PHASE 1b RANDOMIZED, OPEN-LABEL STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH IMMUNOMODULATORY MESENCHYMAL STEM CELLS IN ADULTS WITH COVID-19 INFECTION REQUIRING MECHANICAL VENTILATION

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

Protocol Version	**Date**
Version 1	08 Apr 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: NantKwest, Inc.
Name of Investigational Product: BM-Allo.MSC
Name of Active Ingredient: BM-Allo.MSC
Title of Study: Phase 1b Randomized, Open-Label Study of the Safety of Therapeutic Treatment with Immunomodulatory Mesenchymal Stem Cells in Adults with COVID-19 Infection Requiring Mechanical Ventilation
Study Number: QUILT-COVID-19-MSC
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety and efficacy of BM-Allo.MSC vs best supportive care in subjects who have tested positive for SARS-CoV-2 (COVID-19) and require ventilator support, as assessed by:
    - Mortality within 30 days of randomization.
    - Number of ventilator-free days within 60 days.

Secondary Objectives:

- To further evaluate efficacy of BM-Allo.MSC vs best supportive care in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
    - Days alive off mechanical ventilator support within 60 days of randomization
    - Incidence of SAEs within 30 days
    - Time to an improvement of one category from admission using the ordinal scale.
    - Mean change in the ordinal scale from baseline.
    - Change in NEWS from baseline.
    - Time to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
    - Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
    - Number of days requiring oxygen.
    - Duration of hospitalization.
    - Subject mortality, including date and cause of death (if applicable).
- To further evaluate the safety of BM-Allo.MSC 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, open-label study in adult subjects with Coronavirus Disease 2019 (COVID-19). This clinical trial will evaluate the safety and efficacy of BM-Allo.MSC vs best supporting care in treating patients with severe disease requiring ventilator support during COVID-19 infection. Only subjects with moderate or severe ARDS (per Berlin criteria; see Appendix 1) will be enrolled in this study.

COVID-19 infection causes progressive severe lung infection that can lead to death in a significant number of infected patients. Prior work using allogeneic mesenchymal stem cells (MSCs) in severely infected individuals has shown promise in reversing the severe consequences of infection in critically ill patients. Thus, the potential exists for allogeneic MSCs to slow or halt disease progression and reduce time on ventilators in critically ill patients infected with COVID-19, and thus improve disease outcomes.

A total of 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be enrolled in this study. Subjects will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects).

Subjects in the experimental arm will be administered BM-Allo.MSC (1×10^6 cells/kg IV) on day 1 and day 5 (day 5 only if the subject still requires ventilation on day 5). Subjects will be followed through day 60. Subjects in the control arm will be treated with best supportive care and followed through day 60.

All subjects will be assessed using an ordinal scale that evaluates clinical status at the first assessment of 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.

In addition, all subjects will be assessed using the standard National Early Warning Score (NEWS) score (Royal College of Physicians 2012). The NEWS score has demonstrated an ability to identify 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).

The primary objectives are to evaluate the percentage of subjects reporting each severity rating on the 7-point ordinal scale in adults with COVID-19.

Safety will be assessed for all subjects and will include monitoring of vital signs and incidence and severity of adverse events. Blood samples will be collected for hematology and chemistry analyses.

Safety will be monitored throughout the study. After the first 3 subjects in the experimental arm have each completed the first 14 days of treatment, enrollment will be paused and the NantKwest Safety Review Committee (SRC) will perform an evaluation of safety. Enrollment will continue if the safety evaluation from the initial 3 subjects suggests that the therapy is safe.

Primary Endpoints:

- Mortality within 30 days of randomization
- Number of ventilator-free days within 60 days

Secondary Endpoints:

- Days alive off mechanical ventilator support within 60 days of randomization
- Incidence of SAEs within 30 days
- Time to an improvement of one category from admission using the ordinal scale.
- Mean change in the ordinal scale from baseline.
- Change in NEWS from baseline.
- Time to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
- Number of days requiring oxygen.
- 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 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects) 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. For patients that are intubated and/or sedated, or otherwise unable to provide consent, prospective consent from a legally-authorized representative is required. The patient or his/her legally authorized representative mush be able to provide consent.
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. Requiring mechanical ventilatory support with moderate to severe Acute Respiratory Distress Syndrome (ARDS) as determined by the Berlin criteria:
   a. Bilateral opacities present on a chest radiograph or computed tomographic (CT) scan. These opacities are not fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.
   b. Origin of Edema: Respiratory failure not fully explained by cardiac failure or fluid overload.
   c. Oxygenation: Moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:
      - Moderate: PaO_2/FiO_2 >100 mmHg and ≤ 200 mmHg, on ventilator settings that include PEEP ≥ 5 cm H_2O
      - Severe: PaO_2/FiO_2 ≤100 mmHg on ventilator settings that include PEEP ≥5 cm H_2O

   Subjects receiving extracorporeal membrane oxygenation (ECMO) will not be enrolled in this study.
5. High-sensitivity C-reactive Protein (hs-CRP) serum level > 4.0 mg/dL
6. Acute Physiology and Chronic Health Evaluation (APACHE IV) score > 5
7. Agrees to the collection of nasopharyngeal (OP) swabs and venous blood per protocol.
8. Ability to attend required study visits and return for 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 BM-Allo.MSC. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the dose of BM-Allo.MSC. 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. Known hypersensitivity to any component of the study medication(s).
2. Signs of multisystem organ failure. Liver function tests (LFTs) > 5x normal.
3. Patients intubated > 72 hours.
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 pregnancy test during screening (within 72 hours prior to the first dose) must be documented before MSCs are administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
BM-Allo.MSC	~1×10^6 cells/kg	IV

Duration of Treatment:

Subjects in the experimental arm will be administered BM-Allo.MSC (1×10^6 cells/kg IV) on day 1 and day 5 (day 5 only if the subject still requires ventilation on day 5). Subjects will be followed through day 60. Subjects in the control arm will be treated with best supportive care and followed through day 60.

