PHASE 1b, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH AN IMMUNOMODULATORY AGENT (N-803) IN ADULTS WITH COVID-19

Study Number:	QUILT-COVID-19
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Chief Medical Officer ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Cell Phone: +1-605-610-6391 Email: John.Lee@ImmunityBio.com

Protocol Version	**Date**
Version 1	07 April 2020

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunityBio, Inc.
Name of Investigational Product: N-803, recombinant human superagonist interleukin (IL)-15 complex (also known as ALT-803)
Name of Active Ingredient: N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
Title of Study: Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number: QUILT-COVID-19
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety and efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - The overall safety of N-803 for the treatment of adult patients with COVID-19, including the incidence of adverse events (AEs) and incidence of serious adverse events (SAEs).
  - Subject clinical status, ie, the percentage of subjects reporting each severity rating on the 7-point ordinal scale (detailed in the study design).
  - Changes in lymphocyte counts in adult patients with COVID-19.

Secondary Objectives:

- To further evaluate efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Time to an improvement of one category from baseline using the 7-point ordinal scale.
  - Mean change in the 7-point ordinal scale from baseline.
  - Change in National Early Warning Score (NEWS; detailed in the study design) from baseline.
  - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Number of days requiring oxygen.
  - Duration and incidence of new oxygen use.
  - Number of ventilator free days.
  - Duration and incidence of new mechanical ventilation.
  - Duration of hospitalization; measured in days.
  - Subject mortality, including date and cause of death (if applicable).
- To further evaluate the safety of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Change from baseline in hemoglobin.
  - Change from baseline in platelets.
  - Change from baseline in white blood cell count.

Study Design:

This is a phase 1b, randomized, blinded, placebo-controlled study in adult subjects with COVID-19. This clinical trial is designed to assess the safety and immunostimulatory activity of N-803.

COVID-19 infection has been shown to cause lymphopenia, specifically a suppression of NK and $CD8^+$ T cells, and severe cases and subsequent fatalities are associated with this significant decline in lymphocytes. N-803 has been shown to stimulate both NK and $CD8^+$ T cells and rescue lymphopenia in normal healthy subjects as well as patients with cancer. Thus, the potential exists for N-803 to rescue lymphopenia in patients infected with COVID-19 and improve disease outcomes.

A total of 30 subjects who have tested positive for SARS-CoV-2 and have confirmed mild/moderate COVID-19 symptoms, as evidenced by a NEWS of 0–4, will be randomly assigned (1:1) to the experimental arm or the placebo control arm. Subjects may or may not be receiving care in an outpatient setting. Subjects will be stratified by duration of known symptoms (≤ 48 hours vs > 48 hours). NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes and will be used as a measure of efficacy. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

Subjects assigned to the experimental arm will receive a subcutaneous (SC) injection of N-803 in the abdomen on day 1 and will be followed for a total of 29 days. Subjects assigned to the control arm will receive an SC injection of placebo in the abdomen on day 1 and will be followed for a total of 29 days. In the experimental arm, subjects will be enrolled sequentially into dose levels with 5 subjects per dose level:

- Dose level 1: 3 μg/kg N-803
- Dose level 2: 6 μg/kg N-803
- Dose level 3: 10 μg/kg N-803

The primary objectives are to evaluate preliminary safety and efficacy of N-803 by evaluating the percentage of subjects reporting each severity rating on the 7-point ordinal scale, and the absolute lymphocyte count (ALC) in adults who test positive for SARS-CoV-2 and have confirmed mild COVID-19 symptoms, as evidenced by a NEWS of 0–4.

The 7-point ordinal scale is an assessment of the clinical status and is performed as the first assessment on each study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.

Blood samples will be collected for hematology and chemistry analyses on days 1, 5, 15, and 29. Pharmacodynamics of lymphocyte response (ie, changes in lymphocyte counts), and immunogenicity will also be monitored.

Safety will be assessed for all subjects and will include monitoring of vital signs, and incidence and severity of adverse events using an outpatient home monitoring system.

Safety will be monitored throughout the study. After the 5 subjects in each dose level of the experimental arm have each completed the first 14 days of treatment, enrollment will be paused and the ImmunityBio Safety Review Committee (SRC) and at least one qualified infectious disease physician, independent of the Sponsor and trial, will perform an evaluation of safety. Enrollment into the subsequent dose level will continue if the safety evaluation suggests that the therapy is safe.

Primary Endpoints:

- AEs and SAEs, graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and clinically significant changes in safety laboratory tests and vital signs.
- Percentage of subjects reporting each severity rating on the 7-point ordinal scale.
- Incidence of lymphopenia (ie, ALC < 1000/mm^3) during COVID-19 infection.

Secondary Endpoints:

- Time to an improvement of one category from baseline using the 7-point ordinal scale.
- Mean change in the 7-point ordinal scale from baseline.
- Change in NEWS from baseline.
- Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Number of days requiring oxygen.
- Duration and incidence of new oxygen use.
- Number of ventilator free days.
- Duration and incidence of new mechanical ventilation.
- Duration of hospitalization.
- Subject mortality, including date and cause of death (if applicable).
- Change from baseline in hemoglobin, platelets, and white blood cell (WBC) count.

