Official Title of Study:

Phase 2, Randomized, Double-Blind Placebo Controlled Study of Intravenous Abatacept in the Treatment of Hospitalized COVID-19 Participants with Respiratory Compromise

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CLINICAL PROTOCOL IM101873

Phase 2, Randomized, Double-Blind Placebo Controlled Study of Intravenous Abatacept in the Treatment of Hospitalized COVID-19 Participants with Respiratory Compromise

Protocol Amendment 02

Short Title: Abatacept in the Treatment of COVID-19

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	18-Dec-2020	Clarification of language for one inclusion and one exclusion criterion to address a recruitment barrier.
Revised Protocol 01	16-Jun-2020	The protocol was revised [redacted]. See Summary of Key changes document for details.
Original Protocol	20-May-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The purpose of this revision is to clarify an inclusion and exclusion criterion, and address minor inconsistencies throughout the protocol. The main issue being addressed is the apparent exclusion of participants being created by the current exclusion criterion for recent infections. As currently written, the exclusion criterion related to recent infection appears anchored on the use of antibiotic, when the intent was to exclude participants with recent or active, confirmed and serious infections. One of the main inclusion criteria is the need to identify an abnormal chest image. As noted in Section 9.4.3, this was meant to include several forms of imaging but the language in the inclusion criterion limits imaging to chest X-ray only. Both of these criteria have been updated to clarify their intent and address apparent recruitment barriers.

Minor editorial, grammatical and typographical revisions are also addressed in this revision.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Table 2-1 Screening Procedural Outline (IM101873)	For Chest imaging procedure - added computerized tomography [CT] and high-resolution CT [HRCT] in addition with chest X-ray.	Updated to align with Section 9.4.3.
Section 2, Table 2-4: Post-hospital Follow-up for Participants discharged home or to assisted care facility (Remote Contact)	Table note shown below has been added: "Data collection at Day 28 is required if the participant is discharged from the hospital prior to Day 28."	Table note is added for clarification.
Section 6.1 Inclusion Criterion 2) Type of Participant and Target Disease Characteristics	Criterion 2d) has been modified with the bold text as shown below: d) Abnormal chest **image (ie, chest x-ray, computerized tomography [CT] or high-resolution CT [HRCT])** consistent with COVID-19 and no evidence of any other serious medical condition that would serve as an exclusionary criterion.	Clarifying that any of these 3 forms of chest imaging are sufficient to meet this criterion as previously stated in Section 9.4.3

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria 1) Medical Conditions	Criterion 1b) has been updated as shown below: b) Participants with confirmed, clinically serious acute infection in the previous 30 days: i) Confirmed is defined as culture positive or established by any other lab-based diagnostic testing or imaging. ii) Clinically serious is defined as infection involving deep tissues or organs (eg, cellulitis, upper urinary tract, lower respiratory tract). iii) Exclusion of a highly suspected serious infection (i.e. not yet confirmed) is at the discretion of the investigator.	Needed to clarify the intent of this exclusion. The exclusion is for participants with active and serious infections. The use of antibiotic therapy as a guide to identify these individuals has proven problematic because it was interpreted literally. This clarification anchors the exclusion to confirmation of the presence of infection and its seriousness. It limits the concern to the previous 30 days, and overtly states that investigators can always exclude participants based on clinical acumen.
Section 6.2 Exclusion Criteria 1) Medical Conditions	Criteria 1i) has been updated and wording that participants should not be administered a live virus vaccine for minimum of 3 months following last dose of study medication has now been removed.	Clarifies live vaccine use language.
Section 7.8.2.1 Prohibited Treatments	Third bullet has been added as listed below: 3) Administration of a live virus vaccine within 3 months of receipt of study medication.	Clarifies live vaccine use language.
Section 9.4.3 Chest Imaging	Text within this section has been modified.	Modification is made for clarification purposes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.4 Vital Signs	Text within this section has been modified.	Modification is made to align with the vital sign text mentioned under [redacted]
Appendix 1 Abbreviations and Trademark	Abbreviations list updated	Clarification

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Phase 2, Randomized, Double-blind, Placebo Controlled Study of Intravenous Abatacept in the Treatment of Hospitalized COVID-19 Participants with Respiratory Compromise

Short Title: Abatacept in the Treatment of COVID-19

Study Phase: 2

Rationale:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped RNA beta-coronavirus that is the etiological agent of coronavirus disease 2019 (COVID-19). While most infected individual have mild to no symptoms, around 15% develop a severe pneumonitis characterized by fever, cough, shortness of breath, myalgias, and sputum production. Dyspnea develops in over half of patients at a median of 8.0 days from illness onset. Older patients and those with leukopenia and elevated laboratory markers of systemic inflammation (measured by IL-1β, IL-6, and TNF-α levels) are more likely to require ICU care, mechanical ventilation and progression to acute respiratory distress syndrome (ARDS). Progression to ICU care with ARDS is associated with significant mortality. Abnormal radiographic findings (eg ground glass opacities on HRCT) is a common feature of COVID-19 pneumonia patients. Viral clearance coincides with seroconversion but the role of viral load and the kinetics of viral clearance in the disease process is unclear. It is hypothesized that a dysregulated immune response to the infection with excessive release of cytokines (cytokine storm) leads to the more severe pulmonary and non-pulmonary manifestations of COVID-19. No specific therapy has been established. Use of available anti-viral, anti-malarial and immunomodulatory therapies like corticosteroids and tocilizumab are being studied.

The FDA has recently proposed an example for scheme for classifying the severity of COVID-19 disease. This classification is based on positive RT-PCR, symptoms, vital signs and respiratory or other organ compromise and ranges from infection with no symptoms to critical disease.

In this example, severe disease is primarily defined by the inability to maintain an SpO2 > 93% on room air at sea level and critical disease by reliance on oxygen supplementation devices with greater oxygen delivery capacity than low flow nasal cannula.

Abatacept for the treatment of COVID-19

It is hypothesized that abatacept therapy can modulate the ongoing/emerging dysregulated immune response considered to be driving the progression of disease severity in COVID-19. Abatacept is not a therapy for neutralizing cytokines but for preventing further cellular activation (eg CD4+ T cells, B cells, macrophages) and production of cytokines and interrupting the feedforward pathological process.

Study Population:

Adults (≥ 18 years old) who have a confirmed virological diagnosis of SARS-CoV-2 infection (by real-time PCR) and who are hospitalized (or in the ED awaiting hospitalization) with respiratory compromise as defined by requirement of oxygen supplementation to maintain oxygen saturation

≥ 93% but not requiring mechanical ventilation. Participants should also have abnormal chest X-ray consistent with COVID-19 and not indicated other serious medical condition that would serve as an exclusionary criteria.

Exclusion criteria includes current recent (within 1 month) treatment with other targeted therapies (eg tocilizumab), known secondary infections, or current symptoms of severe, progressive, or uncontrolled organ disease not considered related to COVID-19 infection, systemic corticosteroid within 2 weeks of randomization at doses above prednisone 10 mg, or other equivalent.

Table 1-1: Objectives and Endpoints

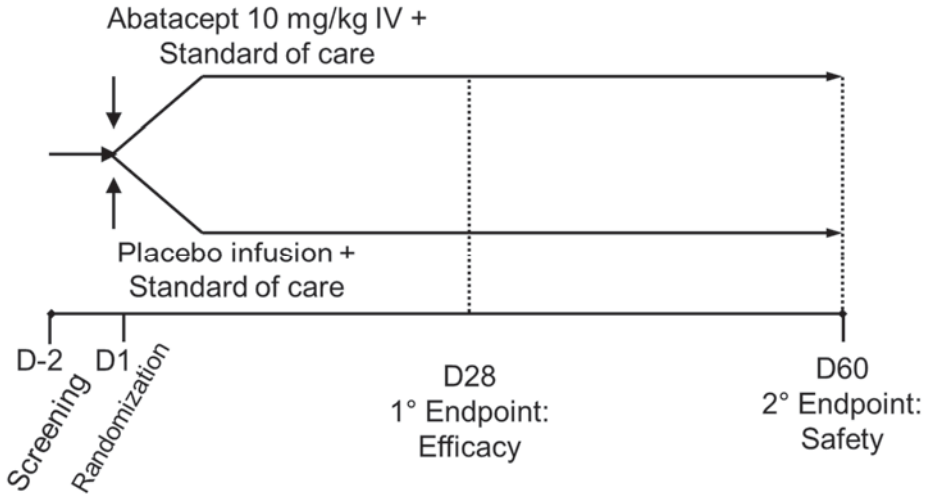
Objective	Endpoint
Primary	
• Prevention of Disease Progression	• Proportion of participants with composite end point of mechanical ventilation or death prior to or on Day 28
Secondary	
• Improvement in clinical status	• Change from baseline in the Ordinal 8-point Outcome Scale on Day 28
• Improvement in mortality	• All-cause mortality on Day 28
• Absence of critical disease	• Proportion of participants alive and free of respiratory failure on Day 28
• Recovery of pulmonary function	• Proportion of participants returned to room air by Day 28
• Shortened hospitalization	• Proportion of participants alive and discharged home by Day 28
• Safety	• Proportion of participants with SAEs and serious infections
[redacted]	

Abbreviations: [redacted] SAE = serious adverse event; [redacted]

Overall Design:

This will be a randomized, double-blinded, placebo controlled study of IV abatacept for the purpose of efficacy and safety signal detection. Participants (≥ 18 years of age) will be those with confirmed COVID-19 disease who are hospitalized (or in the Emergency Department awaiting hospitalization) with respiratory compromise requiring supplemental oxygen but not requiring ventilatory support. Participants will be assessed for clinical responses to abatacept for 28 days and monitored for safety and some efficacy outcomes for a total of 60 days.

Figure 1-1: Study Design Schematic



Screening Period:

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity, and safety assessments. Screening and randomization must be completed within 48 hours of signing the informed consent form. Screening will include testing for viral hepatitis but the decision to randomize will not be based on review of these screening labs. Participants that experience a secondary infection, serious medical complication or require mechanical ventilation prior to study drug infusion should not receive any study drug infusion but remain in the trial and complete all other study procedures.

Double-blind Treatment Period, Days 1 - 28:

On Day 1, eligible participants will be randomized to receive an intravenous (IV) infusion of abatacept or placebo. Randomization will be on a 2:1 ratio, abatacept vs placebo, both on standard of care.

Participants will receive medical care following local standards. Daily progress will be recorded in the study record as required. Participants who, in the opinion of the treating physician, require immunotherapy rescue (eg tocilizumab) should continue to complete the treatment period and post-treatment follow-up observation.

Post-treatment Follow-up Period, Days 29-60:

Participants who complete the 28 day Double-blind Treatment Period will be monitored for study endpoints and will have follow-up information captured for Days 35, 42, 49 and 60, to perform safety and clinical status assessments. If routine safety labs are performed in this period, they should also be captured in the study record. Medical care in this period will also follow local standards and there will be no restrictions on treatment choices.

Post-hospitalization

Participants who are discharged from hospital care at any point before the end of this 60-day period will have remote follow-up visits. Post-hospital care is not considered part of this trial but outcomes up to 60 days are of interest. Participants who are discharged, whether home or to any form of assisted care facility, will be contacted remotely by the study team (eg phone, e-mail) to ascertain clinical status, weekly until Day 60. As a rule, remote contact should be performed approximately every 7 days. If the participants is discharged prior to Day 28, one of the remote contacts should be on Day 28 (± 2 days) to coincide with the study primary endpoint. If discharge occurs after Day 28, remote contacts should occur as close as possible to study Days 35, 42, 49, and 60, at approximately7 day intervals. Level of activity (ie ambulatory status), oxygen requirement (eg home oxygen therapy), current location (eg home) and any intercurrent adverse event (eg infection) will be assessed and added to the study record.

Number of Participants: 129 randomized participants in a 2:1 ratio (abatacept: placebo), both on standard of care.

Treatment Arms and Duration:

There will be 2 treatment arms, abatacept plus standard of care versus placebo plus standard of care. Both arms will last for 60 days with a primary endpoint at Day 28.