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 30 days after administration of BM-Allo.MSC.

Reference Therapy, Dosage, and Mode of Administration:

Best supportive care.

Evaluation of Endpoints:

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

Efficacy: Number of subjects reporting each severity rating on the 7-point ordinal scale and number of subjects with improved NEW scores and 7-point ordinal scale.

Statistical Methods:

All subjects receiving at least one dose of study drug (ie, the treated population) will be included in the safety and efficacy analyses. Statistical analysis will be descriptive and presented by treatment arm. No statistical testing will be performed.

Safety Analyses:

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.

Efficacy Analyses:

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 and the NEWS will also be presented.

Figure 1: Study Treatment Schema

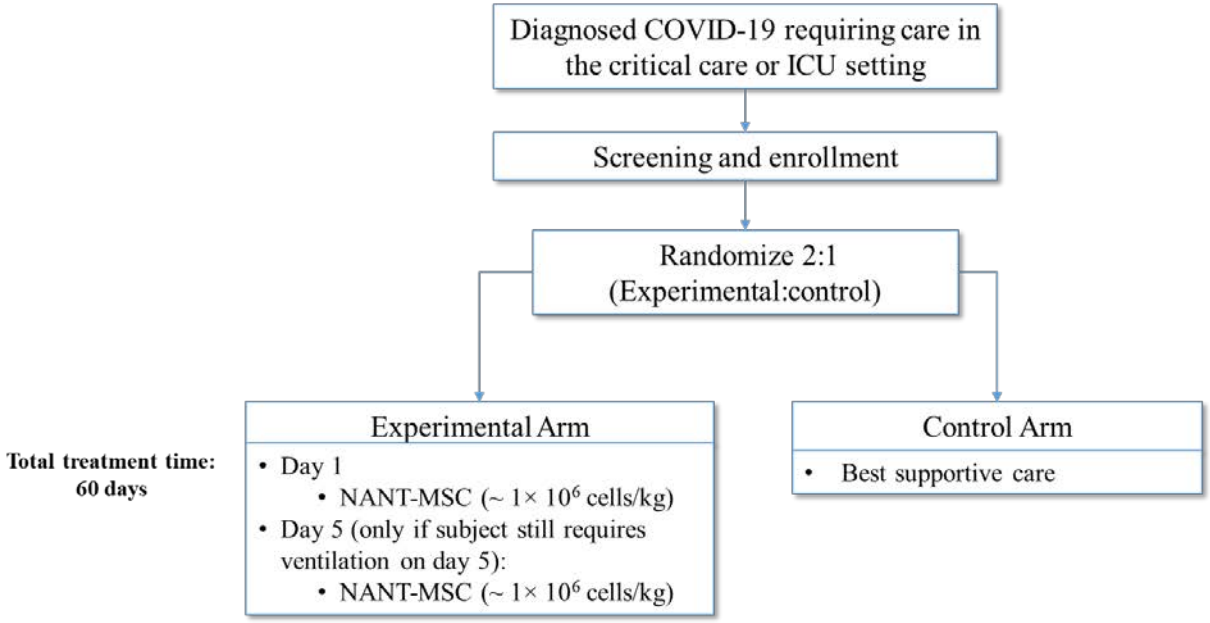

Table 6: Schedule of Events

	Baseline/Screening[a]	**Study Day**						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**EOS**
Windows (days)		**± 1**						**± 4**
General Assessments								
Informed consent	X							
Inclusion/exclusion	X							
Demographics	X							
Medical history	X							
Confirm contraceptive measures	X							
APACHE assessment	X							
High-sensitivity CRP	X							
Physical exam: height, weight[b]	X	X	X					
Vital signs[c]	X	Daily, throughout study period						
SOFA assessment	X	X		X	X	X	X	X
Ordinal scale (7-point)	X	X		X	X	X	X	X
NEWS	X	X		X	X	X	X	X
Concomitant medications[c]	X	Daily, throughout study period						X
Adverse event collection[c]	X	Daily, throughout study period						X

	Baseline/Screening[a]	Study Day						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**EOS**
Windows (days)		**± 1**						**± 4**
Study drug administration								
BM-Allo.MSC		X	X[d]					
Laboratory Assessments								
Chemistry panel[e]	X	X		X	X	X	X	X
Hematology[f]	X	X		X	X	X	X	X
Collect whole blood for immunogenicity and cytokine analyses	X	X		X	X	X	X	X
Pregnancy test[g]	X							

[a] Baseline/screening assessments may be done ≤ 1 calendar day prior to the first dose of BM-Allo.MSC. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1. Assessments performed on day 1 must be performed before dosing.