Enrollment (planned):

A total of 30 subjects will be randomly assigned (1:1) to the experimental arm (n = 15) or the placebo control arm (n = 15) in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Has laboratory-confirmed positive novel coronavirus (SARS-CoV-2) test, as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 72 hours prior to enrollment, or meets the criteria to guide the evaluation and testing of patients under investigation (PUI) for COVID-19 (https://emergency.cdc.gov/han/2020/HAN00428.asp).
4. Has a confirmed NEW score of 0–4.

5. Adequate respiratory and heart function, evidenced by the following laboratory results:
   a. Respiratory rate (RR) < 20 breaths per minute (bpm).
   b. Heart rate (HR) < 90 beats per minute (bpm).
   c. Arterial oxygen saturation (SaO_2) > 93% on room air.
6. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
7. Ability to participate in required study visits and participate in adequate follow-up, as required by this protocol.
8. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception while on study and for at least 1 month after the last dose of N-803. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the last dose of N-803. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Shortness of breath or hypoxia defined by a ratio of partial pressure of arterial oxygen to the percentage of inspired oxygen (PaO2/FiO2) ≤ 300 mmHg or signs of serious lower airway disease.
2. Signs or symptoms of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS)/shock, or cardiac failure; or need for supplemental oxygen.
3. Inflammatory markers (C-reactive protein [CRP], lactate dehydrogenase [LDH], d-dimer, ferritin, and IL-6) > 1.5 × upper limit of normal (ULN).
4. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
5. Pregnant and nursing women. A negative serum or urine pregnancy test during screening prior to the first dose must be documented before N-803 is administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:

Investigational Products	Dosage	Mode of Administration
N-803	3, 6, or 10 μg/kg day 1	SC

Duration of Treatment:

Subjects will receive N-803 on day 1 and will be followed for a total of 29 days.

Duration of Follow-up:

Subjects who receive study treatment for any reason will be followed via regular visits with a health care professional until either death (by any cause) or for a minimum of 29 days past first administration of N-803.

Reference Therapy, Dosage, and Mode of Administration:

Placebo: 1 mL sterile saline solution administered SC.

Evaluation of Endpoints:

Efficacy: Number of patients with ALC < 1000/mm^3 during COVID-19 infection. Number of patients with improved NEW scores and improved 7-point ordinal scale rating.

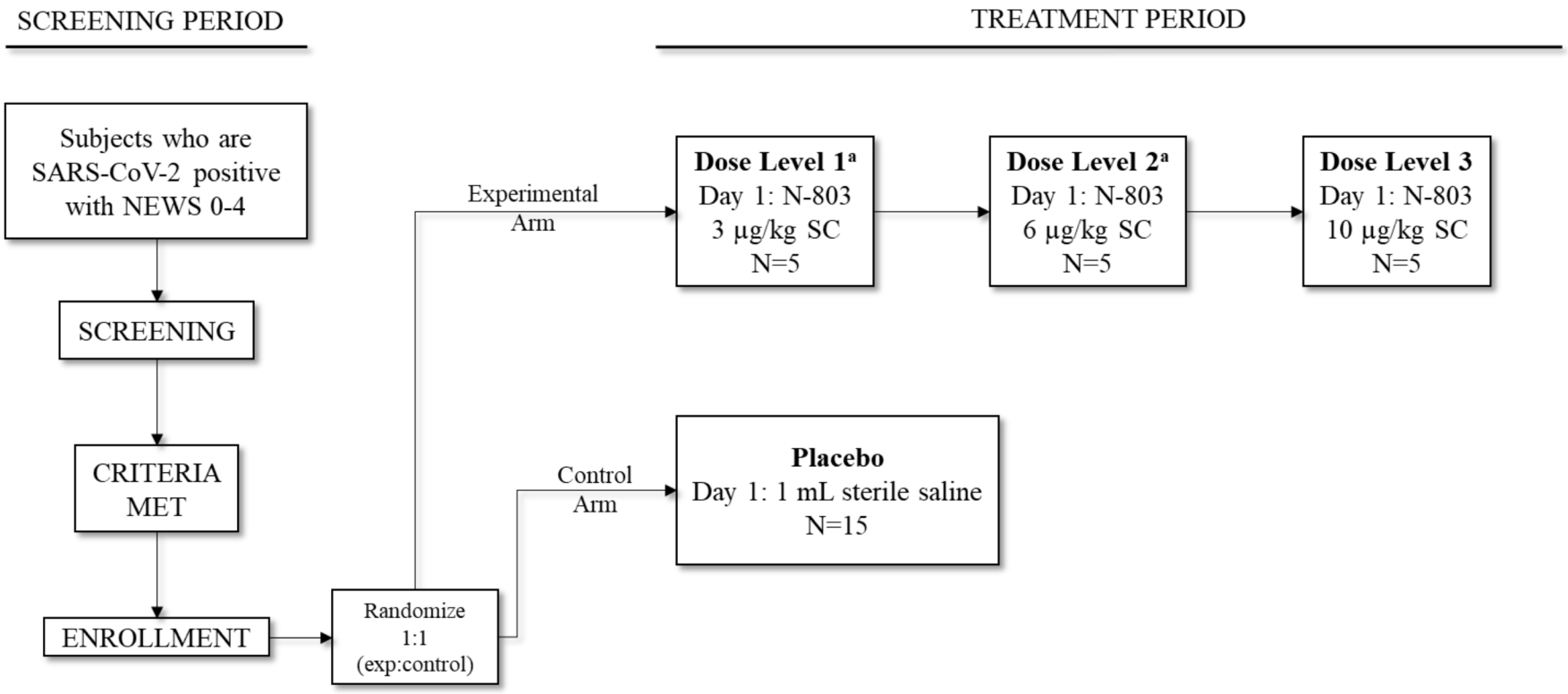
Safety: Safety endpoints include assessments of treatment-emergent AEs, SAEs, and changes in ALC, hemoglobin, platelets, and white blood cell (WBC) count, safety laboratory tests, and vital signs. Toxicities will be graded using CTCAE Version 5.0.

