and phone call records.

All subjects will be given a sequential study ID. The code for this ID with personal identifiers will be maintained in a locked research file accessible only to study personnel. Only research personnel will have access to the research records. The data will be keyed into a secure study website in a coded fashion by the study coordinator. Paper research charts will be kept in a locked file cabinet with limited access. The study coordinator is the only one that has the key to the locked cabinet where the research charts are stored. Laboratory personnel will have access to study specimens. The data is transferred by computer via password protected electronic network. When transferring via electronic networks a password protected encrypted computer will be used.

14. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

14.1 Institutional review board

This study protocol, all procedures and consent forms, and any subsequent protocol amendments must be reviewed and approved by the Institutional Review Board of Stanford University.

14.2 Informed consent form

All study participants will provide written informed consent for participation in the study and future use of biologic specimens. (Appendix 2)

14.3 Publications

The findings from this study may be published in a medical journal. No individual identities will be used in any reports or publications resulting from the study. The researchers will publish results of the trial in accordance with Stanford guidelines.

14.4 Investigator responsibilities

The data will be owned by Stanford University. Stanford agrees to provide Eiger BioPharmaceuticals quarterly reports on data safety as described in this protocol. Within six months after completion of the study, Stanford will provide Eiger with a written report of the Study results. The Study Report may take the form of a written manuscript for publication. If the Agreement is terminated early, the Study Report should include, at a minimum, the results of the Study up until the date of termination.

15. References

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Appendix 1. Informed Consent

Are you participating in any other research studies?_____Yes_____No

PURPOSE OF RESEARCH

You are invited to participate in a research study of Peginterferon Lambda-1a. We hope to learn whether a single injection of this medicine decreases the time until you test negative for SARS-CoV-2, the virus that causes coronavirus disease (COVID-19). We will also assess whether it improves your symptoms and whether it causes any side effects. You were selected as a possible participant in this study because you are an outpatient with mild COVID1-9.

If you decide to terminate your participation in this study, you should notify Dr. Upinder Singh at 650-723-4045

This research study is looking for 120 adults with uncomplicated COVID-19 attending the Stanford Hospital and Clinics. Stanford University expects to enroll all 120 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study has two parts: the first part—which is required for participation--is expected to take approximately 6 months to complete, with each of the 120 participants followed for up to 28 days. The second part, which is optional for study participation, will require an additional 9 months of follow-up per participant. The total study will take one year.

PROCEDURES

This study is to assess whether a new drug, given on one occasion under the skin, can decrease the time until you no longer shed the virus SARS-CoV (Coronavirus) from your respiratory tract. We will also assess whether it helps you feel better faster and whether it causes any side effects. The medication we will use, Peginterferon Lambda 1-a (Lambda), has previously been tested in over 200 healthy people and over 3000 people in the treatment of viral hepatitis. Because we don't know if it will work for SARS-CoV2 (COVID-19), we will give the medication only to half of the people who join the study. The other half will receive a placebo injection of normal saline (salt water). In addition, participants in both groups will receive standard of care for COVID-19. The subjects who get the medication will be chosen at random and enrolled participants will not know whether they are receiving the drug or the placebo. The Lambda and control groups can then be compared to see whether the medication is more effective than the symptomatic care at home. You have a 50% chance of receiving Lambda. Lambda is experimental and is not approved by the FDA.
If you choose to participate, the Protocol Director and her research study staff will ask you to do the following

- At the first visit, you will

- Review the research protocol and ask and answer questions confirming that you understand it.
- Be given an ID number that we ask you to save for future use.
- Provide 30 ml (two tablespoons) of blood by venipuncture. This blood will be used to confirm your eligibility for the study. Any remaining blood will be stored for future studies of immune responses and viral biology in Biobank
- Have you throat and anterior (front part) of your nose swabbed for SARS-CoV2 (the virus that causes COVID-19) and other viruses.
- Be randomized to either receive a single injection under your skin (subcutaneously) of Peginterferon Lambda-1a or placebo along with standard-of-care. Because there is no known treatment for this virus, the standard-of-care is rest at home, quarantine from others, and follow-up with healthcare providers as needed.
- If you receive the injection, wait in clinic for 30 minute to ensure you don't have an allergy to the medication
- Be given a thermometer, blood oxygen monitor and mini-fridge for use at home. You will be instructed in their use.

- At home, after the first visit, you will:
  - Take your temperature and blood oxygen levels daily and record the time when these are obtained
  - Record these values daily in a very short, online questionnaire accessible by computer or cell phone. On this questionnaire, you will also be asked to respond daily to questions about symptoms of COVID-19 or of medication side effects that you experience.
  - Collect a sample of anterior nasal swabs daily in the receptacles provided to.
  - Stool samples (optional) will be collected at home (between days 0-3, 10-14, and 21-28).