[b] Height required at baseline/screening visit only. Weight on day 1 should be used to calculate drug dose.

[c] Vital signs, concomitant medications, and adverse event collection will occur daily throughout the study period (ie, each day beginning day 1 and continuing through day 29). Vital signs of temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate will be assessed at every visit.

[d] Administered only to subjects still requiring mechanical ventilation on day 5.

[e] See Table 5 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to BM-Allo.MSC administration.

[f] Hematology to include CBC with differential (5 part) as outlined in Table 5. Blood draws for lab assessments should occur prior to BM-Allo.MSC administration.

[g] Serum pregnancy tests for females of child-bearing potential.

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APPENDIX 4. SPONSOR SIGNATURE

Study Title:	Phase 1b Randomized, Open-Label Study of the Safety of Therapeutic Treatment with Immunomodulatory Mesenchymal Stem Cells in Adults with COVID-19 Infection Requiring Mechanical Ventilation
Study Number:	QUILT-COVID-19-MSC
Version Number:	1
Final Date:	08 Apr 2020

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

Signed: DocuSigned by: john lee 1844A39ACB86407... Date: 4/8/2020

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PHASE 1B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH IMMUNOMODULATORY MESENCHYMAL STEM CELLS IN ADULTS WITH COVID-19 INFECTION REQUIRING MECHANICAL VENTILATION

Study Number:	QUILT-COVID-19-MSC
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Senior Vice President, Medical Affairs NantKwest, Inc 9920 Jefferson Blvd Culver City, CA 90232 Email: lennie.sender@nantkwest.com Cell Phone: 714-615-2350

Protocol Version	**Date**
Version 1	08 Apr 2020
Version 2	19 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: NantKwest, Inc.
Name of Investigational Product: BM-Allo.MSC
Name of Active Ingredient: BM-Allo.MSC
Title of Study: Phase 1b Randomized, Double-Blind, Placebo-Controlled Study of the Safety of Therapeutic Treatment with Immunomodulatory Mesenchymal Stem Cells in Adults with COVID-19 Infection Requiring Mechanical Ventilation
Study Number: QUILT-COVID-19-MSC
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety of BM-Allo.MSC vs placebo in terms of adverse events within 30 days of randomization.
- To evaluate preliminary efficacy of BM-Allo.MSC vs placebo in subjects who have tested positive for SARS-CoV-2 (COVID-19) and require ventilator support, as assessed by:
    - Mortality and cause of death within 30 days of randomization.
    - Number of ventilator-free days within 60 days of randomization.

Secondary Objectives:

- To further evaluate preliminary efficacy of BM-Allo.MSC vs placebo in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
    - Time from randomization to an improvement of one category in the 7-point ordinal scale.
    - Change in the 7-point ordinal scale from baseline.
    - Change in National Early Warning Score (NEWS) from baseline.
    - Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
    - Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
    - Number of days requiring oxygen within 60 days of randomization.
    - Duration of hospitalization from randomization.
- To further evaluate the safety of BM-Allo.MSC in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
    - Incidence of SAEs within 30 days of randomization.
    - Change from baseline in hemoglobin.
    - Change from baseline in platelets.
    - Change from baseline in white blood cell count.
    - Change from baseline in vital signs.

Study Design:

This is a phase 1b randomized, double-blind, placebo-controlled study in adult subjects with Coronavirus Disease 2019 (COVID-19). This clinical trial will evaluate the preliminary safety and efficacy of BM-Allo.MSC vs placebo in treating subjects with severe disease requiring ventilator support during COVID-19 infection. Only subjects with moderate or severe ARDS (per Berlin criteria; see Appendix 1) will be enrolled in this study.

COVID-19 infection causes progressive severe lung infection that can lead to death in a significant number of infected patients. Prior work using allogeneic mesenchymal stem cells (MSCs) in severely infected individuals has shown promise in reversing the severe consequences of infection in critically ill patients. Thus, the potential exists for allogeneic MSCs to slow or halt disease progression and reduce time on ventilators in critically ill patients infected with COVID-19, and thus improve disease outcomes.

A total of 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be enrolled in this study. Subjects will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects).

Subjects in the experimental arm will be administered BM-Allo.MSC (~1×10^6 cells/kg IV) on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5. Subjects will be followed through day 60. Subjects in the control arm will be administered placebo on a schedule identical to that of the experimental arm and followed through day 60. The investigational product will contain BM-Allo.MSC in 5% albumin (human), USP, and Plasmalyte A USP (1:1 ratio) in a volume of 100 mL. The placebo will consist of 5% albumin (human), USP, and Plasmalyte A USP (1:1 ratio) in a volume of 100 mL.

All subjects will be assessed using a 7-point ordinal scale that evaluates clinical status at the first assessment of 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.

In addition, all subjects will be assessed using the standard National Early Warning Score (NEWS) score (Royal College of Physicians 2012). The NEWS score has demonstrated an ability to identify 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).

Safety will be assessed for all subjects and will include monitoring of vital signs and incidence and severity of adverse events. Blood samples will be collected for hematology and chemistry analyses.