Statistical Methods:

Incidence of subjects with lymphopenia (ie, ALC < 1000/mm^3) during infection and incidence of subjects reporting each severity rating on the 7-point ordinal scale will be presented. Descriptive statistics of improvement in the 7-point ordinal scale rating and NEWS will also be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 5 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, and vital signs.

Figure 1: Study Treatment Schema



[a] Enrollment into the subsequent dose level will continue if the safety evaluation from the first 5 subjects in each dose level suggests that the therapy is safe.

Table 6: Schedule of Events

	Baseline/Screening[a]	**Study Period**			
Study Day	**-2 to 1**	**1**	**5**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
General Assessments					
Informed consent	X				
Inclusion/exclusion	X				
Demographics	X				
Medical history	X				
Confirm contraceptive measures	X				
Physical exam: height, weight[b]	X				
Vital signs[c]	X	X	X	X	X
Ordinal scale (7-point)	X	X	X	X	X
NEWS	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Adverse event collection	X	X	X	X	X

	Baseline/Screening[a]	**Study Period**			
Study Day	**-2 to 1**	**1**	**5**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
Study drug administration					
N-803		X			
Laboratory Assessments					
Chemistry panel[d]	X	X	X	X	X
Hematology[e]	X	X	X	X	X
Pregnancy test[f]	X				
Collect whole blood for immunogenicity and cytokine analyses	X	X	X	X	X
Collect NP swabs	X	X	X	X	X

[a] Baseline/screening assessments may be done any time within 1 calendar day prior to the first dose of N-803. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1.
[b] Height required at baseline/screening visit only. Weight at screening should be used to calculate drug dose.
[c] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Temperature will be documented at each visit and subsequently if clinically indicated.
[d] See Table 5 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to N-803 administration.
[e] Hematology to include CBC with differential (5 part), platelets with hemoglobin and hematocrit, and WBC with differential as outlined in Table 5. Blood draws for lab assessments should occur prior to N-803 administration.
[f] Serum pregnancy tests for females of child-bearing potential.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number:	QUILT-COVID-19
Version Number:	1
Final Date:	07 April 2020

This clinical trial protocol was subject to critical review and has been approved by ImmunityBio. The following personnel contributed to writing and/or approving this protocol:

Signed: DocuSigned by: john lee 1844A39ACB86407... Date: 4/7/2020

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PHASE 1b, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH AN IMMUNOMODULATORY AGENT (N-803) IN ADULTS WITH COVID-19

Study Number:	QUILT-COVID-19
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Chief Medical Officer ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Cell Phone: +1-605-610-6391 Email: John.Lee@ImmunityBio.com

Protocol Version	**Date**
Version 1	07 April 2020
Version 2	29 April 2020

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunityBio, Inc.
Name of Investigational Product: N-803, recombinant human superagonist interleukin (IL)-15 complex (also known as ALT-803)
Name of Active Ingredient: N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
Title of Study: Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number: QUILT-COVID-19
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety and efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - The overall safety of N-803 for the treatment of adult patients with COVID-19, including the incidence of adverse events (AEs) and incidence of serious adverse events (SAEs).
  - Subject clinical status, ie, the percentage of subjects reporting each severity rating on the 7-point ordinal scale (detailed in the study design).
  - Changes in lymphocyte counts in adult patients with COVID-19.

Secondary Objectives:

- To further evaluate efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Time to an improvement of one category from baseline using the 7-point ordinal scale.
  - Mean change in the 7-point ordinal scale from baseline.
  - Change in National Early Warning Score (NEWS; detailed in the study design) from baseline.
  - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Number of days requiring oxygen.
  - Duration and incidence of new oxygen use.
  - Number of ventilator free days.
  - Duration and incidence of new mechanical ventilation.
  - Duration of hospitalization; measured in days.
  - Subject mortality, including date and cause of death (if applicable).
- To further evaluate the safety of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Change from baseline in hemoglobin.
  - Change from baseline in platelets.
  - Change from baseline in white blood cell count.

Study Design:

This is a phase 1b, randomized, blinded, placebo-controlled study in adult subjects with COVID-19. This clinical trial is designed to assess the safety and immunostimulatory activity of N-803.

COVID-19 infection has been shown to cause lymphopenia, specifically a suppression of NK and $CD8^+$ T cells, and severe cases and subsequent fatalities are associated with this significant decline in lymphocytes. N-803 has been shown to stimulate both NK and $CD8^+$ T cells and rescue lymphopenia in normal healthy subjects as well as patients with cancer. Thus, the potential exists for N-803 to rescue lymphopenia in patients infected with COVID-19 and improve disease outcomes.