- Eight required follow-up visits (Treatment Study)
  - Over the subsequent 28 days, you will be asked to attend 8 follow-up visits. We will provide you with a calendar and appointments for these visits. These will occur at
    - 1 day after enrollment
    - 2-4 days after enrollment (no visits will occur on weekends)
    - 4-6 days after enrollment.
    - 7 days after enrollment
    - 9-11 days after enrollment
    - 14 days, 21 and 28 days after enrollment
  - At these visits we will obtain:
    - A swab of your throat for SARS-Cov2
    - On days 4-6, 14, and 28, we will ask for 30 ml (two tablespoons of blood) by venipuncture. These samples will be used to look for medication side

effects and to store for future work on immune responses and viral biology in Biobank.
- Optional finger stick blood will be collected at visit Day 14 and Day 28 on a dry blood spot to validate performance characteristics of a serologic assay in comparison to venipuncture.

- Optional long-term follow-up (Biobank study)
  - If you agree to longer term follow-up, we will collect 30 ml (two tablespoon) blood samples on three occasions, 4 months, 7 months and 10 months after your enrollment, along with additional optional stool samples at 4 months, 7 months and 10 months.
  - At each long-term follow up visit, you will be asked to answer questions about how COVID-19 has affected your health and your quality of life. We will also perform a physical exam, evaluate your oxygen levels after walking, and evaluate your sense of smell.

Your specimens will be sent outside of Stanford for analysis

This research might include whole genome sequencing of specimens. Any of your specimens which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation for three months after receiving Lambda. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study and for at least three months Your doctor will discuss with you what methods of birth control are considered adequate. You should inform your study doctor if your partner becomes pregnant.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Your specimens will be stored with a study ID. After the study is complete, all personal identifiers linked to the study ID will be destroyed. Because your specimens will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the specimens after they are taken.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Genetic Testing and Future Research

As part of the analysis on your specimens, the investigators may do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The results of the study of your specimens from this project will be used for research purposes only, and you will not be told the results of the tests.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff
- Take your temperature and oxygen level daily
- Complete the smart phone/computer questionnaire daily
- Collect anterior nare swab samples daily.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.

- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Upinder Singh.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

- You will be asked to come to our research clinic on nine occasions (eight more following this visit) and twelve occasions if you agree to participate in the longer term follow-up study). This is an inconvenience to you.
- We will collect blood samples on four occasions (save if you agree to the longer term study). Blood draws can cause discomfort, bruising and very, very rarely, infection at the needle site. Some people also feel faint. We will try to minimize these risks by having well-trained blood drawing staff draw your blood.
- We will collect throat swabs on 9 occasions. Throat swabs cause some people to gag and rarely to vomit. We will minimize these risks by having trained personnel do this as rapidly as possible.
- Half of the subjects will receive an experimental drug, Lamda. Those who receive this drug may:
    - Experience discomfort at the injection site for several days
    - Have abnormalities in liver tests for a short period (expected in 20%). These abnormalities are not expected to be severe and the liver tests are expected to rapidly return to normal

    - Have other potential side effects including fatigue, headache or diarrhea. Based on previous studies of healthy individuals, we do not expect these side effects to be common or severe.
- We do not know if this medication will be effective. All subjects, whether receiving treatment or the standard-of-care, may have progression of disease. Because we will be monitoring your symptoms daily, and because you can contact us with any concerns, you will have rapid access to further medical care
- Any study may have unforeseeable consequences to subjects. By carefully monitoring the progress of this study, we will be able to respond to these problems in a timely manner.

POTENTIAL BENEFITS

We hope that this medicine will reduce shedding of SARS-CoV-2 (the virus that causes COVID-19) from your respiratory tract (mouth and nose). Lambda may also reduce the duration of symptoms related to COVID-19, reduce the risk of hospitalization or death from the virus and decrease the risk of any people in your household contracting COVID-19 within 28 days.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES
The alternative to participating is not to participate.

PARTICIPANT'S RIGHTS
You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.
You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov
A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain information on the safety and effectiveness of Peginterferon Lambda-1a. The results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

CONFLICT OF INTEREST
Stanford University has a financial interest in the company supplying materials for this study. Any equity or royalties will be held in an account managed by an independent third party, which will not know about the results of the human subjects research until publicly available.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of this study is to see if the drug, Peginterferon Lambda-1a (Lambda) can reduce shedding of the virus SARS-CoV2 from the respiratory tract. Health information you provide will determine whether you are eligible to participate in the study and whether the medication has affected your symptoms in any way. Blood tests and throat samples you provide will help determine whether the medication causes any side effects and whether it can decrease shedding of the virus.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write

to: Upinder Singh at Lane L134, 300 Pasteur Dr., Stanford University, Stanford CA. 94305-5107.