Safety will be monitored throughout the study. After the first 5 subjects are randomized (giving at least 3 subjects in the experimental arm) enrollment will be paused and the NantKwest Safety Review Committee (SRC) will perform an evaluation of safety once the 5 subjects have completed the 14 day toxicity assessment period. Enrollment will continue if the safety evaluation from the initial 5 subjects suggests that the therapy is safe.

Primary Endpoints:

- Incidence of AEs within 30 days of randomization.
- Mortality within 30 days of randomization.
- Cause of death within 30 days of randomization
- Number of ventilator-free days within 60 days of randomization.

Secondary Endpoints:

- Time from randomization to an improvement of one category using the ordinal scale.
- Change in the 7-point ordinal scale from baseline.
- Change in NEWS from baseline.
- Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
- Number of days requiring oxygen.
- Duration of hospitalization from randomization.
- Incidence of SAEs within 30 days of randomization
- Change from baseline in hemoglobin, platelets, and white blood cell (WBC) count.
- Changes in vital signs from baseline.

Enrollment (planned):

A total of 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects) 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. For subjects that are intubated and/or sedated, or otherwise unable to provide consent, prospective consent from a legally-authorized representative is required. The subject or his/her legally authorized representative must be able to provide consent.
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. Requiring mechanical ventilatory support with moderate to severe Acute Respiratory Distress Syndrome (ARDS) as determined by the Berlin criteria:
   a. Bilateral opacities present on a chest radiograph or computed tomographic (CT) scan. These opacities are not fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.
   b. Origin of Edema: Respiratory failure not fully explained by cardiac failure or fluid overload.
   c. Oxygenation: Moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:
      - Moderate: PaO_2/FiO_2 >100 mmHg and ≤ 200 mmHg, on ventilator settings that include PEEP ≥ 5 cm H_2O
      - Severe: PaO_2/FiO_2 ≤100 mmHg on ventilator settings that include PEEP ≥5 cm H_2O

   Subjects receiving extracorporeal membrane oxygenation (ECMO) will not be enrolled in this study.
5. High-sensitivity C-reactive Protein (hs-CRP) serum level > 4.0 mg/dL
6. Acute Physiology and Chronic Health Evaluation (APACHE IV) score > 5
7. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
8. Ability to attend required study visits and return for 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 BM-Allo.MSC. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the dose of BM-Allo.MSC. 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. Known hypersensitivity to any component of the study medication(s).
2. Signs of multisystem organ failure. Liver function tests (LFTs) > 5x normal.
3. Intubated > 72 continuous hours.
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 pregnancy test during screening (within 72 hours prior to the first dose) must be documented before MSCs are administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
BM-Allo.MSC	~1 × 10^6 cells/kg	IV
Duration of Treatment: Subjects in the experimental arm will be administered BM-Allo.MSC (~1×10^6 cells/kg IV) on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5. Subjects will be followed through day 60. Subjects in the control arm will be treated with placebo on a schedule identical to that of the experimental arm and followed through day 60.		
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 30 days after administration of BM-Allo.MSC.		
Reference Therapy, Dosage, and Mode of Administration: Subjects randomized to the control arm will receive an IV infusion of placebo, consisting of the vehicle solution used for the cell suspension product. The vehicle solution consists of 5% albumin (human), USP, and Plasmalyte A USP (1:1 ratio) in a volume of 100 mL.		

Evaluation of Endpoints:

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

Efficacy: Mortality and cause of death within 30 days of randomization, number of ventilator-free days with 60 days of randomization, number of subjects reporting each severity rating on the 7-point ordinal scale, and number of subjects with improved NEW scores and 7-point ordinal scale.

Statistical Methods:

All subjects receiving at least one dose of study drug (ie, the Safety population) will be included in the safety and efficacy analyses. Statistical analysis will be descriptive and presented by treatment arm. No statistical testing will be performed.

Safety Analyses:

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 AEs by grade and clinically significant changes in safety laboratory tests and vital signs.