A total of 30 subjects who have tested positive for SARS-CoV-2 and have confirmed mild/moderate COVID-19 symptoms, as evidenced by a NEWS of 0–5, will be randomly assigned (1:1) to the experimental arm or the placebo control arm. Subjects must be considered as having a higher risk of COVID-19 progression, which requires care in an inpatient hospital setting. Subjects will be stratified by duration of known symptoms (≤ 48 hours vs > 48 hours). NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes and will be used as a measure of efficacy. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

Subjects assigned to the experimental arm will receive a subcutaneous (SC) injection of 3 µg/kg N-803 in the abdomen on day 1 and will be followed for a total of 29 days. Subjects assigned to the control arm will receive an SC injection of placebo in the abdomen on day 1 and will be followed for a total of 29 days. All subjects must receive care on a monitored inpatient floor for a minimum of 5 days and/or until they meet discharge criteria per institutional guidelines. After discharge, subjects will be monitored by daily phone calls and study visits on days 15 and 29.

The primary objectives are to evaluate preliminary safety and efficacy of N-803 by evaluating the percentage of subjects reporting each severity rating on the 7-point ordinal scale, and the absolute lymphocyte count (ALC) in adults who test positive for SARS-CoV-2 and have confirmed mild COVID-19 symptoms, as evidenced by a NEWS of 0–5.

The 7-point ordinal scale is an assessment of the clinical status and is performed as the first assessment on each study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.

Blood samples will be collected for hematology and chemistry analyses on days 1, 5, 15, and 29. Pharmacodynamics of lymphocyte response (ie, changes in lymphocyte counts), and immunogenicity will also be monitored.

Safety will be assessed for all subjects and will include monitoring of vital signs, and incidence and severity of adverse events using an outpatient home monitoring system.

Safety will be monitored throughout the study. The initial 5 subjects in the experimental arm will be administered N-803 in a staggered fashion, with a 72-hour interval between administration of N-803 to each subject. After the first 5 subjects of the experimental arm have each completed the first 14 days of treatment, enrollment will be paused and the ImmunityBio Safety Review Committee (SRC) and at least one qualified infectious disease physician, independent of the Sponsor and trial, will perform an evaluation of safety. Enrollment will continue if the safety evaluation suggests that the therapy is safe.

Primary Endpoints:

- AEs and SAEs, graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and clinically significant changes in safety laboratory tests and vital signs.
- Percentage of subjects reporting each severity rating on the 7-point ordinal scale.
- Incidence of lymphopenia (ie, ALC < 1000/mm^3) during COVID-19 infection.

Secondary Endpoints:

- Time to an improvement of one category from baseline using the 7-point ordinal scale.
- Mean change in the 7-point ordinal scale from baseline.
- Change in NEWS from baseline.
- Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Number of days requiring oxygen.
- Duration and incidence of new oxygen use.
- Number of ventilator free days.
- Duration and incidence of new mechanical ventilation.
- Duration of hospitalization.
- Subject mortality, including date and cause of death (if applicable).
- Change from baseline in hemoglobin, platelets, and white blood cell (WBC) count.

Enrollment (planned):

A total of 30 subjects will be randomly assigned (1:1) to the experimental arm (n = 15) or the placebo control arm (n = 15) in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Has laboratory-confirmed positive novel coronavirus (SARS-CoV-2) test, as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 72 hours prior to enrollment, or meets the criteria to guide the evaluation and testing of patients under investigation (PUI) for COVID-19 (https://emergency.cdc.gov/han/2020/HAN00428.asp).
4. Has a confirmed NEW score of 0–5.

5. Has at least one of the following high-risk factors associated with a higher risk of COVID-19 progression:
    a. Age ≥ 60 years.
    b. Hypertension currently managed by at least 1 antihypertensive medication.
    c. Type 1 or 2 diabetes.
    d. Chronic obstructive pulmonary disease (COPD) diagnosed per medical history.
6. Adequate respiratory and heart function, evidenced by the following laboratory results:
    a. Respiratory rate (RR) < 20 breaths per minute (bpm).
    b. Heart rate (HR) < 90 beats per minute (bpm).
    c. Arterial oxygen saturation (SaO_2) > 93% on room air.
7. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
8. Ability to participate in required study visits and participate in adequate follow-up, as required by this protocol.
9. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception while on study and for at least 1 month after the last dose of N-803. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the last dose of N-803. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Shortness of breath or hypoxia defined by a ratio of partial pressure of arterial oxygen to the percentage of inspired oxygen (PaO2/FiO2) ≤ 300 mmHg or signs of serious lower airway disease.
2. Signs or symptoms of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS)/shock, or cardiac failure; or need for supplemental oxygen.
3. Inflammatory markers (C-reactive protein [CRP], lactate dehydrogenase [LDH], d-dimer, ferritin, and IL-6) > 1.5 × upper limit of normal (ULN).
4. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
5. Pregnant and nursing women. A negative serum or urine pregnancy test during screening prior to the first dose must be documented before N-803 is administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:

Investigational Products	Dosage	Mode of Administration
N-803	3 µg/kg day 1	SC

Duration of Treatment:
Subjects will receive N-803 on day 1 and will be followed for a total of 29 days.

Duration of Follow-up: After discharge, subjects who receive study treatment for any reason will be monitored by daily phone calls and study visits on days 15 and 29 and may be followed via regular visits with a health care professional until either death (by any cause) or for a minimum of 29 days past first administration of N-803.
Reference Therapy, Dosage, and Mode of Administration: Placebo: 1 mL sterile saline solution administered SC.
Evaluation of Endpoints: **Efficacy**: Number of patients with ALC < 1000/mm^3 during COVID-19 infection. Number of patients with improved NEW scores and improved 7-point ordinal scale rating. **Safety:** Safety endpoints include assessments of treatment-emergent AEs, SAEs, and changes in ALC, hemoglobin, platelets, and white blood cell (WBC) count, safety laboratory tests, and vital signs. Toxicities will be graded using CTCAE Version 5.0.
Statistical Methods: Incidence of subjects with lymphopenia (ie, ALC < 1000/mm^3) during infection and incidence of subjects reporting each severity rating on the 7-point ordinal scale will be presented. Descriptive statistics of improvement in the 7-point ordinal scale rating and NEWS will also be presented. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 5 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, and vital signs.