Study treatment:

Abatacept 10 mg/kg IV, reconstitutes in 100 mL of an appropriate diluent and administered over 30 minutes. The minimum total dose will be 500 mg and the maximum total dose will be 1000 mg.

Table 1-2: Study Treatment for Study IM101873

Medication	Potency	IP/Non-IP
Abatacept	250 mg/vial	IP

Abbreviations: IP = investigational product; mg = milligram; IV= intravenous.
Note: BMS will provide Abatacept to all investigating sites.

Safety Oversight Committee:

Due to the novel design of this study and limitations imposed by the risk of contagion, the study will be monitored by a Safety Oversight Committee (SOC). The SOC will assist in the oversight of the study execution and ongoing assessment of safety and efficacy. Members will be chosen based on clinical expertise in the areas of infectious disease, pulmonary/critical care and

immunotherapy (eg rheumatology) or study outcome interpretation. The SOC will be composed of BMS personnel, site investigators and external experts. External members will constitute the majority of all voting members. The SOC will be provided with periodic data outputs and meet on a regular schedule (ie bi-weekly) or ad hoc basis as needed. The first meeting of the SOC will review the SOC charter and decide on the frequency of SOC data review meetings before finalizing the SOC. In the case that review of subjects grouped by treatment is required to assess changes to study conduct, this will be performed by a group of external members in a closed session. Details of the membership, meeting schedule, purpose and data access is found in the SOC charter.

Statistical considerations

A 25% estimated rate of progression under placebo plus standard of care to one of the elements of the primary endpoint is derived from available literature. A two group continuity corrected χ^2 test with a 0.150 one-sided significance level will have 80% power to detect the difference between a proportion of 10% abatacept treated participants and a proportion of 25% participants in the placebo group with a primary endpoint event (odds ratio of 0.33, ie odds of progression under abatacept versus placebo) when the sample sizes are 86 and 43, respectively (a total sample size of 129). This computation was made using nQuery Advisor version 7. The target sample size for this study is approximately 129 randomized participants.

The comparison between treatment groups of the proportion of participants with primary endpoint event (mechanical ventilation or death) prior to or on Day 28 will be performed using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by the randomization stratification factors age group ($<60, \geq 60$) and remdesivir use as well as baseline severity. Baseline severity will be defined by the Clinical Status scale at randomization. A one-sided significance level of 0.15 will be used to assess statistical superiority of abatacept over placebo. The population of all randomized participants will be used. Randomized participants with no primary endpoint assessment due to withdrawal of consent or for other reasons will be imputed as treatment failures (ie. progressors). The OR along with its 2-sided 70% CI and 95% CI, as well as the absolute treatment difference in proportions with its 95% CI will be presented. The construction of CIs for absolute differences in proportions between treatment groups will be based on minimum risk weights to account for randomization stratification factors and baseline severity.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (IM101873)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Enroll Participant	X	Contact IRT for subject number. If participant does not meet eligibility criteria, contact IRT to screen fail participant.
Inclusion/Exclusion Criteria	X	Confirm hospitalization, positive RT-PCR for SARS-Cov-2
Medical History	X	
Safety Assessments		
Physical Examination	X	Includes height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, blood pressure and heart rate.
Prior and Concomitant Medication Use	X	
Serious Adverse Events Assessment	X	All SAEs must be collected from the date of participant's informed consent until 60 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Smoking History and Current Status	X	
Chest imaging	X	Chest X-ray (CXR), computerized tomography (CT) or high resolution computerized tomography (HRCT)
Laboratory Tests[a]		
SARS-CoV-2-RT-PCR	X	If not previously performed
Hematology (CBC)	X	
Chemistry Panel	X	
Pregnancy Test	X	WOCBP only; see Section 9.4.6 Performed locally.
Viral Hepatitis Serology	X	Includes HCV antibody, HBsAg, HBcAb see Section 9.4.6

Table 2-1: Screening Procedural Outline (IM101873)

Procedure	Screening Visit	Notes
Disease Assessments		
Pulse oximetry on room air	X	

Abbreviations: CBC = complete blood count; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IRT = Interactive Response Technology; RT-PCR = Reverse-transcription polymerase chain reaction; WOCBP = women of childbearing potential.

[a] Only the laboratory tests that are readily available at the study site laboratory, will be performed.

Table 2-2: On Treatment Schedule of Events

Procedure	Day 1	Days 2 - 28 (daily unless otherwise noted)	Hospital Discharge or Early Termination[a]	Notes
Eligibility Assessments				
Inclusion/Exclusion Criteria	X			Review of inclusion/exclusion criteria that are relative to the Randomization day.
Randomization	X			Weight required
Safety Assessments				
Physical Examination	X[b]			
Targeted Physical Examination		X	X	
Vital Signs	X	X	X	Body temperature, blood pressure, respiratory rate, and heart rate.
Monitor for Non-Serious Adverse & Serious Adverse Events	X[b]	X	X	All SAEs must be collected from the date of participant's informed consent until 60 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Concomitant Medication Use	X[b]	X	X	
Laboratory Tests[c]				
Chemistry Panel	X[b]	X	X	As ordered based on clinical need; See Section 9.4.6
[redacted]				
Hematology (CBC)	X[b]	X	X	As ordered based on clinical need;
[redacted]				

Table 2-2: On Treatment Schedule of Events

Procedure	Day 1	Days 2 - 28 (daily unless otherwise noted)	Hospital Discharge or Early Termination[a]	Notes
[redacted]				
Efficacy Assessments				
Pulse Oximetry	X	X	X	
Arterial Blood Gas	X	X	X	Only if required for clinical care
Ordinal 8-point Outcome Scale	X	X	X	See Section 9.1.1.2
Study Treatment				
Drug preparation by pharmacist	X			
Abatacept/placebo dosing	X			
Study Materials				
Provide diary card and outpatient monitoring equipment to participants (if applicable)			X	See section 9.10

Abbreviations: CBC = complete blood count; CXR - chest x-ray; [redacted]

[a] Early Termination only applies for participants who withdraw consent for all study procedures or those who lose ability to consent freely

[b] Findings at screening can be used if randomization occurs on the same day as screening.

[c] Only the laboratory tests that are readily available at the study site laboratory, will be performed, see Section 9.4.6.

Table 2-3: Post-treatment Follow-up Period for Participants in Hospital

Procedure	Day 35	Day 42	Day 49	Day 60 / Day of Hospital Discharge / Early Termination	Notes
Safety Assessments					
Targeted Physical examination	X	X	X	X	
Vital Signs	X	X	X	X	Body temperature, seated blood pressure, respiratory rate, and heart rate.
Ordinal 8-point Outcome Scale	X	X	X	X	See Section 9.1.1.2
Concomitant Medication Use	X	X	X	X	
Adverse Events Assessment	X	X	X	X	
Laboratory Tests[a]					
Hematology (CBC)	X	X	X	X	Only if hospitalized
Chemistry Panel	X	X	X	X	Only if hospitalized; See Section 9.4.6
[redacted]					
Efficacy Assessments					
Pulse Oximetry	X	X	X	X	
Arterial Blood Gas	X	X	X	X	Only while hospitalized and if required for clinical care

Table 2-3: Post-treatment Follow-up Period for Participants in Hospital

Procedure	Day 35	Day 42	Day 49	Day 60 / Day of Hospital Discharge / Early Termination	Notes
Study Materials					
Provide diary card and outpatient monitoring equipment to participants (if applicable)				X[b]	See section 9.10

[a] Only the laboratory tests that are readily available at the study site laboratory, will be performed

[b] Only for participants discharged before Day 60

Table 2-4: Post-hospital Follow-up for Participants discharged home or to assisted care facility (Remote Contact)

Procedure	Weekly starting 7 days after hospital discharge until Day 60	Notes
Remote Contact	X	Defined as any form of communication such as phone or e-mail
Vital Signs	X	Body temperature, seated blood pressure, respiratory rate, and heart rate. Only collected if the subject has the proper equipment for home use, so respiratory rate may not be able to be collected.
Ordinal 8-point Outcome Scale	X	See section 9.1.1.2
Post-discharge condition	X	Level of activity (ie, ambulatory status), oxygen requirements (yes/no, method), current location (eg, home, assisted living)
Concomitant Medication Use	X	
Adverse Events Assessment	X	

Data collection at Day 28 is required if the participant is discharged from the hospital prior to Day 28.

3 INTRODUCTION

Abatacept is being proposed as a therapy that can modulate an ongoing/emerging dysregulated immune response. Abatacept is not a therapy for neutralizing cytokines but for preventing further activation and interrupting the feedforward pathological process. One significant unknown is the appropriate timing of abatacept treatment. Current evidence suggests that once COVID-19 patients develop symptoms of respiratory compromise, their anti-viral responses, including adaptive immune responses, are well underway but the pathological process leading to CRS-like scenario has not yet initiated. It is proposed that abatacept may interrupt this process without greatly interfering with the viral clearance and that any study to be attempted should be aware of these goals and concerns.

3.1 Study Rationale

3.1.1 SARS-CoV-2 and COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped RNA beta-coronavirus that is the etiological agent of coronavirus disease 2019 (COVID-19). While most infected individuals have mild to no symptoms, around 15% develop a severe pneumonitis characterized by fever, cough, shortness of breath, myalgias, and sputum production.[1] Dyspnea develops in over half of patients at a median of 8.0 days from illness onset.[2] Older patients and those with leukopenia and elevated laboratory markers of systemic inflammation (measured by IL-1β, IL-6, and TNF-α levels) are more likely to require ICU care, mechanical ventilation and progression to acute respiratory distress syndrome (ARDS). Progression to ICU care with ARDS is associated with significant mortality. Abnormal radiographic findings (eg, ground glass opacities on HRCT) is a common feature of COVID-19 pneumonia patients. Viral clearance coincides with seroconversion but the role of viral load and the kinetics of viral clearance in the disease process is unclear. It is hypothesized that a dysregulated immune response to the infection with excessive release of cytokines (cytokine storm) leads to the more severe pulmonary and non-pulmonary manifestations of COVID-19. No specific therapy has been established. Use of available anti-viral, anti-malarial and immunomodulatory therapies like corticosteroids and tocilizumab are being studied.

The FDA has recently proposed an example for scheme for classifying the severity of COVID-19 disease.[3] This classification is based on positive RT-PCR, symptoms, vital signs and respiratory or other organ compromise and ranges from infection with no symptoms to critical disease.

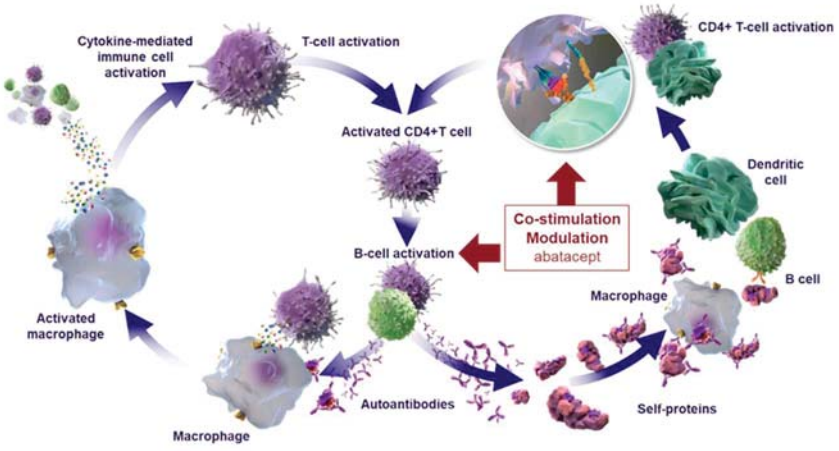
In this example, severe disease is primarily defined by the inability to maintain an $SpO_2 > 93\%$ on room air at sea level and critical disease by reliance on oxygen supplementation devices with greater oxygen delivery capacity than low flow nasal cannula.