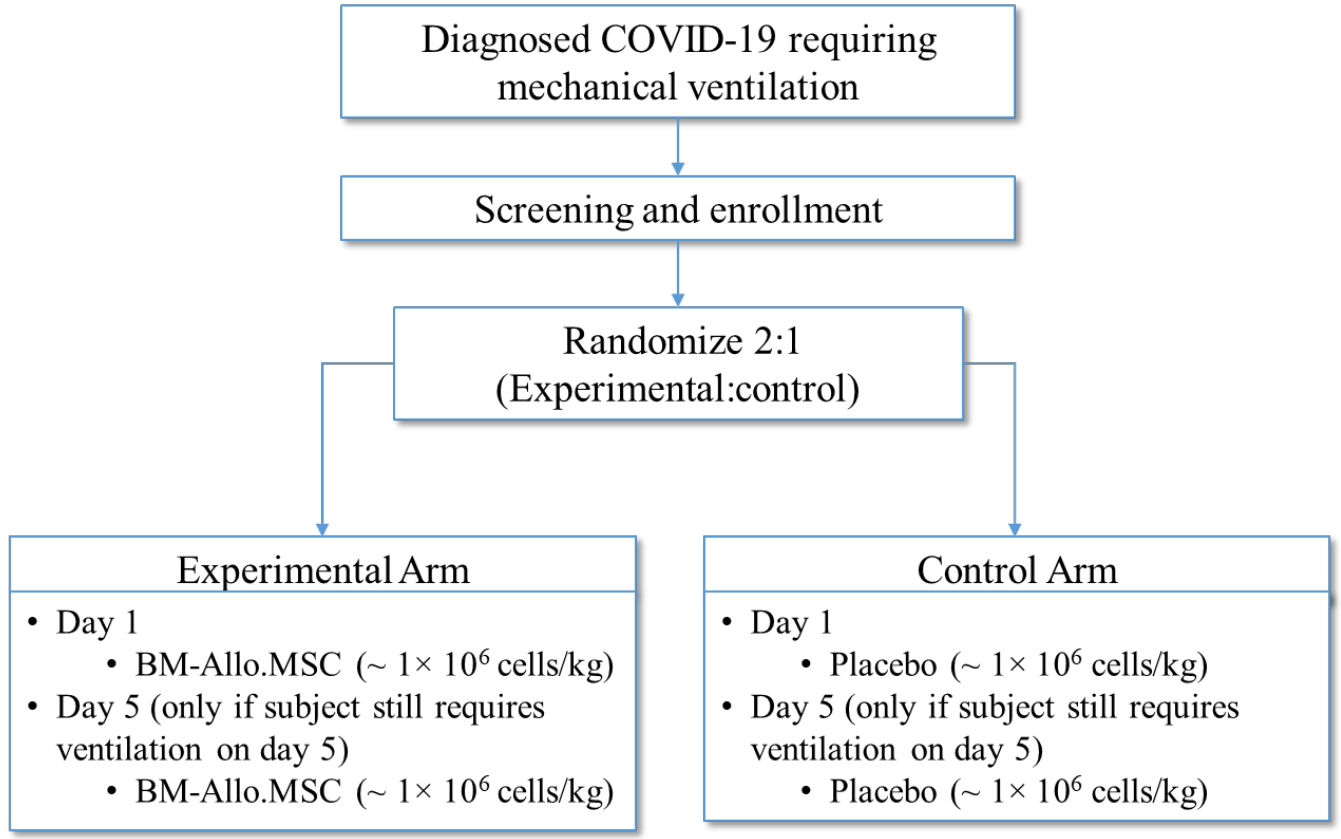
Efficacy Analyses:

The mortality rate within 30 days of randomization and 95% confidence interval will be summarized. Cause of death will be summarized. The mean number of ventilator-free days and number of days requiring oxygen within 60 days of randomization and the mean duration of hospitalization will be summarized.

Time from randomization to an improvement of one category on the 7-point ordinal scale will be summarized. The mean change from baseline on the 7-point ordinal scale at each post-baseline evaluation time point will be summarized.

The mean change from baseline for each parameter of NEWS and the overall score at each post-baseline evaluation time point will be summarized. Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first will be summarized. The mean change from baseline in SOFA score at each post-baseline evaluation time point will be summarized.

Figure 1: Study Treatment Schema



Total treatment time: 60 days

Table 5: Schedule of Events

	Baseline/Screening[a]	**Study Day**						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**60/EOS**
Windows (days)		**± 1**						**± 4**
General Assessments								
Informed consent	X							
Inclusion/exclusion	X							
Demographics	X							
Medical history	X							
Confirm contraceptive measures	X							
APACHE assessment	X							
High-sensitivity CRP	X							
Physical exam: height, weight[b]	X	X	X					
Vital signs[c]	X	Daily, throughout study period						
SOFA assessment	X	X		X	X	X	X	X
Ordinal scale (7-point)	X	X		X	X	X	X	X
NEWS[c]	X	Daily, throughout study period						X
Concomitant medications[c]	X	Daily, throughout study period						X
Adverse event collection[c]	X	Daily, throughout study period						X

	Baseline/Screening[a]	**Study Day**						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**60/EOS**
Windows (days)		**± 1**						**± 4**
Study drug administration								
BM-Allo.MSC or Placebo		X	X[d]					
Laboratory Assessments								
Collect NP swabs	X	X						
Chemistry panel[e]	X	X		X	X	X	X	X
Hematology[f]	X	X		X	X	X	X	X
Collect whole blood for immunogenicity and cytokine analyses	X	X		X	X	X	X	X
Pregnancy test[g]	X	X						

[a] Baseline/screening assessments may be done ≤ 1 calendar day prior to the first dose of BM-Allo.MSC or placebo. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1. Assessments performed on day 1 must be performed before dosing.

[b] Height required at baseline/screening visit only. Weight on day 1 should be used to calculate drug dose.

[c] Vital signs, concomitant medications, NEWS assessment, and adverse event collection will occur daily throughout the study period (ie, each day beginning day 1 and continuing through day 29). Vital signs of temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate will be assessed at every visit.

[d] Dose to be administered on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5.

[e] See Table 4 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to BM-Allo.MSC or placebo administration.

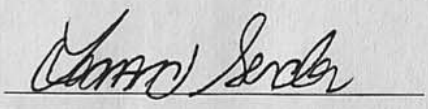
[f] Hematology to include CBC with differential (5 part) as outlined in Table 4. Blood draws for lab assessments should occur prior to BM-Allo.MSC or placebo administration.

[g] Serum pregnancy tests for females of child-bearing potential.