Figure 1: Study Treatment Schema

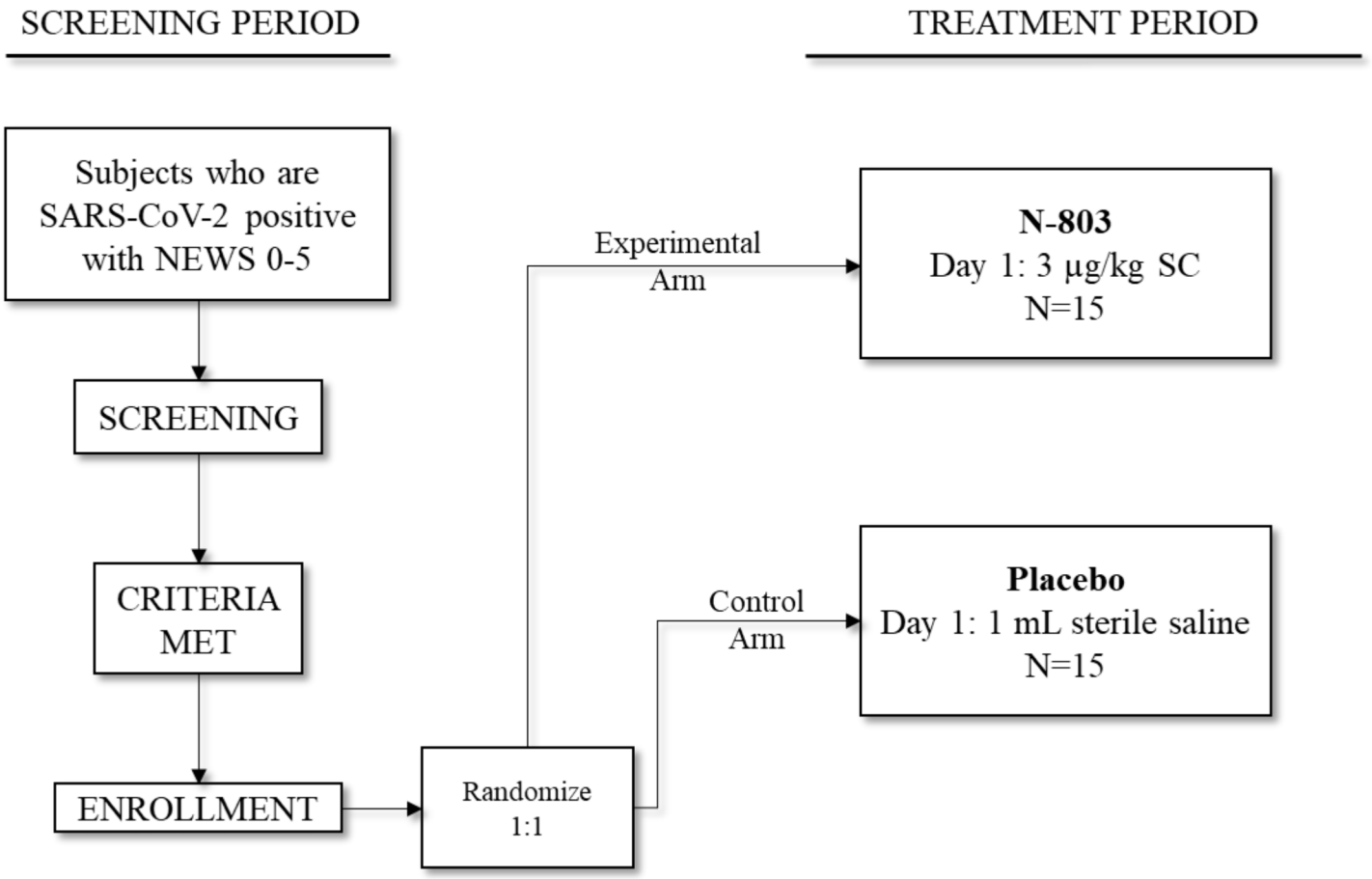

Table 6: Schedule of Events

	Baseline/Screening[a]	**Study Period**			
Study Day	**-2 to 1**	**1**	**Daily until discharge**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
General Assessments					
Informed consent	X				
Inclusion/exclusion	X				
Demographics	X				
Medical history	X				
Confirm contraceptive measures	X				
Physical exam: height, weight[b]	X				
Vital signs[c]	X	X	X	X	X
Ordinal scale (7-point)	X	X	X	X	X
NEWS	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Adverse event collection	X	X	X	X	X

	Baseline/Screening[a]	**Study Period**			
Study Day	**-2 to 1**	**1**	**Daily until discharge**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
Study drug administration					
N-803		X			
Laboratory Assessments					
Chemistry panel[d]	X	X	X	X	X
Hematology[e]	X	X	X	X	X
Pregnancy test[f]	X				
Study Day		**1**	**5**	**15**	**29**
Collect whole blood for immunogenicity and cytokine analyses	X	X	X	X	X
Collect NP swabs	X	X	X	X	X