3.1.2 Abatacept for the treatment of COVID-19

It is hypothesized that abatacept therapy can modulate the ongoing/emerging dysregulated immune response considered to be driving the progression of disease severity in COVID-19. Abatacept is not a therapy for neutralizing cytokines but for preventing further cellular activation (eg, CD4+ T

cells, B cells, macrophages) and production of cytokines and interrupting the feedforward pathological process.

Figure 3.1.2-1: Cellular interactions affected by abatacept



3.1.3 *In vitro evidence of abatacept impact on cytokine production by multiple cell types*

Abatacept was first studied in the setting of a pathological response to a viral infection in a murine model of influenza.[4] In this study, abatacept could prevent development of severe lung injury while not inhibiting an effective memory antiviral response in the setting of secondary infection. This study, along with others, have continued to evolve the understanding of the mechanism of action (MOA) of abatacept which has proven to be much more complex than initially envisioned. Although CTLA-4 is central to the regulation of T cell activation, CTLA-4Ig clearly has effect on other cell types. Since CTLA-4 regulates interactions with T cells and professional antigen presenting cells (APC), it is not surprising that effects on APC populations (ie, dendritic cells, macrophages, B cells) can also be seen, in vitro and clinically.[5] Indeed, in vitro work has demonstrated reverse signaling via CD80 or CD86 in APCs although the full impact of this is not fully understood.[6,7]

Treatment with abatacept has also been shown to have broad effects on cytokines in RA patients. Abatacept shows an impact within 24 hours in human in vitro mixed-lymphocyte reactions (MLR) on IL-2, TNF-a, and IFN-g.[6] In vivo, abatacept reduces the levels of multiple cytokines in RA patients including TNF-a, sIL-2R and IL-6.[8] In addition, abatacept suppresses multiple biomarkers (cytokines and chemokines) in the synovium from RA patients.[9] What these studies don't show, is which cell type(s) was (were) most impacted.

The best evidence for abatacept's direct effects on APCs comes from reports on both in vitro and in vivo effects on macrophages and B cells. Abatacept inhibits pro-inflammatory cytokine (TNF-a, IL-12, INF-g) secretion by in vitro activated human macrophages.[10] Abatacept can also downregulate production of IL-6, TNFα, IL1-β and TGFβ from activated synovial macrophages from RA patients.[11] B cell populations are notably decreased in RA synovium of abatacept-treated

patients.[9] Direct effects of abatacept on plasmablasts has also been proposed.[12] Together, all of this data suggests that abatacept's impact on the immune system is not limited to T cells. Activations of macrophages and B cells are also likely impacted by abatacept therapy.

3.2 Background

Abatacept is a recombinant fusion protein (MW 92 kDa) consisting of the extracellular domain of human CTLA4 and a fragment (hinge - CH2 - CH3 domains) of the Fc domain of human immunoglobulin (Ig) GI that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity. Abatacept is a selective costimulation modulator that inhibits T-cell activation by binding to CD80 and CD86 on antigen presenting cells, thereby blocking the interaction with CD28 on T-cells that provides a costimulatory signal necessary for full activation of T-cells. By inhibiting CD28 mediated T-cell activation upstream of inflammatory cytokines, such as TNF, abatacept utilizes a unique mechanism of action that offers significant therapeutic benefit to patients with a variety autoimmune-mediated diseases.[13] Abatacept, 250 mg for intravenous (IV) infusion, is indicated to treat subjects with rheumatoid arthritis (RA) age 18 and older and subjects with polyarticular juvenile idiopathic arthritis (pJIA) age 6 to 17.[14]

IV-administered abatacept was first approved in the US for the treatment of moderate-to-severe RA in adults in December 2005. Since then, IV abatacept has received marketing approval for the treatment of adult RA in many other countries, including the EU, Canada, Australia, and Japan. IV abatacept was also approved in the US for the treatment of moderately-to-severely active juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age or older in April 2008. In addition, IV abatacept has received marketing approval for the treatment of JIA in several other countries, including the EU, Canada, and Australia. In 2017, abatacept was approved for adult use in psoriatic arthritis (PsA) in the US and has also received marketing approval for the treatment of PsA in several other countries, including the EU, Canada, and Australia. A subcutaneous (SC) formulation of abatacept in a prefilled syringe and autoinjector has been approved for adult RA and PsA patients in the US, EU, and several other countries; it is also approved in the US and EU for use in JIA.

A detailed description of the chemistry, pharmacology, efficacy, and safety of abatacept is provided in the Investigator's Brochure (IB).[15,16]

3.2.1 Clinical Evidence for Abatacept Suppression of Cytokine Release Syndrome

There is some clinical data to inform the impact on cytokine release syndrome (CRS). Patients with active systemic JIA, some with current macrophage activation syndrome (MAS), who were heavily treated with multiple agents, including high dose corticosteroids and anakinra, responded to the addition of abatacept. The time course for the benefit of abatacept is not well described but the ability to decrease doses or suspend some concomitant therapy is reported.

A subject with active immune checkpoint inhibitor-associated myocarditis did demonstrate clinical and biochemical improvement within a day of initiating abatacept therapy.[17] This clinical course

has been seen in other similar patients treated with abatacept (personal communication of unpublished data).

The strongest evidence for rapid onset of abatacept and its effect on CRS is from prevention, not treatment. Use of peripheral blood stem cells (PBSC) for post-transplantation cyclophosphamide (PTCy)-based haploidentical hematopoietic cell transplantation (HCT) is associated with early CRS in over 92% of patients (14% severe CRS).[18] Treatment with abatacept 1 day before the infusion of the PBSC graft (followed by dosing on day +5, +20, +35 and every four weeks thereafter decreased the rate of CRS to 6% (none severe). The continued use of abatacept is because of ongoing donor lymphocyte infusions, which are therapeutic in this context and also believed to be the source of the CRS process.

In a related clinical setting, abatacept has been studied for acute graft-versus-host disease (aGVHD) prevention during unrelated-donor hematopoietic cell transplantation (HCT), in both HLA matched (8/8) and 7/8 mismatched patients.[19,20] Patients who receive mismatched, unrelated donor HCT are at elevated risk of severe aGVHD and death. Abatacept treatment at days -1, +5, +14, and +28 almost completely suppresses severe (Grade III-IV) aGVHD without negative impact on relapse and without significant impact on patient safety. CMV reactivation, but not EBV, was seen more frequently (47% vs 33%, p=0.16) but uncontrolled infections were not a major problem.

The relevance of these reports are that they illustrate the rapid effects of abatacept on feedforward mechanisms that produce CRS. They also suggest that the onset of abatacept's therapeutic effects can be sufficiently rapid as to be clinically relevant in the setting of COVID-19.

3.2.2 Safety

The safety profile of abatacept is well established based on the safety data collected from a number of clinical studies and 14-year post-marketing experience during the treatment of autoimmune/inflammatory diseases; abatacept has been well-tolerated and shown a favorable benefit-risk profile in the approved disease population (ie, RA, PsA, pJIA).

Infections and infusion related reactions (for IV formulation) are identified risks for abatacept, majority of these events are non-serious and do not impact benefit/risk profile of the product. For infections, during the double-blind, placebo-controlled period of RA studies (9 IV studies and 2 SC studies in the integrated safety database), the incidence rate of overall infections was comparable between abatacept group (total of 2,653 subjects with mean exposure duration of 10.8 months) and placebo group (total of 1,485 subjects with mean exposure duration of 10.3 months): 93.21 versus 93.02 per 100 patient-years; a small increase for IR of overall serious infections in abatacept group compared to placebo group (3.0 vs 2.25 per 100 patient-years). Majority of the infections were caused by common pathogens; the most commonly reported PTs of infections were upper respiratory tract infection (IR 14.3 per 100 patient-years) and nasopharyngitis (IR 14.3 per 100 patient-years); the most frequently reported serious infection was pneumonia (IR 0.68 per 100 patient-years) in abatacept group, which was comparable to that in placebo group (IR 0.72 per 100 patient-years). The IR of opportunistic infections appeared to be numerically lower in abatacept group compared to placebo (0.17 vs 0.56 per 100 patient years). For the infusion related reactions

occurred in IV abatacept studies, most of the peri-infusional events that occurred within 24 hours following the start of infusion were non-serious dizziness and nausea; serious events of hypersensitivity/anaphylactic reactions were rare. Safety experience from clinical studies in PsA and pJIA patients was similar to that in RA studies. Ten-year post-marketing epidemiology studies in RA population did not reveal any new safety finding relevant to these two identified risks.

Malignancies and autoimmune disorders have been reported with abatacept use; however, the clinical and post-marketing data do not show an increased risk of these events associated with abatacept use, therefore, the potential role of abatacept in the development of these diseases cannot be concluded based on the available evidence.

3.2.2.1 Concerns Over Abatacept Therapy on Viral Clearance and Secondary Infections

The potential deleterious impact of abatacept on viral clearance is certainly a concern that we recognize. The previously discussed murine model of influenza infection-induced immunopathology clearly demonstrates the risk of blunting anti-viral responses in abatacept-treated mice prior to viral exposure.[4] These concerns are not new. Throughout the abatacept clinical development program, concerns over the impact of therapy on infectious agents has been paramount.

During pre-clinical abatacept development, host resistance models of infection were explored.[13,21] Of note, negative impacts on immune responses were only noted for herpes simplex infections. The observation that abatacept partially inhibits the generation of CD8 cytotoxic T cell (CTL) responses but does not inhibit CD8 T cell cytotoxic activity has been reported, which could also predict deleterious impact on viral responses.[22,23]

In spite of these pre-clinical observations, clinical observations, both from controlled trials and post marketing surveillance, have been of less concern. A review of safety data of viral infections from an integrated safety database of RA clinical studies (includes 7044 participants receiving IV or SC abatacept for a total exposure of 21994.84 patient years during the cumulative period (controlled plus long-term open-label)), reveals the following:

1. During the randomized placebo-controlled double-blind short-term period of the studies, the most frequently (>1.0%) reported PTs of viral infections and infections that could be caused by virus in the ABA group vs. placebo group, respectively, were upper respiratory tract infection (11.9% vs 12.1%), nasopharyngitis (11.8% vs 10%), bronchitis (6.5% vs 5.8%), influenza (5.8% vs 5.9%), pharyngitis (3.5% vs 3.3%), rhinitis (2.4% vs 1.3%), conjunctivitis (2.1% vs 1.5%), gastroenteritis (2.0% vs 3.0%), oral herpes (1.8% vs 1.3%), herpes zoster (1.5% vs 1.4%), pneumonia (1.8% vs 1.1%). The majority of these events were mild or moderate in severity and abatacept use did not cause increased severity of infections compared to placebo.
2. During the DB ST period of the studies, the most frequently reported PTs (≥ 2 cases) of serious viral infections and infections that could be caused by virus in the ABA group and placebo group were pneumonia (0.6% vs 0.6%), bronchitis (0.2% vs 0), gastroenteritis

(0.1% vs 0.1%) and herpes zoster (0.1% vs 0). Among these events, death outcomes were reported for pneumonia and the IRs for fatal pneumonia were 0.08 vs 0.16 per 100 patient-years for abatacept and placebo, respectively.

3. There were no increases for the incident rates of serious infections reported during cumulative period compared to those reported in short-term period.

Of note is the absence of an imbalance in viral pneumonias, specifically influenza. Also, the median event duration for influenza was similar between abatacept treated patients and placebo group. Antibody responses to the conventional seasonal influenza vaccine in abatacept treated RA patients were also studied.[24] The study demonstrated that most participants on abatacept were able to mount an appropriate immune response. While this study did not demonstrate impact on actual influenza rates, it does support the extensive clinical observation that abatacept therapy may not influence anti-influenza responses in a clinically meaningful way.