What Personal Information Will Be Obtained, Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, name and initials, address, email, phone number(s), date of birth, age, sex, race, ethnicity, medical record number, health history and information related to COVID-19 disease and symptoms, symptoms that might relate to medication side effects, vital signs including temperature and blood oxygen saturation levels, laboratory and radioimaging investigation reports, pregnancy test and tests of viral shedding of COVID-19 and other viruses, medication received including study drug, and phone call records.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Upinder Singh
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Eiger Biopharmaceuticals, the manufacturer of Lambda
- The Food and Drug Administration
- The study's Institutional Data Monitoring Committee at Stanford

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on May 1, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment/Reimbursement
You will be paid $40 for each visit to the clinical site to compensate you for travel expenses and inconvenience. For the optional long-term follow up visits at 4, 7 and 10 months, the reimbursement will be $100 per visit. Preferred method of payment is gift card after the completion of each study visit. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment. You will also receive a free thermometer blood oxygen sensor.

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Sponsor
Eiger Biopharmeuticals is providing the medication, Lambda, for this study. Stanford University School of Medicine is providing funding for the conduct of this study via a gift from an unnamed donor unrelated to Eiger Biopharmaceuticals but interested in combatting Covid-19.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Upinder Singh. You may contact her now or later at 650-723-4045.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Upinder Singh at 650-723-4045.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Savita Kamble at 650-736-7388

Alternate Contact: If you cannot reach the Protocol Director, please contact Dr. Julie Parsonnet at 650-725-4561.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;

- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes_____No

Signing your name below means you agree to be in the <u>Treatment Part</u> of the study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant **Date**

_____
Print Name of Adult Participant

Signing your name here means you agree to be in the <u>Biobank Part</u> of the study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant **Date**

_____
Print Name of Adult Participant

_____ _____

Signature of Person Obtaining Consent **Date**

_____
Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness Date

_____
Print Name of Witness

(e.g., staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*

If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.

Appendix 2. Schedule of Events

		Days of follow-up																										Optional f/u		
Assessments	Pre-Screen	0	1	2	3 +/- 1	4	5 +/- 1	6	7	8	9	10 +/- 1	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	112	196	280
Phone Screen and Questionnaires	X																															
At home																																
Daily questionnaire			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temp, O2 sat monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Anterior Nares Swab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Stool Sample collection**					X											X														X	X	X
In Clinic																																
Clinic Visit		X	X		X		X		X			X				X							X							X	X	X
Written Informed Consent		X																														
Medical History	X	X																												X	X	X
Concomittant Medications-Online Q	x	X	X		X		X		X			X				X							X							X	X	X
Physical Exam◆		X					X									X														X	X	X
Vital Signs*		X	X		X		X		X			X				X							X							X	X	X
Respiratory Status Assessments by Clinical staff		X																												X	X	X
O/P Swab collection	Covid +	X	X		X		X		X			X				X							X							X	X	X
Phlebotomy		X					X									X														X	X	X
CBC, CMP, CRP, D-dimer		X					X									X														X	X	X
Biobank		X					X									X														X	X	X
Seum Pregnancy Test		X																														
Randomization		X																														
Study Drug/Placebo Dosing		X																														
1 hr Post dose monitoring		X																														
Adverse Event-Online Q		X	X		X		X		X			X				X							X							X		
Finger stick Blood sample (Optional)																X														X		
*Vital Signs (Pulse, RR, Temp, BP, O2sat)																														X	X	X
◆ PE if clinically warrented																														X	X	X
**collect stool at home (between days 0-3, 10-14, and 21-28;																														X	X	X
Six-minute walk test																														X	X	X

Appendix 3. DAIDS Toxicity Table (clarification Aug 2017)

Division of AIDS Table for Grading the Severity of ADULT AND PEDIATRIC Adverse Events Version 2.1,

July 2017

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

Glossary/Definitions of terms used in tables:

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.

BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal

Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Instructions for use

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

General Considerations

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:
Grade 1 indicates a mild event
Grade 2 indicates a moderate event
Grade 3 indicates a severe event
Grade 4 indicates a potentially life-threatening event
Grade 5 indicates death (Note: This grade is not specifically listed on each page of the grading table).