[a] Baseline/screening assessments may be done any time within 1 calendar day prior to the first dose of N-803. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1.
[b] Height required at baseline/screening visit only. Weight at screening should be used to calculate drug dose.
[c] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Temperature will be documented at each visit and subsequently if clinically indicated.
[d] See Table 5 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to N-803 administration.
[e] Hematology to include CBC with differential (5 part), platelets with hemoglobin and hematocrit, and WBC with differential as outlined in Table 5. Blood draws for lab assessments should occur prior to N-803 administration.
[f] Serum pregnancy tests for females of child-bearing potential.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number:	QUILT-COVID-19
Version Number:	2
Final Date:	29 April 2020

This clinical trial protocol was subject to critical review and has been approved by ImmunityBio. The following personnel contributed to writing and/or approving this protocol:

Signed: DocuSigned by: john lee 1844A39ACB86407... _____ Date: 4/30/2020 _____

John Lee, MD
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PHASE 1b, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH AN IMMUNOMODULATORY AGENT (N-803) IN ADULTS WITH COVID-19

Study Number:	QUILT-COVID-19
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
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Protocol Version	**Date**
Version 1	07 April 2020
Version 2	29 April 2020
Version 3	14 May 2020

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunityBio, Inc.
Name of Investigational Product: N-803, recombinant human superagonist interleukin (IL)-15 complex (also known as ALT-803)
Name of Active Ingredient: N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex)
Title of Study: Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number: QUILT-COVID-19
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety and efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - The overall safety of N-803 for the treatment of adult patients with COVID-19, including the incidence of adverse events (AEs) and incidence of serious adverse events (SAEs).
  - Subject clinical status, ie, the percentage of subjects reporting each severity rating on the 7-point ordinal scale (detailed in the study design).
  - Incidence of lymphopenia (ie, absolute lymphocyte count [ALC] < 1000/mm^3) during COVID-19 infection.

Secondary Objectives:

- To further evaluate efficacy of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Time to an improvement of one category from baseline using the 7-point ordinal scale.
  - Change in the 7-point ordinal scale from baseline.
  - Change in National Early Warning Score (NEWS; detailed in the study design) from baseline.
  - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
  - Number of oxygenation free days.
  - Incidence and duration of new oxygen use.
  - Number of ventilator free days.
  - Incidence and duration of new mechanical ventilation.
  - Duration of hospitalization.
  - Subject mortality and cause of death.
- To further evaluate the safety of N-803 in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
  - Change from baseline in hemoglobin.
  - Change from baseline in platelets.
  - Change from baseline in white blood cell count.
  - Change from baseline in vital signs.

Exploratory Objectives:

- Assessment of therapy-induced changes in immune responses and correlations with subject outcomes.

- Pharmacokinetics (PK) of N-803.

Study Design:

This is a phase 1b, randomized, blinded, placebo-controlled study in adult subjects with COVID-19. This clinical trial is designed to assess the safety and immunostimulatory activity of N-803.

COVID-19 infection has been shown to cause lymphopenia, specifically a suppression of NK and $CD8^+$ T cells, and severe cases and subsequent fatalities are associated with this significant decline in lymphocytes. N-803 has been shown to stimulate both NK and $CD8^+$ T cells and rescue lymphopenia in normal healthy subjects as well as patients with cancer. Thus, the potential exists for N-803 to rescue lymphopenia in patients infected with COVID-19 and improve disease outcomes.

A total of 30 subjects who have tested positive for SARS-CoV-2 and have confirmed mild/moderate COVID-19 symptoms, as evidenced by a NEWS of 0–5, will be randomly assigned (1:1) to the experimental arm or the placebo control arm. Subjects must be considered as having a higher risk of COVID-19 progression, which requires care in an inpatient hospital setting. Subjects will be stratified by duration of known symptoms (≤ 48 hours vs > 48 hours). NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes and will be used as a measure of efficacy. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

Subjects assigned to the experimental arm will receive a subcutaneous (SC) injection of 3 μg/kg N-803 in the abdomen on day 1 and will be followed for a total of 29 days. Subjects assigned to the control arm will receive an SC injection of placebo in the abdomen on day 1 and will be followed for a total of 29 days. All subjects must receive care on a monitored inpatient floor for a minimum of 5 days and/or until they meet discharge criteria per institutional guidelines. After discharge, subjects will be monitored by daily phone calls and study visits on days 15 and 29.

The primary objectives are to evaluate preliminary safety and efficacy of N-803 by evaluating the percentage of subjects reporting each severity rating on the 7-point ordinal scale, and the absolute lymphocyte count (ALC) in adults who test positive for SARS-CoV-2 and have confirmed mild COVID-19 symptoms, as evidenced by a NEWS of 0–5.

The 7-point ordinal scale is an assessment of the clinical status and is performed as the first assessment on each study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.

Blood samples will be collected for hematology and chemistry analyses on days 1, 5, 15, and 29. Pharmacodynamics of lymphocyte response (ie, changes in lymphocyte counts), HLA antibody testing, therapy-induced changes in immune responses, and immunogenicity will also be monitored.

Safety will be assessed for all subjects and will include monitoring of vital signs, and incidence and severity of adverse events using an outpatient home monitoring system.