APPENDIX 4. SPONSOR SIGNATURE

Study Title:	Phase 1b Randomized, Double-Blind, Placebo-Controlled Study of the Safety of Therapeutic Treatment with Immunomodulatory Mesenchymal Stem Cells in Adults with COVID-19 Infection Requiring Mechanical Ventilation
Study Number:	QUILT-COVID-19-MSC
Version Number:	2
Final Date:	19 May 2020

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

Signed:  Date: 05-19-2020

Lennie Sender, MD
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Email: lennie.sender@nantkwest.com
Cell Phone: 714-615-2350

PHASE 1B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY OF THERAPEUTIC TREATMENT WITH IMMUNOMODULATORY MESENCHYMAL STEM CELLS IN ADULTS WITH COVID-19 INFECTION REQUIRING MECHANICAL VENTILATION

Study Number:	QUILT-COVID-19-MSC
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Senior Vice President, Medical Affairs NantKwest, Inc 9920 Jefferson Blvd Culver City, CA 90232 Email: lennie.sender@nantkwest.com Cell Phone: 714-615-2350

Protocol Version	**Date**
Version 1	08 Apr 2020
Version 2	19 May 2020
Version 3	10 Sep 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: NantKwest, Inc.
Name of Investigational Product: BM-Allo.MSC
Name of Active Ingredient: BM-Allo.MSC
Title of Study: Phase 1b Randomized, Double-Blind, Placebo-Controlled Study of the Safety of Therapeutic Treatment with Immunomodulatory Mesenchymal Stem Cells in Adults with COVID-19 Infection Requiring Mechanical Ventilation
Study Number: QUILT-COVID-19-MSC
Study Phase: Phase 1b

Study Objectives:

Primary Objectives:

- To evaluate preliminary safety of BM-Allo.MSC vs placebo in terms of adverse events within 30 days of randomization.
- To evaluate preliminary efficacy of BM-Allo.MSC vs placebo in subjects who have tested positive for SARS-CoV-2 (COVID-19) and require ventilator support, as assessed by:
    - Mortality and cause of death within 30 days of randomization.
    - Number of ventilator-free days within 60 days of randomization.

Secondary Objectives:

- To further evaluate preliminary efficacy of BM-Allo.MSC vs placebo in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
    - Time from randomization to an improvement of one category in the 7-point ordinal scale.
    - Change in the 7-point ordinal scale from baseline.
    - Change in National Early Warning Score (NEWS) from baseline.
    - Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
    - Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
    - Number of days requiring oxygen within 60 days of randomization.
    - Duration of hospitalization from randomization.
- To further evaluate the safety of BM-Allo.MSC in subjects who have tested positive for SARS-CoV-2 (COVID-19), as assessed by:
    - Incidence of SAEs within 30 days of randomization.
    - Change from baseline in hemoglobin.
    - Change from baseline in platelets.
    - Change from baseline in white blood cell count.
    - Change from baseline in vital signs.

Study Design:

This is a phase 1b randomized, double-blind, placebo-controlled study in adult subjects with Coronavirus Disease 2019 (COVID-19). This clinical trial will evaluate the preliminary safety and efficacy of BM-Allo.MSC vs placebo in treating subjects with severe disease requiring ventilator support during COVID-19 infection. Only subjects with moderate or severe ARDS (per Berlin criteria; see Appendix 1) will be enrolled in this study.

COVID-19 infection causes progressive severe lung infection that can lead to death in a significant number of infected patients. Prior work using allogeneic mesenchymal stem cells (MSCs) in severely infected individuals has shown promise in reversing the severe consequences of infection in critically ill patients. Thus, the potential exists for allogeneic MSCs to slow or halt disease progression and reduce time on ventilators in critically ill patients infected with COVID-19, and thus improve disease outcomes.

A total of 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be enrolled in this study. Subjects will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects).

Subjects in the experimental arm will be administered BM-Allo.MSC ($0.7\text{-}1.3\times10^6$ cells/kg IV) on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5. Subjects will be followed through day 60. Subjects in the control arm will be administered placebo on a schedule identical to that of the experimental arm and followed through day 60.

BM-Allo.MSC and placebo may be provided to the clinical treatment site as a cryopreserved preparation. The cryopreserved product will contain BM-Allo.MSC in 5% albumin (human), USP, and CryoStor 10 (CS10) (in 1:1 ratio) in a volume of 100 mL. The placebo will consist of 5% albumin (human), USP, and CS10 (1:1 ratio) in a volume of 100 mL.

All subjects will be assessed using a 7-point ordinal scale that evaluates clinical status at the first assessment of 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.

In addition, all subjects will be assessed using the standard National Early Warning Score (NEWS) score (Royal College of Physicians 2012). The NEWS score has demonstrated an ability to identify 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).

Safety will be assessed for all subjects and will include monitoring of vital signs and incidence and severity of adverse events. Blood samples will be collected for hematology and chemistry analyses.

Safety will be monitored throughout the study. After the first 5 subjects are randomized (giving at least 3 subjects in the experimental arm) enrollment will be paused and the NantKwest Safety Review Committee (SRC) will perform an evaluation of safety once the 5 subjects have completed the 14 day toxicity assessment period. Enrollment will continue if the safety evaluation from the initial 5 subjects suggests that the therapy is safe.