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Laboratory Values

General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites

should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) Specify type, if applicable	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities1 Hypertension (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction Report only one	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block Report only one > 16 years of age	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block or ventricular delay of 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block of ventricular delay of 3.0 seconds	Complete AV block
Prolonged QTc Interval2	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism Report only one	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash Specify type, if applicable	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Endocrine and Metabolomic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

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Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)

Dysphagia or Odynophagia Report only one and specify location	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis Report only one and specify location	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA

Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskelatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] ≥ 30 years of age	BMD t-score -2.5 to -1	NA	NA	NA

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment

< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis6 ≥ 30 years of age	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see Cognitive, Behavioral, or Attentional Disturbance below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions

of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) Specify type, if applicable	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on parttime basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a fulltime basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay < 18 years of age Specify type, if applicable	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress Report only one	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speechlanguage related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA

Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or panuveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with	Symptoms causing greater than minimal interference	Symptoms causing inability to perform usual social &	NA

	usual social & functional activities	with usual social & functional activities	functional activities	
Cytokine Release Syndrome7	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain8 (not associated with study agent injections and not specified elsewhere) Specify location	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[7] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[8] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Serum Sickness9	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight10 > 5 to 19 years of age	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with lifethreatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with lifethreatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

Urinary

[9] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[10] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness Report only one	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR	Potentially lifethreatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Redness11 Report only one > 15 years of age	social & functional activities		Symptoms causing inability to perform usual social & functional activities	
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially lifethreatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling Report only one > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age
≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age

[11] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Laboratory Values*
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without lifethreatening consequences	pH < 7.3 with lifethreatening consequences
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without lifethreatening consequences	pH > 7.5 with lifethreatening consequences
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High Report only one	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0
Bilirubin Direct Bilirubin13, High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with lifethreatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

13 Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; mmol/L) ≥ 7 days of age	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
< 7 days of age	11.5 to < 12.4 2.88 to < 3.10	12.4 to < 12.9 3.10 to < 3.23	12.9 to < 13.5 3.23 to < 3.38	≥ 13.5 ≥ 3.38
Calcium (Ionized), High (mg/dL; mmol/L)	> ULN to < 6.0 > ULN to < 1.5	6.0 to < 6.4 1.5 to < 1.6	6.4 to < 7.2 1.6 to < 1.8	≥ 7.2 ≥ 1.8
Calcium, Low (mg/dL; mmol/L) ≥ 7 days of age	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
< 7 days of age	6.5 to < 7.5 1.63 to < 1.88	6.0 to < 6.5 1.50 to < 1.63	5.50 to < 6.0 1.38 to < 1.50	< 5.50 < 1.38
Calcium (Ionized), Low (mg/dL; mmol/L)	< LLN to 4.0 < LLN to 1.0	3.6 to < 4.0 0.9 to < 1.0	3.2 to < 3.6 0.8 to < 0.9	< 3.2 < 0.8
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline

Creatinine Clearance12 or eGFR, Low *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; mmol/L) Fasting, High	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Nonfasting, High	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75

Glucose, Low (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
< 1 month of age	50 to 54 2.78 to < 3.00	40 to < 50 2.22 to < 2.78	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without lifethreatening consequences	Increased lactate with pH < 7.3 with lifethreatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; mmol/L) Cholesterol, Fasting, High ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA

[12] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High ≥ 18 years of age	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
> 2 to < 18 years of age	110 to < 130 2.85 to < 3.34	130 to < 190 3.34 to < 4.90	≥ 190 ≥ 4.90	NA
Triglycerides, Fasting, High	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to < 1,000 >5.7 to 11.4	> 1,000 > 11.4
Magnesium13, Low (mEq/L; mmol/L)	1.2 to < 1.4 0.60 to < 0.70	0.9 to < 1.2 0.45 to < 0.60	0.6 to < 0.9 0.30 to < 0.45	< 0.6 < 0.30
Phosphate, Low (mg/dL; mmol/L) > 14 years of age	2.0 to < LLN 0.65 to < LLN	1.4 to < 2.0 0.45 to < 0.65	1.0 to < 1.4 0.32 to < 0.45	< 1.0 < 0.32
1 to 14 years of age	3.0 to < 3.5 0.97 to < 1.13	2.5 to < 3.0 0.81 to < 0.97	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
< 1 year of age	3.5 to < 4.5 1.13 to < 1.45	2.5 to < 3.5 0.81 to < 1.13	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
Potassium, High (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Sodium, High (mEq/L; mmol/L)	146 to < 150 146 to < 150	150 to < 154 150 to < 154	154 to < 160 154 to < 160	≥ 160 ≥ 160
Sodium, Low (mEq/L; mmol/L)	130 to < 135 130 to < 135	125 to < 130 125 to < 130	121 to < 125 121 to < 125	≤ 120 ≤ 120
Uric Acid, High (mg/dL; mmol/L)	7.5 to < 10.0 0.45 to < 0.59	10.0 to < 12.0 0.59 to < 0.71	12.0 to < 15.0 0.71 to < 0.89	≥ 15.0 ≥ 0.89