Review of the post-marketing safety experience (estimated exposure at 763,109 p-y as of 30-Sep-2019 in over more than 13 years) identified 21 cases of coronavirus infection by 13-Apr-2020; events of confirmed COVID-19 or suspected COVID-19 were reported in 13 of these cases. The majority of these cases contained minimal information and robust assessment of the impact of abatacept on COVID-19 is not possible. One literature report from Japan reported possible COVID-19 in a [redacted] received abatacept and tacrolimus to treat RA and interstitial lung disease (ILD). The patient developed respiratory compromise and ultimately required ventilatory support. Testing of sputum but not other sources was positive for SAR-CoV-2. A recent published letter describes 8 patients being treated with targeted therapies for chronic arthritis in Italy. Among them were 2 patients receiving therapy with abatacept, 1 with confirmed and one with suspected SARS-CoV-2 infection. Only 1 of the patients required hospitalization, and then only briefly for oxygen therapy and all recovered without incident.[25] Belatacept is a related drug to abatacept with a similar mechanism of action. In a recent report,[26] a [redacted] kidney transplant patient on belatacept and MMF became infected with SARS-CoV-2 and had a mild clinical course with rapid recovery. The authors hypothesized that ongoing immunotherapy with belatacept may protect from severe clinical course of COVID-19 by limiting cytokines/chemokines production.

The abatacept label has a warning for risk of serious infections, including fatal sepsis and pneumonia. The clear risk for abatacept use is in bacterial infections, mostly of the respiratory and urinary tract. This includes a higher rate of complications in patients with COPD. The abatacept label also warns about treatment initiation in patients with an active infection until the infection is controlled. Of note, extensive experience in the use of abatacept to treat RA in elderly patients with co-morbidities has been reported.[27] This suggests that among biologic DMARD therapies, abatacept may have less risk of infections.[28,29,30]

Based on the review of safety data relevant to viral infections from clinical studies and post marketing experience, there is no evidence suggesting increased risk of severe respiratory illnesses

associated with abatacept use. Current evidence suggests that once COVID-19 patients develop symptoms of respiratory compromise, their anti-viral responses, including adaptive immune responses, are well underway but the pathological process leading to CRS-like scenario has only just begun. It is proposed that abatacept may interrupt this process without greatly interfering with the viral clearance and that any study to be attempted should be aware of these goals and concerns. The viral clearance and COVID-19 progression during abatacept use will be closely monitored during the study.

[redacted]

3.3 Benefit/Risk Assessment

Current evidence indicates that once COVID-19 patients develop symptoms of respiratory compromise, their anti-viral responses, including adaptive immune responses, are well underway but the pathological process leading to CRS-like scenario has only just begun. The Sponsor proposes that abatacept may interrupt this process without greatly interfering with the viral clearance.

Preclinical work indicates that abatacept can suppress or control cytokine production, including clinical scenarios consistent with cytokine release syndrome. Clinical work in multiple complex disease states also suggest abatacept therapy can suppress or help manage excessive cytokine production.

Abatacept has been studied in human clinical trials for over 15 years. Most patients studied have chronic, immune mediated diseases with use of concomitant immunosuppressant therapies and co-morbid conditions. The most notable risk for abatacept use is increased risk of bacterial infections, particularly of the respiratory and urinary tract. Based on the review of safety data relevant to viral infections from clinical studies and post marketing experience, there is no evidence suggesting increased risk of viral respiratory illnesses, severe or otherwise, associated with abatacept use.

The study of the therapeutic potential of abatacept in symptomatic patients with COVID-19 at high risk for progression to respiratory failure is warranted. Concerns over the negative impact on viral clearance or secondary bacterial infections are appropriate. These concerns are mitigated by the relatively short course of treatment in the setting of hospitalized monitoring and care, monitoring of viral clearance during the study and an oversight by a Safety Oversight Committee (SOC).

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of abatacept may be found in the [Investigator's Brochure.[15,16]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• Prevention of Disease Progression	• Proportion of participants with composite end point of mechanical ventilation or death prior to or on Day 28
Secondary	
• Improvement in clinical status	• Change from baseline in the Ordinal 8-point Outcome Scale on Day 28
• Improvement in mortality	• All-cause mortality on Day 28
• Absence of critical disease	• Proportion of participants alive and free of respiratory failure on Day 28
• Recovery of pulmonary function	• Proportion of participants returned to room air by Day 28
• Shortened hospitalization	• Proportion of participants alive and discharged home by Day 28
• Safety	• Proportion of participants with SAEs and serious infections
[redacted]	

Table 4-1: Objectives and Endpoints

[redacted]

Abbreviations: [redacted] SAE = serious adverse event; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a randomized, double-blinded, placebo controlled study of IV abatacept for the purpose of efficacy and safety signal detection. Participants (≥ 18 years of age) will be those with confirmed COVID-19 disease who are hospitalized (or in the ED awaiting hospitalization) with respiratory compromise requiring supplemental oxygen but not requiring ventilatory support. This protocol will provide guidance for standard medical care but not make specific recommendations for treatment, given the dynamic nature of evolving clinical care of COVID-19. Participants will be assessed for clinical responses to abatacept for 28 days and monitored for safety and some efficacy outcomes for a total of 60 days. If the decision is made to treat the participant with a restricted immunomodulatory therapy (eg, anti-IL-6) after treatment with study drug, the subject should not be discontinued from the study. Rather, they should be followed for the full 60-day observation period.

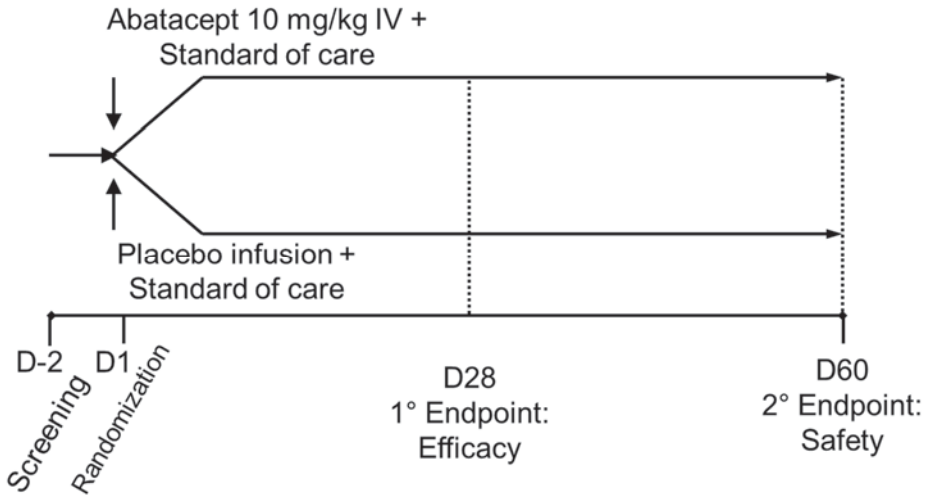
Participants may be discharged from hospital care at any point before the end of this 60-day period. Post-hospital care is not considered part of this trial but outcomes up to 60 days are of interest. Participants who are discharged, whether home or to another location like an assisted care facility, will be contacted remotely by the study team to ascertain clinical status periodically. Level of activity (ie, ambulatory status), oxygen requirements (eg, oxygen therapy), current location (eg, home) and any intercurrent adverse event (eg, infection) will be assessed and captured in the study record.

Due to constraints imposed as part of infectious control measures for hospitalized patients and personnel during the COVID-19 pandemic, access to the participant and samples obtained from the participant will be more limited. Required study procedures and laboratory assessments have been limited to those considered necessary. Routine clinical care decisions, eg, changes to oxygen supplementation, and safety laboratory monitoring will be at the discretion of the clinical team but will be captured in the study record. The core principal of this study protocol is to identify suitable study participants, and to describe the therapeutic intervention and the key measures (eg, oxygenation, safety labs) that are part of routine care to be captured in the study record for analysis.

The study will include 129 randomized participants in a 2:1 ratio, abatacept: placebo, both on standard of care.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



5.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity, and safety assessments. Screening and randomization must be completed within 48 hours of signing the informed consent form. Screening will include testing for viral hepatitis but the decision to randomize will not be based on review of these screening labs (See Section 9.4.4). Participants that experience a secondary infection, serious medical complication or require mechanical ventilation prior to study drug infusion should not receive any study drug infusion but remain in the trial and complete all other study procedures.

5.1.2 Double-blind Treatment Period, Days 1 - 28

On Day 1, eligible participants will be randomized to receive an intravenous (IV) infusion of abatacept or placebo. Randomization will be on a 2:1 ratio, abatacept vs placebo, both with standard of care.

Participants will receive medical care following local standards (see Section 7.8.1). Daily progress will be recorded in the study record as required. Participants who, in the opinion of the treating physician, require immunotherapy rescue (eg, tocilizumab) should continue to complete treatment period and post-treatment follow-up observation.

5.1.3 Post-treatment Follow-up Period, Days 29 - 60

Participants who complete the 28 day Double-blind Treatment Period will be monitored for study endpoints and will have follow-up information captured for Days 35, 42, 49 and 60, to perform safety and clinical status assessments. If routine safety labs are performed in this period, they

should also be captured in the study record. Medical care in this period will also follow local standards and there will be no restrictions on treatment choices. (See Table 2-3).

5.1.4 Post-hospitalization

Participants who are discharged from hospital care at any point before the end of this 60-day period will have remote follow-up visits. Post-hospital care is not considered part of this trial but outcomes up to 60 days are of interest. Participants who are discharged, whether home or to any form of assisted care facility, will be contacted remotely by the study team (eg, phone, e-mail) to ascertain clinical status, weekly until Day 60. As a rule, remote contact should be performed approximately every 7 days. If the subject is discharged prior to Day 28, one of the remote contacts should be on Day 28 (± 2 days) to coincide with the study primary endpoint. If discharge occurs after Day 28, remote contacts should occur as close as possible to study Days 35, 42, 49 and 60, at approximately 7 day interval. Level of activity (ie, ambulatory status), oxygen requirement (eg, home oxygen therapy), current location (eg, home) and any intercurrent adverse event (eg, infection) will be assessed and added to the study record. (See Table 2-4)

5.1.5 Safety Oversight Committee

Due to the novel design of this study and limitations imposed by the risk of contagion, the study will be monitored by a Safety Oversight Committee (SOC). The SOC will assist in the oversight of the study execution and ongoing assessment of safety and efficacy. Members will be chosen based on clinical expertise in the areas of infectious disease, pulmonary/critical care and immunotherapy (eg, rheumatology) or study outcome interpretation. The SOC will be composed of BMS personnel, site investigators and external experts. External members will constitute the majority of all voting members. The SOC will be provided with periodic data outputs and meet on a regular schedule (ie, bi-weekly) or ad hoc basis as needed. The first meeting of the SOC will review the SOC charter and decide on the frequency of SOC data review meetings before finalizing the SOC. In the case that review of subjects grouped by treatment is required to assess changes to study conduct, this will be performed by a group of external members in a closed session. Details of the membership, meeting schedule, purpose and data access is found in the SOC charter.

5.2 Number of Participants

One hundred and twenty nine (129) participants will be randomized.

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened. End of study is defined as last visit or scheduled procedure shown in Section 2 (Schedule of Activities) for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

The goal of this Phase 2 study is to establish evidence for the efficacy and safety of the use of abatacept IV to prevent participants hospitalized with COVID-19, with respiratory compromise and evidence of immune activation, from progressing in severity. To do so, we have chosen to execute a blinded, placebo controlled, randomized study design. The main safety concern is the

possibility of a negative impact on viral clearance with clinical impact or an increase in the risk of secondary bacterial infection. Because of the unprecedented level of infectious risk in the general population, including hospital staff, usual study procedures and monitoring are not feasible.[35] The study has to be streamlined for ease and speed of execution. While a lot has been reported to infer the clinical course for COVID-19 patients, there are still many unknowns including the efficacy of all currently used disease specific effective therapies. Interpretation of open-label treatment experience in the setting of an ongoing potentially lethal pandemic is fraught with challenges.[36] The potential differential patient care and use of concomitant medication in an open-label setting will be confounded with the treatment effect. Only a blinded, randomized study can reliably provide information for interpretation but this presents other complex bioethical concerns and challenges. In a blinded study the impact on clinical decision for off-label use of other available immunotherapies would be the same in both treatment arms. This study design will partly mitigate the above concerns by adopting a randomization ratio favoring active treatment (ie, 2:1), allowing background therapy, utilizing a safety oversight committee to assess safety, and a sample size with robust power but with a higher level of significance in order to increase the speed to a larger, definite study if a positive signal is detected.