Primary Endpoints:

- Incidence of AEs within 30 days of randomization.
- Mortality within 30 days of randomization.
- Cause of death within 30 days of randomization
- Number of ventilator-free days within 60 days of randomization.

Secondary Endpoints:

- Time from randomization to an improvement of one category using the ordinal scale.
- Change in the 7-point ordinal scale from baseline.
- Change in NEWS from baseline.
- Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first.
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score on days 8, 15, 22, and 29.
- Number of days requiring oxygen.
- Duration of hospitalization from randomization.
- Incidence of SAEs within 30 days of randomization
- Change from baseline in hemoglobin, platelets, and white blood cell (WBC) count.
- Changes in vital signs from baseline.

Enrollment (planned):

A total of 45 subjects receiving care in the critical care or ICU setting with mechanical ventilation for COVID-19 will be randomized 2:1 to the experimental arm (30 subjects) and control arm (15 subjects) 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. For subjects that are intubated and/or sedated, or otherwise unable to provide consent, prospective consent from a legally-authorized representative is required. The subject or his/her legally authorized representative must be able to provide consent.
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. Requiring mechanical ventilatory support with moderate to severe Acute Respiratory Distress Syndrome (ARDS) as determined by the Berlin criteria:
   a. Bilateral opacities present on a chest radiograph or computed tomographic (CT) scan. These opacities are not fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.
   b. Origin of Edema: Respiratory failure not fully explained by cardiac failure or fluid overload.
   c. Oxygenation: Moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:
      - Moderate: PaO_2/FiO_2 >100 mmHg and ≤ 200 mmHg, on ventilator settings that include PEEP ≥ 5 cm H_2O
      - Severe: PaO_2/FiO_2 ≤100 mmHg on ventilator settings that include PEEP ≥5 cm H_2O

   Subjects receiving extracorporeal membrane oxygenation (ECMO) will not be enrolled in this study.
5. High-sensitivity C-reactive Protein (hs-CRP) serum level > 4.0 mg/dL
6. Acute Physiology and Chronic Health Evaluation (APACHE IV) score > 5
7. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
8. Ability to attend required study visits and return for 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 BM-Allo.MSC. Non-sterile male subjects must agree to use a condom while on study and for up to 1 month after the dose of BM-Allo.MSC. 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. Known hypersensitivity to any component of the study medication(s), including dimethyl sulfoxide (DMSO).
2. Signs of multisystem organ failure. Liver function tests (LFTs) > 5x normal.
3. Intubated > 72 continuous hours.
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 pregnancy test during screening (within 72 hours prior to the first dose) must be documented before MSCs are administered to a female subject of child-bearing potential.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
BM-Allo.MSC	0.7-1.3 × 10^6 cells/kg	IV
Duration of Treatment: Subjects in the experimental arm will be administered BM-Allo.MSC (0.7-1.3×10^6 cells/kg IV) on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5. Subjects will be followed through day 60. Subjects in the control arm will be treated with placebo on a schedule identical to that of the experimental arm and followed through day 60.		
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 30 days after administration of BM-Allo.MSC.		
Reference Therapy, Dosage, and Mode of Administration: Subjects randomized to the control arm will receive an IV infusion of placebo, provided to the clinical treatment site as a cryopreserved preparation. The cryopreserved placebo consists of 5% albumin (human), USP, and CryoStor 10 (1:1 ratio) in a volume of 100 mL.		

Evaluation of Endpoints:

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

Efficacy: Mortality and cause of death within 30 days of randomization, number of ventilator-free days with 60 days of randomization, number of subjects reporting each severity rating on the 7-point ordinal scale, and number of subjects with improved NEW scores and 7-point ordinal scale.

Statistical Methods:

All subjects receiving at least one dose of study drug (ie, the Safety population) will be included in the safety and efficacy analyses. Statistical analysis will be descriptive and presented by treatment arm. No statistical testing will be performed.

Safety Analyses:

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 AEs by grade and clinically significant changes in safety laboratory tests and vital signs.

Efficacy Analyses:

The mortality rate within 30 days of randomization and 95% confidence interval will be summarized. Cause of death will be summarized. The mean number of ventilator-free days and number of days requiring oxygen within 60 days of randomization and the mean duration of hospitalization will be summarized.

Time from randomization to an improvement of one category on the 7-point ordinal scale will be summarized. The mean change from baseline on the 7-point ordinal scale at each post-baseline evaluation time point will be summarized.

The mean change from baseline for each parameter of NEWS and the overall score at each post-baseline evaluation time point will be summarized. Time from randomization to discharge or to a NEWS of ≤ 2 maintained for 24 hours, whichever occurs first will be summarized. The mean change from baseline in SOFA score at each post-baseline evaluation time point will be summarized.