Safety will be monitored throughout the study. The initial 10 subjects randomized (5 subjects per arm) will be administered study treatment in a staggered fashion, with a 72-hour interval between administration to each subject. After the first 10 subjects have each completed the first 14 days of treatment, enrollment will be paused and the ImmunityBio Safety Review Committee (SRC) and at least one qualified infectious disease physician, independent of the Sponsor and trial, will perform an evaluation of safety. Enrollment will continue if the safety evaluation suggests that the therapy is safe.

Primary Endpoints:

- AEs and SAEs, graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and clinically significant changes in safety laboratory tests and vital signs.
- Percentage of subjects reporting each severity rating on the 7-point ordinal scale.
- Incidence of lymphopenia (ie, ALC < 1000/mm^3) during COVID-19 infection.

Secondary Endpoints:

- Time to an improvement of one category from baseline using the 7-point ordinal scale.
- Change in the 7-point ordinal scale from baseline.
- Change in NEWS from baseline.
- Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Incidence and duration of new oxygen use.
- Number of oxygenation free days.
- Number of ventilator free days.
- Incidence and duration and incidence of new mechanical ventilation.
- Duration of hospitalization.
- Subject mortality and cause of death.
- Change from baseline in hemoglobin, platelets, and white blood cell (WBC) count.
- Change from baseline in vital signs.

Exploratory Endpoints:

- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Pharmacokinetics (PK) of N-803.

Enrollment (planned):

A total of 30 subjects will be randomly assigned (1:1) to the experimental arm (n = 15) or the placebo control arm (n = 15) in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Has laboratory-confirmed positive novel coronavirus (SARS-CoV-2) test, as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 72 hours prior to enrollment, or meets the criteria to guide the evaluation and testing of

patients under investigation (PUI) for COVID-19 (https://emergency.cdc.gov/han/2020/HAN00428.asp).

4. Has a confirmed NEW score of 0–5.
5. Receiving care in an inpatient hospital setting.
6. Has at least one of the following high-risk factors associated with a higher risk of COVID-19 progression:
   a. Age ≥ 60 years.
   b. Hypertension currently managed by at least 1 antihypertensive medication.
   c. Type 1 or 2 diabetes.
   d. Chronic obstructive pulmonary disease (COPD) diagnosed per medical history.
7. Adequate respiratory and heart function, evidenced by the following laboratory results:
   a. Respiratory rate (RR) < 20 breaths per minute (bpm).
   b. Heart rate (HR) < 90 beats per minute (bpm).
   c. Arterial oxygen saturation (SaO_2) > 93% on room air.
8. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
9. Ability to participate in required study visits and participate in adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception while on study and for at least 1 month after the last dose of N-803. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the last dose of N-803. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Shortness of breath or hypoxia defined by a ratio of partial pressure of arterial oxygen to the percentage of inspired oxygen (PaO2/FiO2) ≤ 300 mmHg or signs of serious lower airway disease.
2. Signs or symptoms of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS)/shock, or cardiac failure; or need for supplemental oxygen.
3. Inflammatory markers (C-reactive protein [CRP], lactate dehydrogenase [LDH], d-dimer, ferritin, and IL-6) > 1.5 × upper limit of normal (ULN).
4. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
5. Pregnant and nursing women. A negative serum or urine pregnancy test during screening prior to the first dose must be documented before N-803 is administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
N-803	3 µg/kg day 1	SC

Duration of Treatment:

Subjects will receive N-803 on day 1 and will be followed for a total of 29 days.

Duration of Follow-up:

After discharge, subjects who receive study treatment for any reason will be monitored by daily phone calls and study visits on days 15 and 29 and may be followed via regular visits with a health care professional until either death (by any cause) or for a minimum of 29 days past first administration of N-803.

Reference Therapy, Dosage, and Mode of Administration:

Placebo: 1 mL sterile saline solution administered SC.

Evaluation of Endpoints:

Efficacy: Number of patients with ALC < 1000/mm^3 during COVID-19 infection. Changes in NEWS and 7-point ordinal scale.

Safety: Safety endpoints include assessments of treatment-emergent AEs, SAEs, and changes in safety laboratory tests and vital signs. Toxicities will be graded using CTCAE Version 5.0.

Statistical Methods:

Incidence of subjects with lymphopenia (ie, ALC < 1000/mm^3) during COVID-19 infection and incidence of subjects reporting each severity rating on the 7-point ordinal scale will be presented. Descriptive statistics of improvement in the 7-point ordinal scale rating and NEWS will also be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE version 5 in terms of treatment-emergent AEs, SAEs, and changes in safety laboratory tests and vital signs from baseline.