5.5 Justification for Dose

Abatacept is available in 2 formulations, lyophilized for intravenous infusion and pre-filled syringe for subcutaneous injection. Pharmacokinetic evaluation over 2 decades of clinical development has shown that the most relevant PK parameter are trough (Cmin) levels which are best at predicting maximal efficacy and are driven by weight based dosing. Superior efficacy is observed with 10 mg/kg dosing in RA patients. Dosing frequency of Day 1, 15, 28 and every 28 days afterwards was established as an efficacious dosing regimen for reaching target Cmin levels.

Evidence based on pharmacokinetic, pharmacodynamic and clinical efficacy data suggest that higher doses of abatacept would not be more effective in RA patients. Higher doses of abatacept at 30 mg/kg have been tested in BMS sponsored trials. In patients with PsA, higher doses did not produce better efficacy but did not result in any increase in safety signal. In inflammatory bowel disease, no clinical efficacy was seen. In lupus nephritis, higher doses were thought needed due to urinary losses of abatacept due to the severe proteinuria unique to this disease. None of these studies suggested higher abatacept doses were associated with increased safety concerns.

More frequent dosing and higher doses of abatacept have been used empirically in many settings. While BMS is aware that this happens on occasion in the clinical practice for the care of RA patients, it happens most notably in the off-label treatment of other disease states. Children with active, refractory systemic onset JIA have been treated with empirical doses of up to 18 mg/kg every 3 weeks.[37] Common variable immunodeficiency (CVID) is a group of genetically defined conditions characterized by immune dysregulation and immunodeficiency, many of which are characterized by CTLA-4 deficiency or impaired expression.[38] Successful treatment with abatacept has been reported extensively with infusion as high as 20 mg/kg every 2 weeks.[39,40] Immune checkpoint inhibitor associated myocarditis is a rapidly progressive adverse event with

high morbidity and mortality. Abatacept has been used successfully to reverse this process in refractory cases using weekly IV doses of 500 mg or higher.[17]

The largest experience with alternative abatacept dosing regimens comes from the study of acute graft-versus-host disease (aGVHD) prevention investigator initiated program.[19,20] In this setting, abatacept was given at 10 mg/kg on days -1, +5, +14, and +28. Preliminary PK analysis shows Cmins above 40 mg/mL, which is well above the Cmin known to show optimal efficacy for RA patients.[41]

There is not enough information available to suggest that an alternative to the approved IV dose is required in the setting of COVID-19 but there is empirical evidence that higher doses (either on a per weight basis or frequency) may be beneficial and not carry untoward risk. Given the nature of the clinical course, it is likely that a single abatacept dose of 10 mg/kg will be sufficient for clinical effect since supratherapeutic drug levels will be achieved for all study participants for at least 3 weeks.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participant is willing to participate in the study and has signed the Informed Consent Form (ICF).

2) Type of Participant and Target Disease Characteristics

a) Adults with a confirmed virological diagnosis of SARS-CoV-2 infection (by RT-PCR). Any positive test, at either the time of or prior to hospitalization, is suitable. Results must be documented.

b) Hospitalized (or in the Emergency Department awaiting a bed after hospitalization)

c) Respiratory compromise as defined by requirement of oxygen supplementation to maintain oxygen saturation ≥ 93% but not requiring mechanical ventilation.

d) Abnormal chest image (ie, chest X-ray, computerized tomography [CT] or high-resolution CT [HRCT]) consistent with COVID-19 and no evidence of any other serious medical condition that would serve as an exclusionary criterion.

3) Age and Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants
   i) Females, ages ≥ 18 years or local age of majority
   ii) Women who are not of childbearing potential are exempt from contraceptive requirements
   iii) Women participants must have documented proof that they are not of childbearing potential.
   iv) WOCBP must have a negative highly sensitive urine/serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) performed during screening prior to the start of study treatment.
      (1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive
   v) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
   vi) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.
   vii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4)
   viii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
      (1) Is not a WOCBP

      OR

      (2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 70 days and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

b) Male Participants
   i) Males, ages ≥ 18 years or local age of majority
   ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.
   iii) Azoospermic males are exempt from contraceptive requirements.
   iv) No additional contraceptive measures are required to be used

6.2 Exclusion Criteria

1) Medical Conditions

a) Woman who are breastfeeding
b) Participants with confirmed, clinically serious acute infection in the previous 30 days:
   i) Confirmed is defined as culture positive or established by any other lab-based diagnostic testing or imaging.

ii) Clinically serious is defined as infection involving deep tissues or organs (eg, cellulitis, upper urinary tract, lower respiratory tract).

iii) Exclusion of a highly suspected serious infection (ie, not yet confirmed) is at the discretion of the investigator.

c) Participants with history of chronic or recurrent bacterial infection (eg, chronic pyelonephritis, osteomyelitis, bronchiectasis).

d) Medical history of known or suspected active or latent tuberculosis (TB), active hepatitis B, hepatitis C or HIV infection.

e) TB risk will be further ascertained by review of history and most recent CXR.

f) Hepatitis B virus (HBV) testing will be ordered (surface antigen and core antibody). If either is positive, reflex testing for HBV DNA by PCR will be obtained.

g) Hepatitis C virus (HCV) testing will be ordered (HCV antibody). If positive, reflex testing for HCV RNA by PCR will be obtained.

h) Current clinical findings of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, endocrine, neurological, or cerebral disease, including severe and uncontrolled infections, such as sepsis and opportunistic infections (except COVID-19). Caution should be used when randomizing participants with severe COPD or frequent COPD exacerbations. Concomitant medical conditions that, in the opinion of the Investigator, might place the participant at unacceptable risk for participation in this study.

i) Participants who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Participants who are in close contact with others who have received a live vaccine may be enrolled at the Investigator's discretion.

j) Participants with a history of (within 12 months of signing the ICF), or known current problems with drug or alcohol abuse history or known cirrhosis, including alcoholic cirrhosis.

k) Participants who are impaired, incapacitated, or incapable of completing study related assessments.

2) Prior/Concomitant Therapy

a) Participants who have been exposed within 1 month or five half-lives, whichever is longer, to any treatment with an approved or investigational targeted immunotherapy including, but not limited to, infliximab, etanercept, anakinra, rituximab, tocilizumab, golimumab, certolizumab, sirolumab, tofacitinib, baricitinib, upadacitinib, or filgotinib.

b) Systemic corticosteroid within 2 weeks of randomization at doses above prednisone 10 mg, or other equivalent.

c) Prior exposure to BMS-188667 (abatacept).

3) Physical and Laboratory Test Findings

a) Hemoglobin (Hgb) < 8.5 g/dL.

b) White Blood Count (WBC) < 3,000/mm^3 (3× 10^9/L).

c) Platelets < 75,000/mm^3 (100× 10^9/L).

d) Serum creatinine > 2× ULN.

e) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5× ULN.

f) Any test results that, in the opinion of the Investigator, might place the participants at unacceptable risk for participation in this study.

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to the IP and/or its excipients

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Rescreening is not allowed.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as shown in Table 7-1.

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Table 7-1: Study treatments for IM101873

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Open Label	Packaging / Appearance	Storage Conditions (per label)
Abatacept for injection	250 mg/ vial	IP	Open Label	Vial / White to off-white, whole or fragmented cake in a vial.	Refer to the label on the container

Abbreviations: IP = investigational product

Note: BMS will provide Abatacept to all investigating sites.

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Abatacept	10 mg/kg	Day 1	IV
Placebo	Normal saline or 5% Dextrose in water[a]	Day 1	IV

Abbreviations: IV = intravenous; kg = kilogram; mg = milligram

[a] Normal Saline or 5% Dextrose in water will be provided by the investigational site

Each investigator will be responsible for supplying any intravenous administrative solutions [Sterile Water for Injection (SWFI), 5% Dextrose in Water Injection (D5W), 0.9% Sodium Chloride Injection (NS)] needed for the reconstitution and dilution of investigational product identified in the protocol. D5W and NS will act as the intravenous placebo for this study. Handling and dispensing instructions will be provided separately to the unblinded pharmacist.

The dose of abatacept will be 10 mg/kg with a maximum dose of 1000 mg. Study medication will be administered in a fixed volume of 100 mL at a constant infusion rate over approximately 30 minutes. The IV line must be flushed with 25 mL of D5W or NS solution at the end of the infusion.

The administration window will be within 24 hours of randomization.

7.2 Method of Treatment Assignment

All participants will be randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Participants will be randomized to receive either abatacept or placebo according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010).

During the screening visit, the investigative site will call into the enrollment option of the Interactive Response Technology (IRT) designated by BMS for assignment of a 5-digit participant number that will be unique across the study. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003....

00010). The patient identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to randomize the participant into the double-blind panel. Participants meeting all eligibility criteria will be randomized in a 2:1 ratio to treatment arms. The randomization schedule will be generated using permuted blocks of fixed size within each stratum, defined by age group and remdesivir use. Once enrolled in IRT, enrolled participants will be randomized through the IRT prior to the start of study treatment. At randomization the participants will be stratified according to age group at randomization (< 60 vs ≥60) and by remdesivir Use (Yes [RemYes] vs No [RemNo]). Remdesivir Use = Yes, will be defined as a subject having been dosed with remdesivir or for whom the decision to dose with remdesivir based on availability is Yes. Remdesivir Use = No will be defined as subjects that will not utilize or have not utilized remdesivir. The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

This is a randomized, double-blinded study. Access to treatment codes will be restricted from all participants, and site and BMS personnel prior to primary database lock, with exceptions as specified below.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is through IRT. For information on how to unblind in an emergency, consult the IRT manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

7.4 Dosage Modification

Dose Modifications in the Absence of Adverse Events

In the absence of adverse events, participants will complete their scheduled infusions as prescribed by protocol.

Dose Modifications for Adverse Events

If there is evidence of toxicity (eg, infusion reaction) that, in the judgment of the Investigator, could place the subject at increased risk, study drug administration should be interrupted.

7.5 Management of Possible Acute Hypersensitivity Reactions to Abatacept

Hypersensitivity or acute allergic reactions may occur as a result of the protein nature of abatacept. Should any of these reactions occur during the course of the study, they need to be reported as specified in Section 9.2 (Adverse Events). In this study, participants' vital signs will be monitored before and following study drug administration. Appropriate emergency equipment and qualified personnel should be available where the participants are treated in the event of a serious anaphylactic reaction.

The following information is provided to assist in the recognition of hypersensitivity reactions and in the management of those reactions should they occur during or after the administration of abatacept. Care should be taken to treat any acute toxicities expeditiously, should they occur. When IV dosing of abatacept is conducted, equipment such as a portable tank or wall-source of oxygen, endotracheal intubation set, oral airway, mask, ambu-bag, syringes, injectable epinephrine, injectable antihistamine, and injectable corticosteroids should be kept in the vicinity where the subject is treated.

Signs and management of potential acute hypersensitivity reactions include:

a) Symptomatic Hypotension should be managed by discontinuing the infusion of study medication, placing the subject in the Trendelenburg position and administering intravenous fluid. Additional medical intervention may also include the use of epinephrine, corticosteroids, anti-histamines and pressor agents.

b) Dyspnea should be managed by discontinuing the infusion of study medication and observing the subject for worsening of the event and for the appearance of additional signs and symptoms of anaphylaxis. Antihistamines, epinephrine and corticosteroids may be administered as indicated.

c) Acute pain in the chest, back or extremities may also be a sign of anaphylaxis and may be treated as described above for dyspnea.

d) Chills, fever, urticaria or generalized erythema may all be signs of an allergic reaction to protein products. Such signs and symptoms may be treated with acetaminophen and antihistamines.

The decision of whether to complete the infusion of study medication if symptoms improve or have resolved will be left to the medical judgment of the Investigator.

7.6 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.6.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.7 Treatment Compliance

Study drug will be administered intravenously in the clinical facility.