Figure 1: Study Treatment Schema

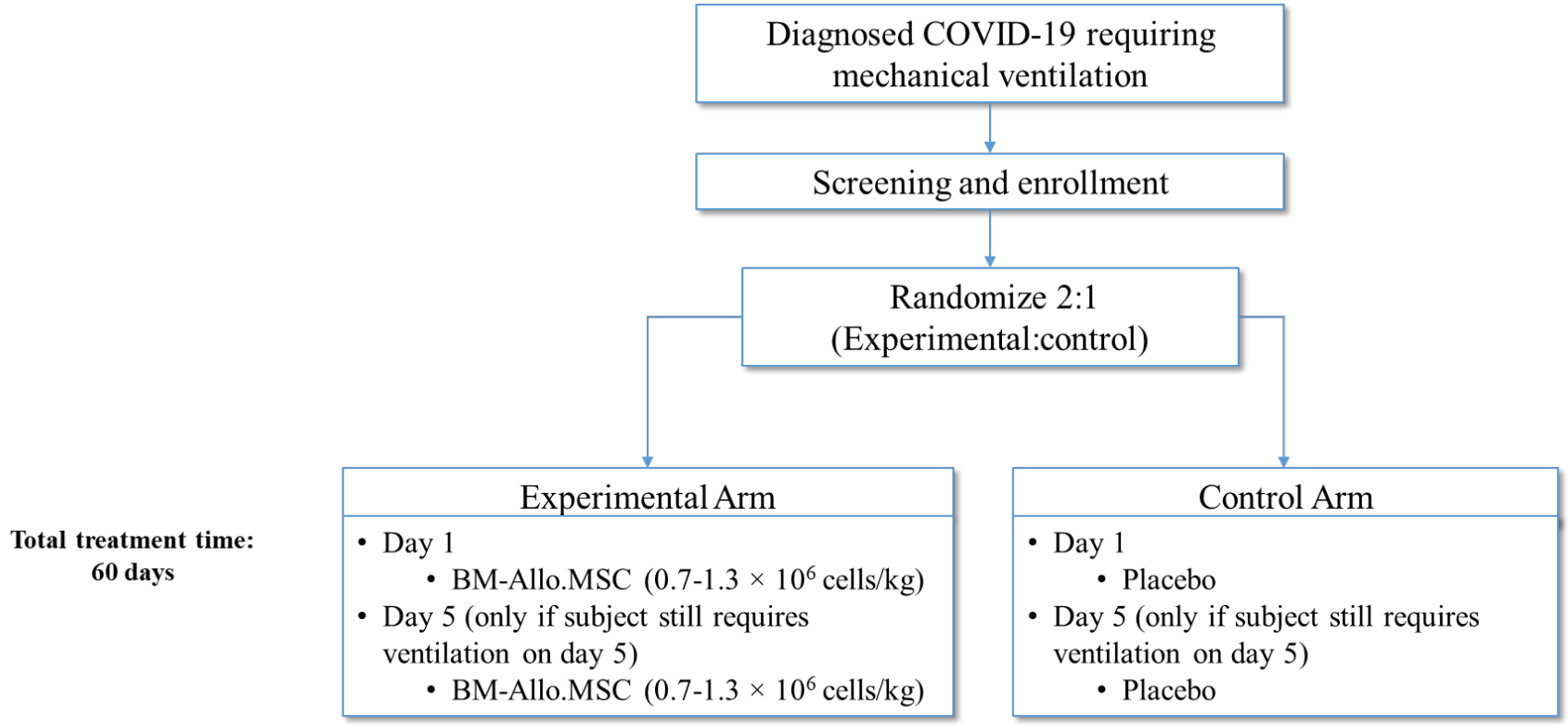

Table 5: Schedule of Events

	Baseline/Screening[a]	**Study Day**						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**60/EOS**
Windows (days)		**± 1**						**± 4**
General Assessments								
Informed consent	X							
Inclusion/exclusion	X							
Demographics	X							
Medical history	X							
Confirm contraceptive measures	X							
APACHE assessment	X							
High-sensitivity CRP	X							
Physical exam: height, weight[b]	X	X	X					
Vital signs[c]	X	Daily, throughout study period						
SOFA assessment	X	X		X	X	X	X	X
Ordinal scale (7-point)	X	X		X	X	X	X	X
NEWS[c]	X	Daily, throughout study period						X
Concomitant medications[c]	X	Daily, throughout study period						X
Adverse event collection[c]	X	Daily, throughout study period						X

	Baseline/Screening[a]	Study Day						
Study Day	**-1 or 1**	**1**	**5**	**8**	**15**	**22**	**29**	**60/EOS**
Windows (days)		**± 1**						**± 4**
Study drug administration								
BM-Allo.MSC or Placebo		X	X[d]					
Laboratory Assessments								
Collect NP swabs	X	X						
Chemistry panel[e]	X	X		X	X	X	X	X
Hematology[f]	X	X		X	X	X	X	X
Collect whole blood for immunogenicity and cytokine analyses	X	X		X	X	X	X	X
Pregnancy test[g]	X	X						

[a] Baseline/screening assessments may be done ≤ 1 calendar day prior to the first dose of BM-Allo.MSC or placebo. Day 1 assessments do not need to be repeated if baseline/screening is done on study day 1. Assessments performed on day 1 must be performed before dosing.

[b] Height required at baseline/screening visit only. Weight on day 1 should be used to calculate drug dose.

[c] Vital signs, concomitant medications, NEWS assessment, and adverse event collection will occur daily throughout the study period (ie, each day beginning day 1 and continuing through day 29). Vital signs of temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate will be assessed at every visit.

[d] Dose to be administered on day 1 followed by day 5 (±1 day), if subject still requires ventilation on day 5.

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Study Number:	QUILT-COVID-19-MSC
Version Number:	3
Final Date:	10 Sep 2020

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

Signed: _____ Date: 9/11/2020

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