Figure 1: Study Treatment Schema

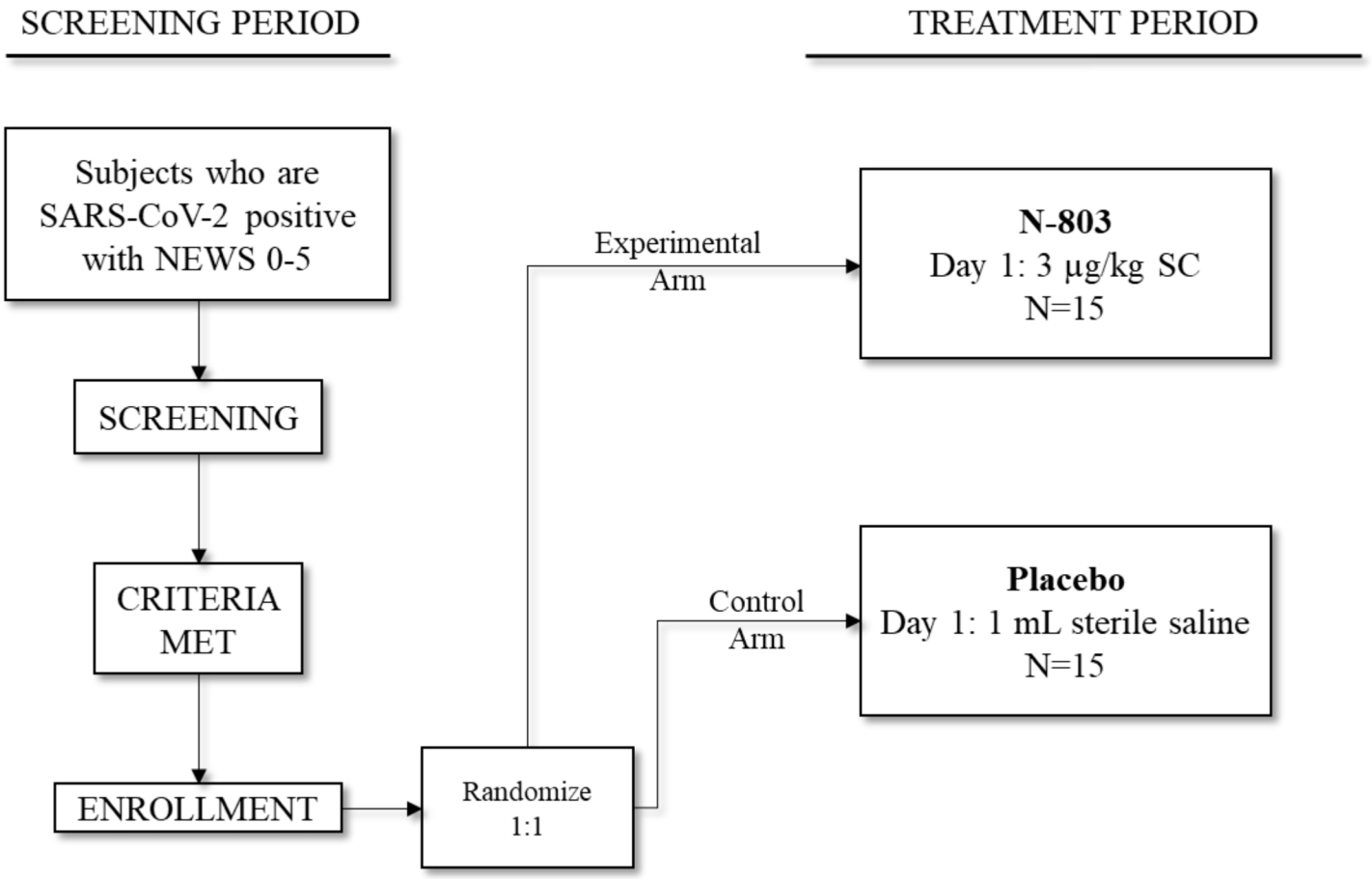

Table 6: Schedule of Events

	Baseline/Screening[a]	**Study Period**			
Study Day	**-2 to 1**	**1**	**Daily until discharge**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
General Assessments					
Informed consent	X				
Inclusion/exclusion	X				
Demographics	X				
Medical history	X				
Confirm contraceptive measures	X				
Physical exam: height, weight[b]	X				
Vital signs[c]	X	X	X	X	X
Ordinal scale (7-point)	X	X	X	X	X
NEWS	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Adverse event collection	X	X	X	X	X

	Baseline/Screening[a]	Study Period			
Study Day	**-2 to 1**	**1**	**Daily until discharge**	**15**	**29 (EOS)**
Windows (days)		**± 1**			
Study drug administration					
N-803		X			
Laboratory Assessments					
Chemistry panel[d]	X	X	X	X	X
Hematology[e]	X	X	X	X	X
Pregnancy test[f]	X				
Other Assessments					
Study Day		**1**	**5**	**15**	**29**
Collect whole blood for cytokine analyses	X	X	X	X	X
Collect whole blood for immunology analysis	X	X	X	X	X
PK sampling[g]		X	X		
Collect NP swabs	X	X	X	X	X

[a] Baseline/screening assessments may be done any time within 1 calendar day prior to the first dose of N-803. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1.
[b] Height required at baseline/screening visit only. Weight at screening should be used to calculate drug dose.
[c] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Temperature will be documented at each visit and subsequently if clinically indicated.
[d] See Table 5 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to N-803 administration.
[e] Hematology to include CBC with differential (5 part), platelets with hemoglobin and hematocrit, and WBC with differential as outlined in Table 5. Blood draws for lab assessments should occur prior to N-803 administration.
[f] Serum pregnancy tests for females of child-bearing potential.
[g] Whole blood for PK analysis will be collected prior to injection and at 0.5, 1, 2, 4, 8, 24, 48, 72, 96, and 120 hours post injection, as detailed in Section 6.3.2.

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1b, randomized, blinded, placebo-controlled study of the safety of therapeutic treatment with an immunomodulatory agent (N-803) in adults with COVID-19.
Study Number:	QUILT-COVID-19
Version Number:	3
Final Date:	14 May 2020

This clinical trial protocol was subject to critical review and has been approved by ImmunityBio. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 5/14/20

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