7.8 Concomitant Therapy

7.8.1 Standard of Care

The management of COVID-19 is ever evolving.[42,43,44,45] Beyond routine management and supportive care for hospitalized patients, specific COVID-19 therapies are not defined but new relevant insight have emerged.[35] Current specific therapeutics fall into 3 categories, antiviral, immune-based and, most recently, antithrombotic therapies. The following outlines current guidelines to help inform care for participants enrolled in the study.

7.8.1.1 Antiviral agents

Early repurposing of available antiviral agents was utilized based on empirical or *in vitro* evidence. All were initially developed as therapies for other viral infection like HIV (eg, lopinavir–ritonavir) and Ebola (remdesivir). The results for many of these initial efforts have been reported. Currently, only limited use of remdesivir is supported by available clinical data. Other compounds (eg,

lopinavir–ritonavir, chloroquine or hydroxychloroquine) are not recommended outside of the context of a clinical trial. This study will not be studying any of these possible agents.

Use of remdesivir is not required but is encouraged as part of standard of care in this study. Because abatacept is a large protein, drug-drug interactions are not anticipated. Infusion of abatacept and remdesivir should not be given concurrently in order not to confound attribution of possible infusion reactions or hypersensitivity events. Data from ACTT1 suggest clinically meaningful improvements associated with use in severe to critical patients. Remdesivir is not approved by the FDA but is available through an FDA emergency use authorization. This authorization is limited to severe to critical patients and is therefore suitable for subject enrolled in this study. Availability of remdesivir is currently unknown and neither is the supply reliability once available. Because of this, some but not all subject enrolled in this study may be treated with remdesivir. In order to control for the impact of remdesivir use, subject will be stratified at randomization by remdesivir use. Remdesivir use will be defined as yes if the participant has already been dosed or the decision to dose has been made because remdesivir is available.

7.8.1.2 Immune-based Therapies

Multiple therapies with immunomodulatory properties have been proposed for management of COVID-19 and have been used off label. The most common are anti-malarial agents (ie, chloroquine & hydroxychloroquine, with or without + Azithromycin) and corticosteroids. Other immunotherapies have been propose and many are currently being studied. Use of these targeted therapies are restricted (see Section 7.8.2). The following are guidance for other immune-based therapies.

Use of anti-malarial therapies is not recommended. Available data does not suggest robust efficacy but suggests possible toxicities. A recent report suggests use of hydroxychloroquine in COVID-19 patients can lead to corrected QT interval prolongation.[46] If hydroxychloroquine is used in study participants, the clinical team should strongly consider ECG monitoring.

Routine use of systemic corticosteroids (CS) is not recommended unless indicated for other reasons (eg, hypersensitivity reaction).[47] Use of CS will be allowed but should be minimized as much as possible. Prior use of CS at doses above prednisone 10 mg per day, or equivalent, in the 2 weeks prior to randomization is an exclusion criteria. Use of topical or inhaled CS is not restricted.

7.8.1.3 Antithrombotic Therapies

COVID-19 has been recognized as being associated with higher risk of thrombotic events above the rate observed in hospitalized, ill patients. The optimal assessment, screening, prophylaxis and treatment of these is unknown. [redacted] Any prophylaxis, anticoagulant or antiplatelet, for venous or arterial thrombosis should follow standard of care for other hospitalized adults. If during the course of this study, evidence emerges to support COVID-19-specific prophylaxis as reflected in guidelines (eg, NIH COVID-19 Treatment Guidelines), consideration should be given to follow these.

7.8.1.4 Oxygen Supplementation

Oxygen supplementation is a key element of standard of care for the management of COVID-19. The protocol does not mandate nor advice use of any specific device and amount of oxygen. All decision on oxygen supplementation will follow local practice and will be captured in the study record.

7.8.1.5 Rescue Therapy

This protocol does not define nor require rescue therapy but it recognizes that off-label use of targeted immunotherapies (eg, tocilizumab) for some participants has been defined by institutional treatment protocol or used on an ad hoc basis. The use of these agents is left at the discretion of the clinical team. The use of these agents in close temporal relationship to abatacept has not been studied. Participant who are treated with one of these agents after randomization should remain in the study and followed for outcome assessment.

7.8.1.6 Other Therapies

Use of Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARBs) or HMG-CoA Reductase Inhibitors (Statins) previously prescribed for cardiovascular disease (or other indications) should be continued when feasible.

7.8.2 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to randomization in the study are described below. Medications taken within 4 weeks prior to randomization must be recorded on the CRF.

7.8.2.1 Prohibited Treatments

1) Prior exposure to BMS-188667 (abatacept).
2) Exposure to any investigational drug or placebo within 1 month of study drug administration.
3) Administration of a live virus vaccine within 3 months of receipt of study medication.

7.8.2.2 Restricted Treatments

1) Use of an approved targeted immunotherapy is restricted including, but not limited to, infliximab, etanercept, anakinra, rituximab, tocilizumab, golimumab, certolizumab, sirolumab, tofacitinib, baricitinib, upadacitinib, or filgotinib. If use of one of these agents after randomization is considered, please notify the medical monitor. Participants should remain in the study to capture study outcomes.
2) Use of convalescent plasma and hyperimmune globulin is restricted. Administration should be avoided on the same day as study drug.

7.9 Treatment After the End of the Study

Since this is a single dose study, at the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

Participants should remain in the protocol for the duration even if the decision is made to provide other immunomodulatory therapy. Capture of all outcomes, including choices to seek alternative therapy are necessary for proper assessment of both safety and efficacy outcomes.

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8.1.1 Post Study Treatment Study Follow up

In this study, overall survival, activity level, and oxygen supplementation are key endpoints of the study. Post Treatment Follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. All participants are required to complete the 60-day observation period visits regardless of hospitalization status for collection of outcome and/or survival follow-up data as required.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a

participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

9.1.1 Primary and Secondary Objectives

9.1.1.1 Prevention of Disease Progression

The primary objective will be to determine the impact of therapy on prevention of disease progression as defined below using a composite endpoint. This endpoint will be reached if the participant ever requires use of invasive mechanical ventilation or experience death.

Invasive mechanical ventilation is defined as the delivery of positive pressure to the lungs via an endotracheal tube (or tracheostomy).

9.1.1.2 Improvement in Clinical Status

The WHO has recommended clinical study for COVID-19 use a composite clinical endpoint and recommend use of an ordinal scale that measures participant's clinical status.[48] Ordinal data is a kind of categorical data with a set order or scale to it. Ordinal scales have been adopted in some current prospective clinical studies.[49] The following 8-point scale was proposed for the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT) (ClinicalTrials.gov Identifier: NCT04280705). It will be used in this study.

1) Death
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3) Hospitalized, on non-invasive mechanical ventilation or high-flow oxygen devices
4) Hospitalized, requiring supplemental oxygen
5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7) Not hospitalized, limitation on activities and/or requiring home oxygen
8) Not hospitalized, no limitation on activities

Patients may change between states in this scale multiple times during any 24-hour period. The study team will record in the study record only the worst (ie, lowest) state for each day (midnight to midnight). The determination of the worst state to be recorded should be made as soon as possible after the completion of the day to be assessed.

ICU admission is defined as transfer of care within the hospital to a specialized medical care unit distinct from routine or intermediate (ie, stepdown) care. Given the increased demand for ICU beds as a consequence of the COVID-19 pandemic, all forms of ICUs (eg, surgical) and non-ICU beds have been converted into ICU care beds. Progression into any of these will be considered to meet these criteria.

Other elements of each point have been defined with the exception of ECMO (extra-corporeal membrane oxygenation). This scale captures similar information to the primary endpoint but has the advantage of capturing improvement. The "limitations of activities" in state #6 includes need for home oxygen therapy. Based on inclusion criteria, all study subjects will be in category 3 or 4, and can be extracted from the clinical record.

9.1.1.3 Improvement in Mortality

Mortality for this endpoint will be based on all-cause mortality at Day 28 which represent participants who are in state1 of the Ordinal 8-point Outcome Scale.

For participants deaths, data will be collected on whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care will be recorded (eg, brain death, patient/family request, resource constraint).

9.1.1.4 Absence of Critical Disease

This endpoint is related to the primary endpoint. It is defined as the proportion of participants alive and free of respiratory failure on Day 28. Respiratory failure is defined by the type of resources required as defined by the use of any of these: mechanical ventilation, ECMO or oxygen delivery by noninvasive positive pressure or high-flow nasal cannula. Participants in state 4-8 of the Ordinal 8-point Outcome Scale meet this definition.

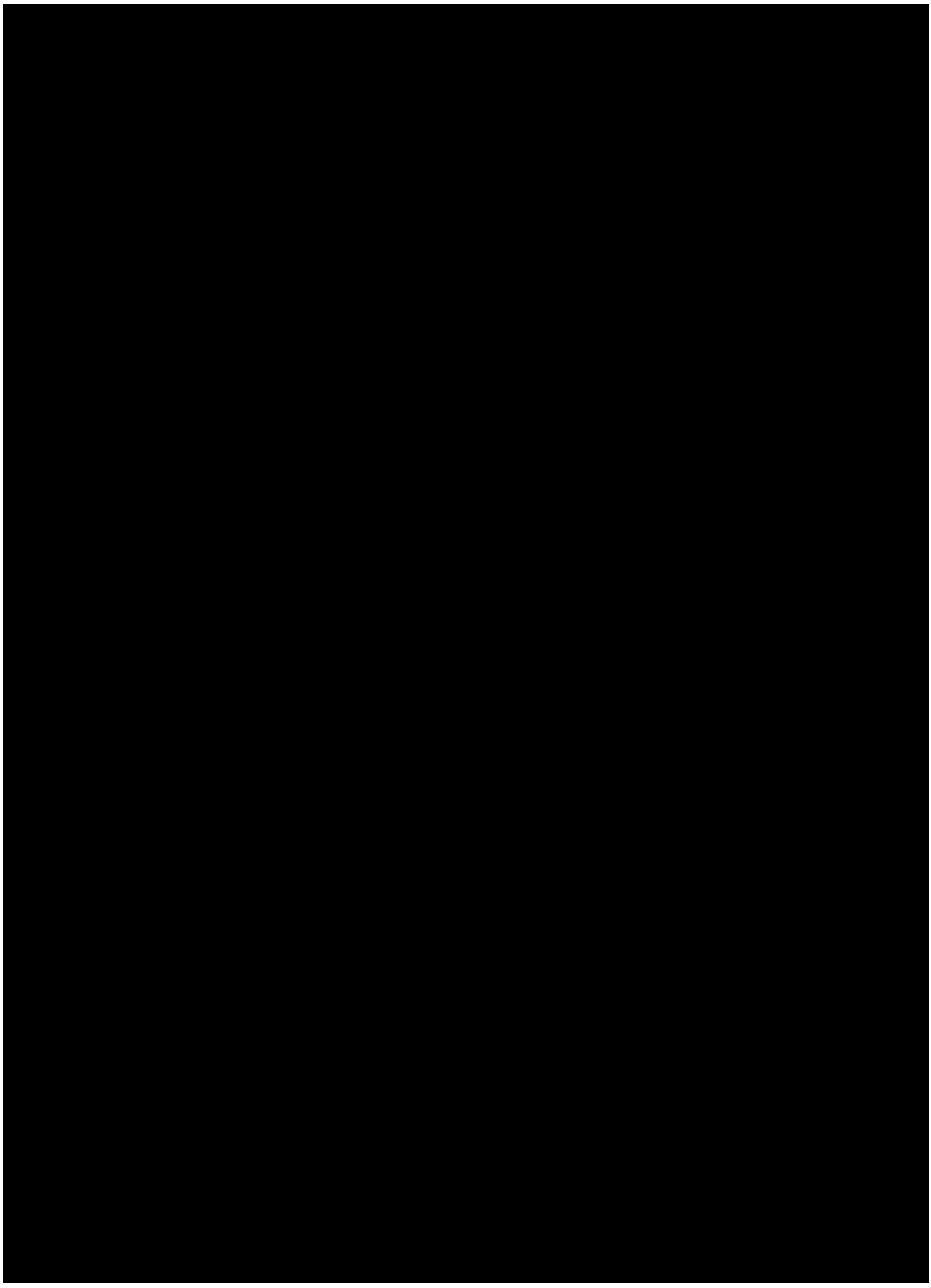
9.1.1.5 Recovery of Pulmonary Function

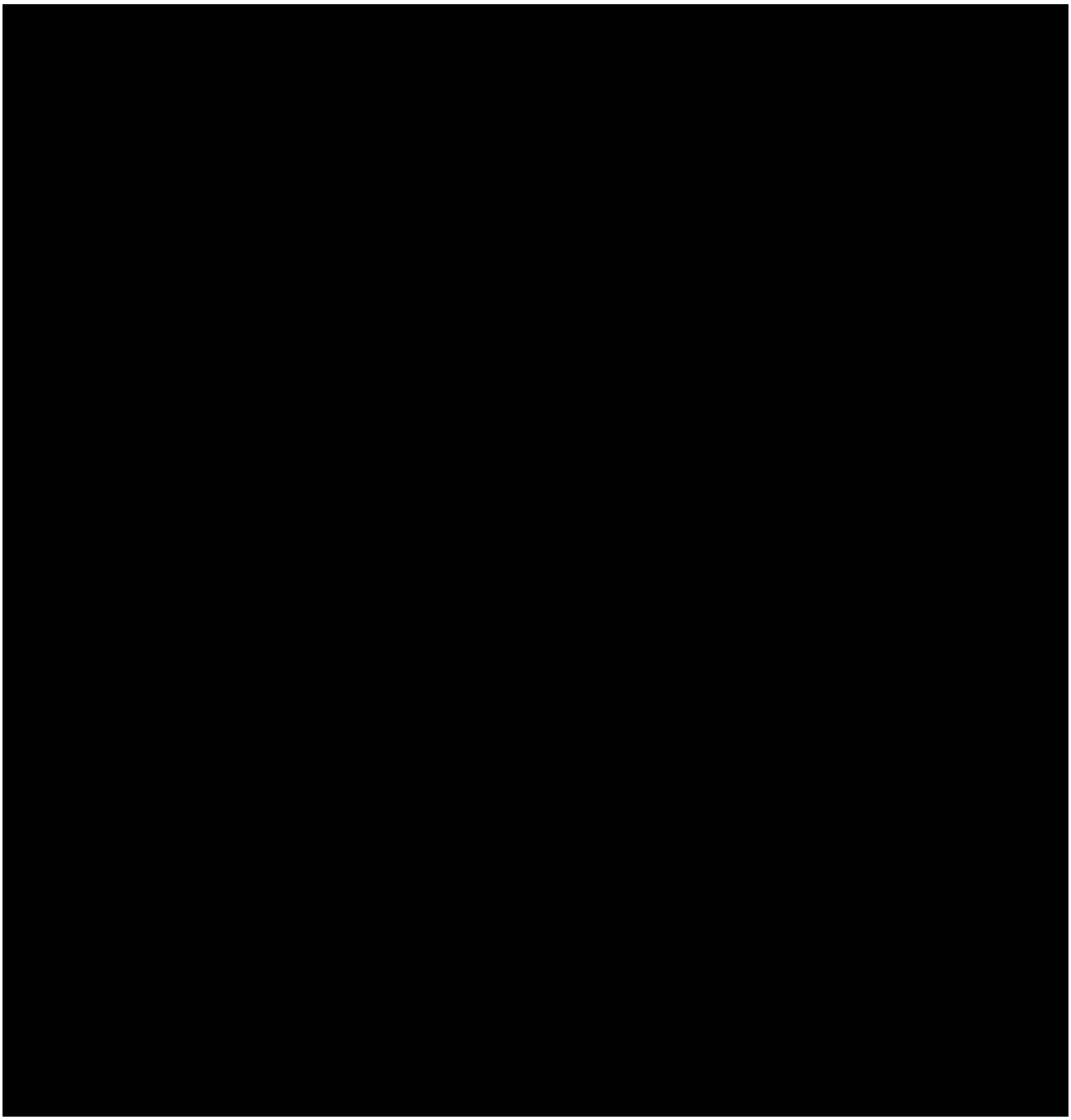
All participants randomized will be oxygen dependent and dependence on oxygen has been noted to be prolonged even after hospital discharge. We will assess recovery of pulmonary function by determining the proportion of patients returning to room air by Day 28. Participants in state 5, 6 and 8 of the Ordinal 8-point Outcome Scale meet this definition. Some participants in state 7 will.

9.1.1.6 Shortened Hospitalization

This endpoint will be defined as the proportion of participants alive and discharged home by Day 28. Home as a location will include any new facility that provides ongoing support short of full medical care such as a rehabilitation facility or assisted living facility. Participants in state 7-8 of the Ordinal 8-point Outcome Scale meet this definition.

Length of hospitalization will be defined as the number of days from the day of randomization to the date of discharge or Day 28, whichever is sooner, measured in days.





9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.5.1 in the Investigator's Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period through 60 days s after discontinuation of dosing.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 70 days after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for, 70 days after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined at the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2.4 for reporting details).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities Section 2.

9.4.1 New infections

Any new infections that develop during the 60 day study period will be captured as an AE. Type, site and source of culture will be documented in the study record.

9.4.2 Physical Examinations

Refer to Schedule of Activities Section 2.

9.4.3 Chest Imaging

Radiological assessment of symptomatic patients with COVID-19 has been reported to reveal parenchymal abnormalities, regardless of the method used, whether chest x-ray (CXR), computerized tomography (CT) or high resolution computerized tomography (HRCT).[54] These include bilateral involvement and multilobar ground-glass opacification.[31] Clinical improvement is also associated with improvement by radiographic assessments.

Because of the restrictions active during the pandemic, the protocol cannot require specific imaging be performed after hospitalization. At screening, it is understood that similar restrictions may be present at study sites, but screening with radiographic chest imaging is considered appropriate due to its utility in identifying other relevant chest disease. Some form of chest imaging (CXR, CT, or HRCT) will be required at screening as part of the inclusion criteria and will also be considered part of TB screening. The reports for this imaging and any additional chest imaging of the lungs performed during the 60 day study period, will be included in the study record.

9.4.4 Vital Signs

Vital signs (VS) will be useful for assessing the clinical progress of study participants. Since VS are captured at varying frequency during hospitalization and not all values will be of reporting utility, the study record will only capture daily values of most interest. For each day (ie, 24 hour

period, midnight to midnight) the participant is hospitalized, vital signs will be extracted from the hospital record and captured in the study record. [redacted]

Refer to Schedule of Activities Section 2.

9.4.5 Tuberculosis Screening

Screening for active or latent tuberculosis is routinely performed in abatacept trials. Screening is based on medical history, symptoms, physical exam, CXR and specific testing, either a tuberculin skin test or interferon gamma release assay [(IGRA) eg., T-spot®, QuantiFERON®] approved for local use. Abatacept has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Due to the severity of COVID-19, the usual delay to complete TB screening is not feasible and the risk, especially in low risk populations, is low. A tuberculin skin test or IGRA should be performed at screening but randomization does not need to await results if all other aspects of the TB screening, including CXR, are not suggestive of infection. If testing reveals a positive result, medical advice should be obtained to determine whether therapy is warranted.

If a tuberculin skin test is performed, it should be interpreted according to the applicable local Health Authority and/or Medical Society guidelines. Documentation of the test results should be recorded in the study record.

9.4.6 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

A local laboratory will perform the analyses and will provide reference ranges for these tests. All lab results will be available in an unblinded fashion to hospital clinical staff caring for the participant.

The study will rely on routine safety labs performed as part of routine hospital care. When available, the hematology and chemistry labs listed below will be included in the study record.

[redacted]

Screening for active viral hepatitis B or C is routine in abatacept studies and will be performed in this study, although in a different fashion. Hepatitis B reactivation has been seen in patients treated with abatacept but only in the setting of continuous use, and is a labeled warning. Reactivation of hepatitis C is not a labeled warning. Speed of screening and treatment precludes the feasibility of completing assessment during the screening period and are not warranted. Screening antibodies test will be performed but results will not be needed prior to randomization. If positive results are

noted, confirmatory nucleic acid reflex testing should be ordered and if positive monitor as appropriate.

Table 9.4.6-1: Clinical Safety Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Creatinine Blood urea nitrogen (BUN) Uric acid Glucose Total protein Albumin	Sodium Potassium Chloride Calcium Phosphorus Creatinine kinase
[redacted]	
Serology	
Hepatitis B surface antigen, hepatitis B core antibody. If either are positive, reflex to hepatitis B DNA testing	
Hepatitis C antibody. If positive reflex to HCV RNA testing	
Other Analyses	
Pregnancy test (WOCBP only: screening)	

9.5 Pharmacokinetics and Immunogenicity Assessments

9.5.1 Pharmacokinetic Assessments

Pharmacokinetic (PK) parameters are not evaluated in this study. [redacted]

9.5.2 Immunogenicity Assessments

9.5.2.1 Immunogenicity: Blood Collection

Blood samples for determination of antibodies to abatacept and time-matched PK samples will be from residual volume [redacted] on Days 1, 28/ET and 60. For logistical reasons, blood samples will only be obtained for participants who are hospitalized. Sample collection for subjects after hospital discharge will not occur. Samples will be assayed for the presence of abatacept specific antibodies.

9.5.2.2 Immunogenicity: Sample Analysis

Anti-abatacept (BMS-188667) Antibody A validated, sensitive, electrochemiluminescence assay (ECL) method will be used to analyze anti-abatacept antibodies in serum. Samples that are confirmed positive for antibodies specific to the CTLA-4 region of abatacept and have abatacept serum concentrations of ≤ 1 µg/mL will be further analyzed with a validated, in vitro, cell-based bioassay to determine whether the sera contained abatacept neutralizing activity.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study. [redacted]

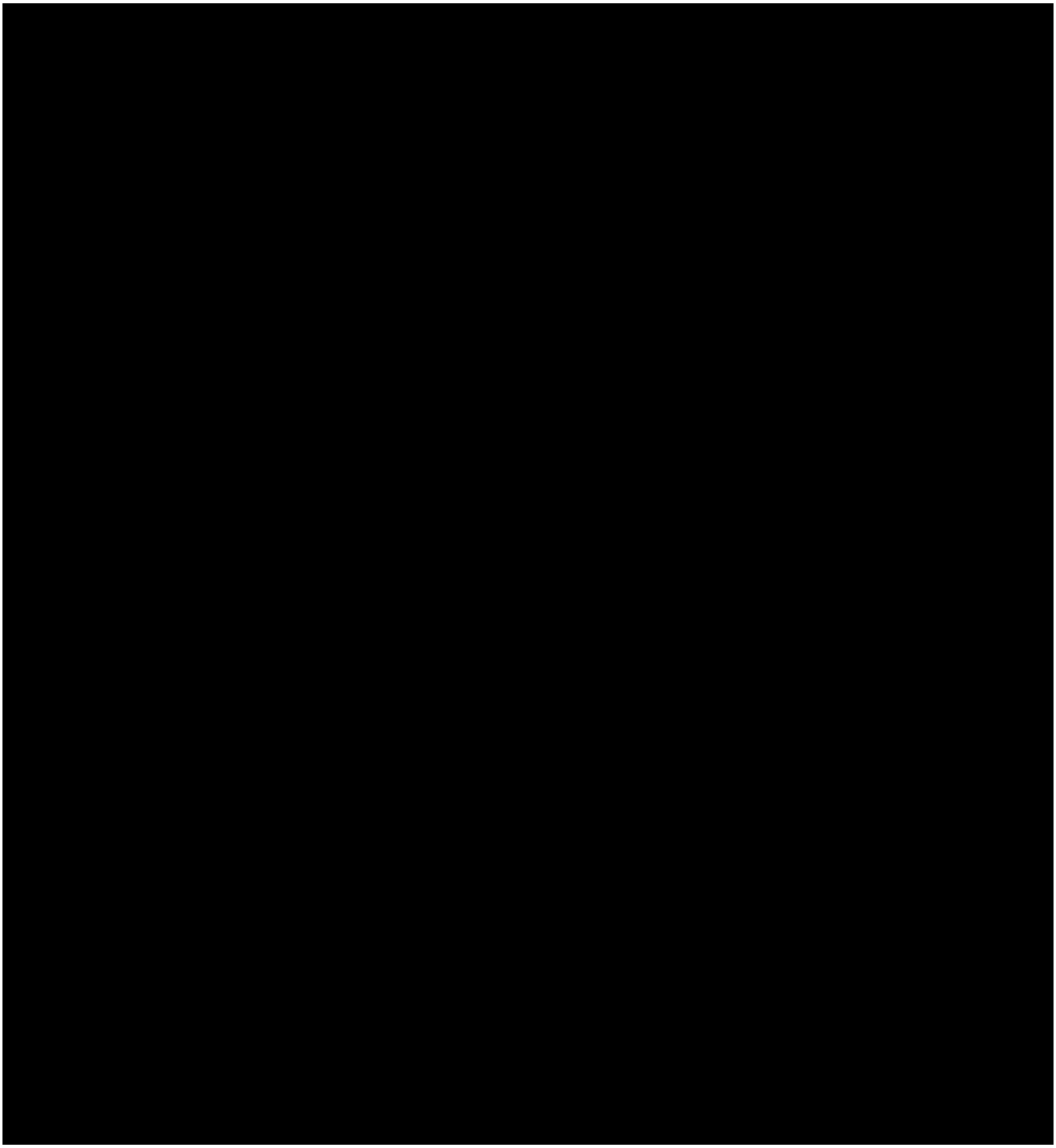
9.7 Pharmacogenomics

Not applicable.

[redacted]

[redacted]

[redacted]



9.9 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9.10 Study Materials

For participants who are discharged from the hospital prior to Day 60, will be provided with the following supplies and document:

- Diary Cards to record body temperature, blood pressure, heart rate, oxygenation, activity level, oxygen use, and symptoms
- Digital thermometer
- Oximeter
- Digital blood pressure monitor
- Subject Alert Card

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

A 25% estimated rate of progression under placebo plus standard of care to one of the elements of the primary endpoint (mechanical ventilation or death) of hospitalized COVID-19 untreated patients (in particular patients without targeted therapy) was derived from available literature[1,2,55,56,57,58] and anecdotal feedback. Rates of progression in these reports ranged from 8% to 32%. All reports are from China and include hospitalized patients that had respiratory symptoms. There are different definitions of progression in these reports but most are based on ICU and/or death.

A two group continuity corrected χ^2 test with a 0.150 one-sided significance level will have 80% power to detect the difference between a proportion of 10% abatacept treated participants and a proportion of 25% participants in the placebo group with a primary endpoint event (odds ratio of .33, ie, odds of progression under abatacept versus placebo) when the sample sizes are 86 and 43, respectively (a total sample size of 129). This computation was made using nQuery Advisor version 7. The target sample size for this study is approximately 129 randomized participants.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Intent-to-treat (ITT) Population	All randomized participants, also those randomized and never treated. This population will be used for all efficacy analysis. Analyses using the ITT analysis population will group the participants according to the treatment group to which they are randomized.

Population	Description
Per-protocol (PP) Analysis Population	The PP Population includes all randomized participants excluding the participants with relevant protocol deviations. Relevant protocol deviations are those that may potentially impact the primary endpoint. The relevant protocol deviation criteria will be defined in the statistical analysis plan. If more than 10% of subjects in either treatment group have relevant protocol deviations, the PP Analysis Population will be used for a sensitivity analysis of the primary endpoint.
As-treated Analysis Population	This population includes all randomized participants except those randomized who are not treated. Analyses using the as-treated analysis population will group the participants according to the treatment they received: abatacept or placebo. All safety analyses will use the As-treated Analysis Population.

10.3 Statistical Analyses

To avoid missing data, the data obtained after hospital discharge will be considered for inclusion in all analyses. A description of the participant population will be included in the clinical study report, including subgroups of age, gender and race. Demography and baseline disease characteristics will be presented by randomized treatment group and overall for the ITT population. Continuous variables such as age and weight will be summarized using means, standard deviations, median and ranges. Categorical variables such as gender and race, and ordinal scale score will be summarized using frequencies and proportions.

10.3.1 Efficacy Analyses

Statistical analysis methods for efficacy analyses are provided in Table 10.3.1-1. The primary efficacy endpoint will be formally tested for difference between the treatment groups. Nominal p-values for treatment comparison will be provided for selected secondary endpoints.

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary Efficacy Endpoint	The comparison between treatment groups of the proportion of participants with primary endpoint event (mechanical ventilation or death) prior to or on Day 28 will be performed using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by the randomization stratification factors age group (< 60, ≥ 60) and remdesivir use as well as baseline severity. Baseline severity will be defined by the Clinical Status scale at randomization. A one-sided significance level of 0.15 will be used to assess statistical superiority of abatacept over placebo. The ITT population will be used. Randomized

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
	participants with no primary endpoint assessment due to withdrawal of consent or for other reasons will be imputed as treatment failures (ie. progressors). The OR along with its 2-sided 70% CI and 95% CI, as well as the absolute treatment difference in proportions with its 95% will be presented. The construction of CIs for absolute differences in proportions between treatment groups will be based on minimum risk weights[59] to account for randomization stratification factors and baseline severity. A supplemental analysis of the primary endpoint comparison between the treatment groups will be based on logistic regression with age as a continuous covariate and factors for baseline severity and remdesivir stratification in the model. The nominal p-value for the Chi-square test based on this model will be presented. The primary endpoint is a composite endpoint. The number and percentage of participants progressing to each of the components will be presented by treatment group. The proportion and 95% CI of participants with mechanical ventilation or who died prior to or on Day 28 within treatment group as well as the difference in proportions between the treatment groups and its 95% CI will also be presented by site, age-subgroup ($< 60, \geq 60$), remdesivir use (stratification factor), gender, and baseline severity. Kaplan-Meier estimates for the time from randomization to progression to the primary endpoint will be presented. The p-value for the treatment comparison based on the stratified log-rank test, stratified by age-group and remdesivir use, will be presented as a sensitivity analysis of the primary endpoint.
Secondary Binary Endpoints:	Proportions and 95% CIs for the binary efficacy endpoints will be presented by treatment group. CIs for proportions within treatment groups will be based on normal approximation. Difference in proportions and 95% CI will be presented, as well as the nominal p-value derived from the CMH Chi-square test stratified by baseline severity and the randomization stratification factors. The construction of CIs for differences in proportions between treatment groups will be based on minimum risk weights to account for randomization stratification factors and baseline severity. A missing response value due to withdrawal of consent or for other reasons will be imputed as a non-responder or progressing.

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
Secondary Endpoint: Change from baseline in Ordinal 8-point Outcome Scale	The nominal p-value will be presented for the comparison between treatment groups of the proportion of participants with change from baseline to Day 28 by 1, 2, 3, or 4 categories of worsening, no worsening, or 1, 2, 3, or 4 categories of improvement based on the CMH Row Mean Scores statistic stratified by the randomization stratification factors age-group and remdesivir and baseline severity. Further analyses based on changes in the ordinal 8-point outcome scale will be detailed in the SAP.

10.3.2 Safety Analyses

The proportion (%) of participants with SAEs, AEs of special interest, and participants with laboratory marked abnormalities will be provided by treatment group. Summaries will include all events from randomization up to 60 days using the as-treated analysis population. AEs of special interest are infections and infusion reactions.

[redacted]

10.3.4 Interim Analyses

A SOC will assist in the oversight of the study execution and ongoing assessment of safety and efficacy. The Charter for the SOC will include details on boundaries to be used for establishing early evidence of efficacy at interim analysis.

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APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
µg	microgram
ABA	abatacept
AE	adverse event
aGVHD	acute graft-versus-host disease
ALT	alanine aminotransferase
APC	antigen presenting cells
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BMS	Bristol Myers Squibb
BUN	blood urea nitrogen
[redacted]	[redacted]
[redacted]	[redacted]
CBC	complete blood count
CD	cluster of differentiation
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CRO	contract research organization
[redacted]	[redacted]
CRS	cytokine release syndrome
CS	corticosteroids
CTAg	Clinical Trial Agreement
CTLA4	cytotoxic T-lymphocyte-associated protein 4

Term	Definition
CXR	chest X-ray
D	day
DMARD	disease modifying anti-rheumatic drug
ECMO	extracorporeal membrane oxygenation
ED	emergency department
eg	exempli gratia (for example)
ET	early termination
EUDAMED	European Database on Medical Devices
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCT	hematopoietic cell transplantation
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hr	hour
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin

Term	Definition
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IU	International Unit
IV	intravenous(ly)
JIA	juvenile idiopathic arthritis
kg	kilogram
L	liter
MD	Doctor of Medicine
mg	milligram
min	minute
mL	milliliter
mm	millimeter
N	number of subjects or observations
NCT	national clinical trial number
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PK	pharmacokinetics
PP	per-protocol
R	randomize
R&D	research and development
RA	rheumatoid arthritis
Rand.	randomization
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Term	Definition
SC	subcutaneous
SOC	Safety Oversight Committee
SOP	Standard Operating Procedures
SUSAR	suspected, unexpected serious adverse reaction
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
V	visit
VS	vital sign
WBC	white blood cell
WHO	World Health Organization
Wk	week
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable

If	Then
commercial supply, or a specialty pharmacy)	under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

If..	Then
	If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- Participant recruitment (eg, among the top quartile of enrollers)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Pregnancy must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for

human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c] • Bilateral tubal occlusion

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide

• Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 01, 16-Jun-2020

The purpose of this revision is to incorporate the changes [redacted]. The changes include revising the study design from a randomized, open-label controlled study to a randomized, double-blinded, placebo controlled study and other updates to protocol sections listed below.

The Synopsis has been updated to align with the protocol section changes listed below. Minor grammatical and typographical revisions are also addressed in this revision.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Changed title to: Phase 2, Randomized, **Double-Blind Placebo** Controlled Study of Intravenous Abatacept in the Treatment of Hospitalized COVID-19 Participants with Respiratory Compromise	To align with the change to the study design from a randomized, open-label controlled study to a randomized, double-blinded, placebo controlled study [redacted]
Section 2 Schedule Of Activities, Table 2-2; **Section 7 Treatment; Table 7.1-1 Selection and Timing of Dose**	Placebo added as a Study Treatment. Added the requirements for blinding and process for unblinding.	To align with the change to the study design from a randomized, open-label controlled study to a randomized, double-blinded, placebo controlled study [redacted].
Section 5 Study Design; **Section 10 Statistical Considerations**	All sections updated to reflect study design change from 'randomized open-label controlled' to 'randomized double-blinded placebo controlled' study. Schematic updated to include placebo.	To align with the change to the study design from a randomized, open-label controlled study to a randomized, double-blinded, placebo controlled study [redacted]
Section 5.1.5 Safety Oversight Committee	Clarified the Safety Oversight Committee (SOC) process for meetings and frequency and that external members of the SOC will constitute the majority of all voting members.	Changes made [redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria 2a) Prior/Concomitant Therapy	Criteria 2a) has been updated with the bold text shown below: "Participants who have been exposed within 1 month **or five half-lives, whichever is longer,** to any treatment with an approved or investigational targeted immunotherapy including, but not limited to, infliximab, etanercept, anakinra, rituximab, tocilizumab, golimumab, certolizumab, sirolumab, tofacitinib, baricitinib, upadacitinib, or filgotinib."	Added information [redacted]
[redacted]		
Section 9.4.6 Clinical Safety Laboratory Assessments	Deleted HIV-1 and HIV-2 testing.	Corrected information in the protocol.
Section 9.5 Pharmacokinetics <u>and Immunogenicity Assessments</u>	Section 9.5 has been updated and immunogenicity assessment details have been added.	To assess the immunogenicity of abatacept [redacted]
[redacted]		