Hematology

[13] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	 300 to < 400 300 to < 400	 200 to < 300 200 to < 300	 100 to < 200 100 to < 200	 < 100 < 100
Absolute Lymphocyte Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	 600 to < 650 0.600 x 109 to < 0.650 x 109	 500 to < 600 0.500 x 109 to < 0.600 x 109	 350 to < 500 0.350 x 109 to < 0.500 x 109	 < 350 < 0.350 x 109
Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L) > 7 days of age	 800 to 1,000 0.800 x 109 to 1.000 x 109	 600 to 799 0.600 x 109 to 0.799 x 109	 400 to 599 0.400 x 109 to 0.599 x 109	 < 400 < 0.400 x 109
2 to 7 days of age	1,250 to 1,500 1.250 x 109 to 1.500 x 109	1,000 to 1,249 1.000 x 109 to 1.249 x 109	750 to 999 0.750 x 109 to 0.999 x 109	< 750 < 0.750 x 109
≤ 1 day of age	4,000 to 5,000 4.000 x 109 to 5.000 x 109	3,000 to 3,999 3.000 x 109 to 3.999 x 109	1,500 to 2,999 1.500 x 109 to 2.999 x 109	< 1,500 < 1.500 x 109
Fibrinogen, Decreased (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding

Hemoglobin14, Low (g/dL; mmol/L)15 ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
36 to 56 days of age (male and female)	8.5 to 9.6 5.26 to 5.99	7.0 to < 8.5 4.32 to < 5.26	6.0 to < 7.0 3.72 to < 4.32	< 6.0 < 3.72
22 to 35 days of age (male and female)	9.5 to 11.0 5.88 to 6.86	8.0 to < 9.5 4.94 to < 5.88	6.7 to < 8.0 4.15 to < 4.94	< 6.7 < 4.15
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 6.81 to 8.10	9.0 to < 11.0 5.57 to < 6.81	8.0 to < 9.0 4.96 to < 5.57	< 8.0 < 4.96
≤ 7 days of age (male and female)	13.0 to 14.0 8.05 to 8.72	10.0 to < 13.0 6.19 to < 8.05	9.0 to < 10.0 5.59 to < 6.19	< 9.0 < 5.59
INR, High	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN

[14] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[15] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

(not on anticoagulation therapy)				
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 109 to < 125.000 x 109	50,000 to < 100,000 50.000 x 109 to < 100.000 x 109	25,000 to < 50,000 25.000 x 109 to < 50.000 x 109	< 25,000 < 25.000 x 109
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 109 to 2.499 x 109	1,500 to 1,999 1.500 x 109 to 1.999 x 109	1,000 to 1,499 1.000 x 109 to 1.499 x 109	< 1,000 < 1.000 x 109
≤ 7 days of age	5,500 to 6,999 5.500 x 109 to 6.999 x 109	4,000 to 5,499 4.000 x 109 to 5.499 x 109	2,500 to 3,999 2.500 x 109 to 3.999 x 109	< 2,500 < 2.500 x 109

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA

Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A. Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin16, High (mg/dL; µmol/L)17 Term Neonate18				
< 24 hours of age	4 to < 7 68.4 to < 119.7	7 to < 10 119.7 to < 171	10 to < 17 171 to < 290.7	≥ 17 ≥ 290.7
24 to < 48 hours of age	5 to < 8 85.5 to < 136.8	8 to < 12 136.8 to < 205.2	12 to < 19 205.2 to < 324.9	≥ 19 ≥ 324.9
48 to < 72 hours of age	8.5 to < 13 145.35 to < 222.3	13 to < 15 222.3 to < 256.5	15 to < 22 256.5 to < 376.2	≥ 22 ≥ 376.2
72 hours to < 7 days of age	11 to < 16 188.1 to < 273.6	16 to < 18 273.6 to < 307.8	18 to < 24 307.8 to < 410.4	≥ 24 ≥ 410.4
7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	≥ 25 ≥ 427.5

[16] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[17] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[18] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate20 35 to < 37 weeks gestational age	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 171 to < 239.4	≥ 14 ≥ 239.4
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 102.6 to < 171	≥ 10 ≥ 171
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 85.5 to < 136.8	≥ 8 ≥ 136.8
7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	≥ 25 ≥ 427.5
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN