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

NCT Number: NCT04472494

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

PHASE 2, RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED STUDY OF INTRAVENOUS ABATACEPT IN THE TREATMENT OF HOSPITALIZED COVID-19 PARTICIPANTS WITH RESPIRATORY COMPROMISE
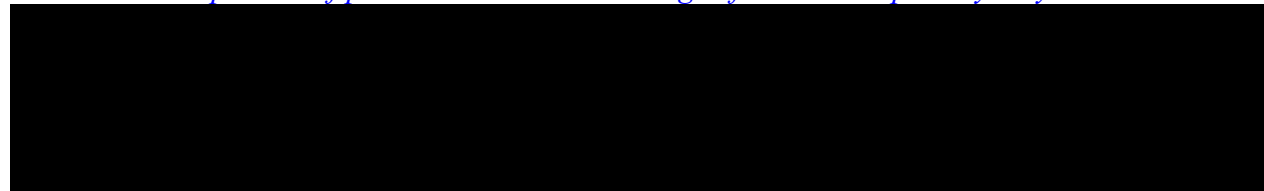

PROTOCOL(S) IM101873

VERSION # 2
DATE: 01-OCT-2021

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1 BACKGROUND AND RATIONALE

Research Hypothesis:

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 (e.g. CD4+ T cells, B cells, macrophages) and production of cytokines and interrupting the feedforward pathological process.

Schedule of Analyses:

A first database lock for analysis of the study data is planned after all patients have completed 28 days of the Double-blind Treatment period. This database lock will be used for final analysis of the primary endpoint and all secondary endpoints that relate to the 28-day study period. A second database lock for analysis will occur after all patients complete the 60-day follow-up after randomization in the study. There is no planned interim analysis.

2 STUDY DESCRIPTION

2.1 Study Design

This is a randomized, double-blind, controlled study of IV abatacept for the purpose of efficacy and safety signal detection. Participants ($\geq$ 18 years of age) will have confirmed COVID-19 disease and be hospitalized (or in the ED awaiting hospitalization) with respiratory compromise requiring supplemental oxygen but not requiring mechanical ventilatory support. Participants will be assessed for clinical responses to abatacept for 28 days and monitored for safety outcomes for a total of 60 days. If the decision is made to treat the participant with a restricted immunomodulatory therapy (e.g. 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.

Patients 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. Subjects who are discharged, whether home or to an assisted care facility, will be contacted remotely by the study team to ascertain clinical status. Level of activity (i.e. ambulatory status), oxygen requirements (e.g. oxygen therapy), current location (e.g. home) and any intercurrent adverse event (e.g. infection) will be assessed and added to 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 the study protocol is to identify suitable

study participants, and to describe the therapeutic intervention and the key measures (e.g. oxygenation, safety labs) that are part of routine care to be captured in the study record for analysis.

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

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: **Study Design Schematic**
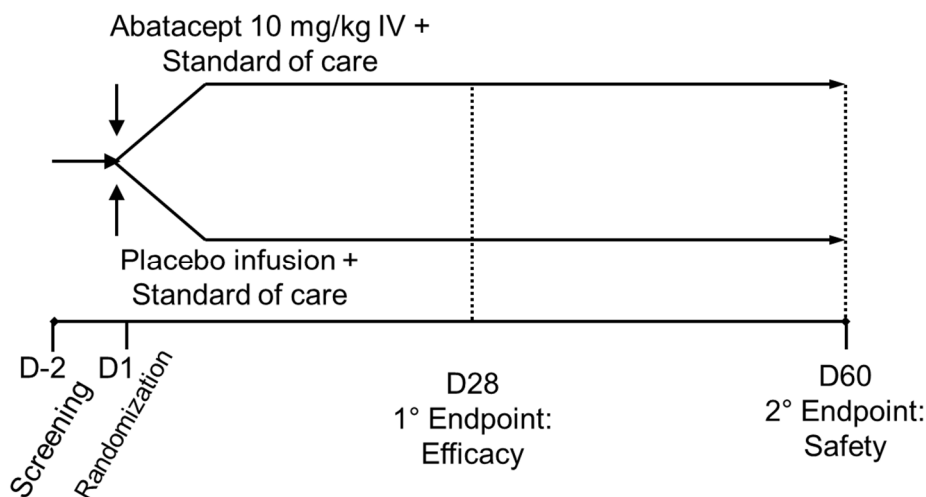
2.1.1 Screening Period

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. Participants that are randomized and 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.

2.1.2 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. Daily progress will be recorded in the study record as required. Participants who, in the opinion of the treating physician, require additional immunotherapy (e.g., tocilizumab) should continue to complete treatment period and post-treatment follow-up observation.

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2.1.3 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 visits on Days 35, 42, 49 and 60, to perform safety assessments. Medical care in this period will also follow local standards and there will be no restrictions on treatment choices.

2.1.4 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 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.

2.2 Treatment Assignment

All participants will be randomized using an Interactive Response Technology (IRT). 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. 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 (<60, ≥60 years), and remdesivir use or intended use (yes/no).

2.3 Blinding and Unblinding

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.

- The BMS Bioanalytical Science Department or its designee will be unblinded to the randomized treatment assignments in order to accurately perform sample analysis for the PK and immunogenicity samples.
- An unblinded pharmacist will prepare the study drug at the site.
- Management of study drug supply will be performed by an unblinded site monitor and operations lead.

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.

2.4 Protocol Amendments

Amendment 1, dated 19 October 2020, was a Site Specific amendment.

Amendment 2, dated 18 December 2020, clarified an inclusion and exclusion criterion, and address minor inconsistencies throughout the protocol. The main issue was to clarify the exclusion criterion for recent infections to exclude participants with recent or active, confirmed serious infections. The inclusion criterion for the need to identify an abnormal chest image was modified to include computerized tomography (CT) and high resolution CT (HRCT) in addition with chest X-ray as chest imaging procedures

2.5 Safety Monitoring

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.

3 OBJECTIVES

Table 3-1: **Objectives and Endpoints**

Objective	Endpoint
Primary	
• Prevention of Disease Progression	• Proportion of participants with composite end point of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or death prior to or on Day 28
Secondary	
• Improvement in clinical status	• Change from baseline in the Ordinal 8-point Clinical Status 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 from the hospital by Day 28
• Safety	• Proportion of participants with SAEs and serious infections

Abbreviations:

SAE = serious adverse event;

3.1 Primary Objectives

See Table 3-1

3.2 Secondary Objectives

See Table 3-1

4 ENDPOINTS

See Table 3-1

5 SAMPLE SIZE AND POWER

A 25% estimated rate of progression under standard of care to one of the elements of the primary endpoint (invasive mechanical ventilation (or ECMO) or death) of hospitalized COVID-19 untreated patients (in particular patients without targeted therapy) was derived from available literature[1,2,3,4] and anecdotal feedback at the time of the protocol development. 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 0.33, i.e. 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Screening Period

The Screening Period comprises the time period from the day of enrollment (ie. the day of informed consent) up to the day prior Day 1. Day 1 is the day of the study drug infusion, except for randomized patients that are never treated for whom Day 1 is the day of randomization only.

6.1.2 Double-blind Treatment Period, Days 1 - 28

The Double-blind Treatment Period starts on Day 1. During hospitalization the daily progress will be recorded in the study record as required by protocol up to Day 28. For subjects discharged prior to Day 28 the data collected remotely will be included in the analyses for the Double-blind Treatment Period. The last day of the Double-blind Treatment Period will be Day 28. The final analyses of the primary and secondary endpoints will be performed after all subjects have completed the Double-blind Treatment Period.

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

Participants who complete the double-blind treatment period will be monitored for study endpoints and will have follow-up visits on Days 35, 42, 49 and 60, to perform safety assessments. Patients who are discharged from hospital care at any point before the end of the 60-day period will have

remote follow-up visits. The data collected remotely after Day 28 will be included in the analyses of the Post-treatment Follow-up Period.

6.1.4 Cumulative Study Period, Days 1 - 60

The Cumulative Study Period comprises all data collected during days 1-60.

6.2 Treatment Regimens

See Section 6.3 for analysis of as randomized versus as treated.

6.3 Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent
Modified Intent-to-treat (MITT) Population	All randomized and treated participants. This population will be used for all efficacy analysis. Analyses using the MITT analysis population will group the participants according to the treatment group to which they are randomized. In this double-blind study, it can be assumed that events that happen after randomization that would prevent a patient from being treated are independent from the treatment assignment. Therefore, only randomized and treated patients will be included in analyses.
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 are defined in APPENDIX 1 of this SAP. 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 who are not treated. Analyses using the as-treated analysis population will group the participants according to whether they received: abatacept or placebo (as-treated). All safety analyses will use the As-treated Analysis Population.

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7 STATISTICAL ANALYSES

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7.1   General Methods

The primary efficacy endpoint will be formally tested for difference between the treatment groups. Nominal p-values for treatment comparisons will be provided for selected secondary ██ ██████ endpoints.

7.2   Study Conduct

Relevant protocol deviations, which could have an impact on the primary endpoint, will be identified for all subjects who are randomized. The criteria for relevant protocol deviations are provided in APPENDIX 1.

All relevant protocol deviations will be listed and summarized by treatment group. If at least 10% of the subjects in one of the treatment arms in the MITT analysis population have relevant protocol deviations, a per-protocol analysis will be performed for the primary endpoint. The per-protocol analysis will exclude data from subjects with relevant protocol deviations.

7.3   Study Population

7.3.1   Subject Disposition

Subject disposition will be summarized for the Screening Period based on the Enrolled population; and for the Double-blind Treatment Period and the Post-treatment Follow-up Period by randomized treatment using the MITT population. The summaries will include Number of Subjects in the population and number of and percentage of subjects completing the period, not completing the period and reasons of not completing as collected on the CRF. For the Double-blind Treatment summary, the number and percentage of subjects randomized and not treated will also be displayed.

7.3.2   Demography and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by randomized treatment group and overall based on the MITT analysis population. Continuous variables will be summarized using means, standard deviations, median, Q1, Q3 and ranges (minimum and maximum), based on non-missing observations. The distribution of categorical variables will be summarized by treatment group using frequency and percentage. For categorical variables, percentages will be calculated out of the total number of subjects in the MITT population, overall and by treatment group (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic and missing is included as a category).

The demography table should display age, race, ethnicity, gender, the age-group ($<60, \geq 60$) based on the age recorded in the eCRF as well as the stratification factor age-group from the IRT, the stratification factor remdesivir use (Yes/No) from the IRT, and number and percentage of subjects per site.

Baseline disease characteristics will include: time in days from confirmed disease diagnosis of COVID-19 to randomization, as well as the stratification factor of use or intended use of remdesivir

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from the IRT, height, weight, BP, HR, respiratory rate, temperature, oxygen supplementation and assessment of clinical status. The duration of symptoms will be summarized both continuously and categorically ($\leq$10 days, > 10 days). Duration of symptoms will be computed as date of Day 1 - date of first symptomatic +1.

Smoking history was collected on the CRF but will not be summarized or listed.

7.4 Extent of Exposure

7.4.1 Study Therapy

The exposure to study drug will be summarized by the number of subjects receiving study drug infusion by treatment group for the as-treated study population.

7.4.2 Study Conduct

See section 7.2.

7.4.3 Concomitant Therapy

Concomitant medication during a study period is defined as a medication with either a recorded medication start date falling within the study period, or a recorded medication start date prior to the first day of study period without any recorded medication stop date prior to the start of the period.

Missing and partial date handling of start and stop dates of concomitant medications, is described in Section 8.3. The World Health Organization (WHO) dictionary is used to code non-study medications.

All concomitant medications will be summarized prior to randomization, for the double-blind treatment period (by randomized treatment group, MITT population) and for the cumulative period from Day 1 to Day 60 (by randomized treatment group, MITT population).

A comprehensive listing of all concomitant medications will be provided for the MITT population.

7.5 Efficacy

Table 7.5-1:   **Efficacy Statistical Analyses**

Endpoint	Statistical Analysis Methods
Mean Change from Baseline for continuous variables	Descriptive summaries by treatment group of continuous variables (e.g. temperature) will include the unadjusted mean (SD) at baseline and on study measurement timepoints as well as the treatment group difference between the means and the associated SE, and 95% confidence interval.
Proportions for binary endpoints	• 95% CIs for proportions within treatment groups will be based on normal approximation. • Except for subgroup analyses, the construction of 95% CIs for absolute differences in proportions between treatment groups will be based on minimum risk weights[5] to account for randomization

Table 7.5-1:   **Efficacy Statistical Analyses**

Endpoint	Statistical Analysis Methods
	stratification factors as well as for baseline severity. For subgroup analyses the stratification variables and baseline severity will not be taken into account in the computation of the confidence limits for the treatment difference but will be based on normal approximation.
	• Except where mentioned otherwise, a missing response value due to withdrawal of consent or for other reasons will be imputed as a non-responder or progressing.

7.5.1 Primary Efficacy Endpoint Proportion of participants with composite end point of invasive mechanical ventilation (or ECMO) or death prior to or on Day 28

The comparison of the proportion of participants with primary endpoint event (invasive mechanical ventilation (or ECMO) or death) prior to or on Day 28 will be performed using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by age group ($<60, \geq 60$), remdesivir-use stratification factor and baseline severity (clinical scale evaluation as recorded on the 8 point scale). A two-sided significance level of 0.30 will be used to assess the p-value for the difference between abatacept versus placebo. The MITT population will be used.

The primary endpoint will be derived as follows.

- Death on or prior to Day 28 will be derived as 'Yes' if a date of death is collected on the 'Death Data' CRF and (date of death - date of study medication +1) ≤ 28.

- Use of invasive mechanical ventilation prior to or on Day 28 will be derived as 'yes' if there is an 'Oxygen Supplementation' CRF form with Oxygen Delivery Device equal to 'Invasive Mechanical Ventilation' and (date on oxygen supplementation CRF - date of study medication +1) ≤ 28 or if there is a 'Clinical Status' CRF form indicating 'Hospitalized, on invasive mechanical ventilation or ECMO' and (date on 'Clinical Status' CRF - date of study medication +1 ≤ 28.

- Randomized subjects with no primary endpoint assessment due to withdrawal of consent will be imputed as treatment failures (ie. progressing to invasive mechanical ventilation (or ECMO) or death).

- Subjects without a death date and without evidence of invasive mechanical ventilation or ECMO on or prior to Day 28 for which all assessments are missing in the interval of Day 25-31, but with a hospital discharge date before Day 28, and has a normal follow up visit after Day 31, will be imputed as treatment success.

A listing of subjects with imputed values for the primary endpoint will be provided, including the reason for imputation.

The primary estimand of the treatment difference in proportion of subjects who died or experienced invasive mechanical ventilation (or ECMO) on or before Day 28 is the odds ratio (abatacept vs. placebo) in the MITT population that would be observed if all patients dropping out before Day 28 or with missing primary endpoint assessments as described above would have died or experienced invasive mechanical ventilation (or ECMO) prior to or on Day 28.

Within treatment group proportions of patients with primary endpoint event and 95% CI will be presented. The OR along with its 2-sided 70% CI (alpha=30%) and 95% CI (based on the Mantel-Haenszel estimates), 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[5] to account for randomization stratification factors and baseline severity.

The primary endpoint is a composite endpoint. The number and percentage of patients progressing to death, and the number and percentage of patients progressing to invasive mechanical ventilation (or ECMO) prior to or on Day 28 will be presented by treatment group.

7.5.1.1 Supplemental analysis of the primary endpoint.

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 odds ratio and 95% CI as well as the nominal p-value for the treatment comparison from the Chi-square test based on this model will be presented.

7.5.1.2 Subgroup analyses of the primary endpoint

The proportion and 95% CI of participants with invasive 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 based on normal approximation will also be by presented by the following subgroups of the MITT population. *There will be no summary statistics for subgroups with less than 5 patients in any treatment group.*

- age-subgroup (<60, ≥60 years) (stratification factor) and (18- <40, 40- < 65, ≥ 65 years)
- gender
- site
- race
- ethnicity
- duration of symptoms ≤10 days, > 10 days
- use of remdesivir as concomitant medication - note that this subgroup is not defined at baseline and may be confounded with the treatment effect
- use or intended use of remdesivir (stratification factor)
- baseline severity according to the 8-point clinical evaluation ordinal scale

7.5.1.3 Time from randomization to invasive mechanical ventilation (or ECMO) or death

The KM estimates of proportion of participants with invasive mechanical ventilation (or ECMO) or death over time will be plotted. The hazard ratio and its 95% CI for the treatment comparison will be derived from a stratified Cox regression model with treatment as the sole covariate. The nominal p-value will be based on the stratified log-rank test. Stratification variables in these analyses are age-group, and remdesivir-use stratification factor, and baseline severity (clinical evaluation ordinal scale). Ties will be handled using Breslow's methodology. Subjects who do not experience death or invasive mechanical ventilation will be censored at the earlier of the date of end of study (Day 60), or last-contact date (for subjects who withdraw consent to be followed up or are lost to follow-up).

7.5.1.4 PP analysis of the primary endpoint

If more than 10% of patients in either treatment group have relevant protocol deviations then the primary endpoint will be assessed using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by age group (<60, ≥ 60) and remdesivir use stratification factors and baseline severity based on the PP Analysis population. The nominal p-value will be presented. Within treatment group proportions and 95% CIs will be presented. The OR along with its 2-sided 70% CI and 95% CI and the absolute treatment difference in proportions with its 95% CI will be presented.

7.5.1.5 As observed analysis of the primary endpoint

The as-observed analysis of the primary endpoint will summarize the primary endpoint including subjects who either died or had invasive mechanical ventilation or ECMO prior to or on Day 28 or had a record of oxygen supplementation or clinical status in the Day 28 visit window (Days 25-31). Results of this analysis should be interpreted with care and are only valid under the non-verifiable assumption that the reason that subjects had missing Day 28 visits is totally independent from their (unobserved) clinical status and from the treatment received. The only maybe useful information from this analysis will be that, when compared to the primary analysis, it allows for assessing the number of subjects imputed as treatment failures in the primary analysis.

7.5.2 Secondary Efficacy Endpoints

7.5.2.1 Change from baseline in the Ordinal 8-point Clinical Status Scale on Day 28

The WHO recommends that a clinical study for COVID-19 use a composite clinical endpoint and recommends use of an ordinal scale that measures participant's clinical status.[6] 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.[7] 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

For all analyses based on the Ordinal 8-point Clinical Status Scale the status of death will be carried forward through all remaining visits.

- The proportion of participants in each category of the outcome scale will be provided by treatment group at baseline and each assessment time point. A bar chart over time will be used to illustrate the percentage of subjects in each category over time and by treatment group. A category of missing will be included at the top to depict the percentage of subjects with missing data.

- Adjusted mean changes from baseline in the Ordinal 8-point Clinical Status Scale and corresponding 95% CIs as well as the difference in changes between treatment groups and corresponding 95% CI will be presented based on an ANOVA model with factors for treatment, age-group, remdesevir use stratification factor, and baseline severity. 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. This same analysis will be performed daily up to Day 7 and on Day 14, 21, 35, 42, 49 and 60.

- The point estimate and 95% CI will be provided for the proportion of subjects who had improvement (2 points or more) in clinical status assessment that occurred within 28 days. The p-value for the comparison of the proportion of subjects with 2 points or more improvement within 28 days based on the CMH test stratified by age-group, and remdesivir-use stratification factor and baseline severity will be provided.

- The time to first improvement from baseline by 2 point or more on the ordinal clinical assessment scale will be compared between the treatment groups. Death will be a competing risk in this analysis. The p-value for the treatment group comparison will be from a stratified Gray's test. stratified by the randomization stratification factors age-group and remdesivir and baseline severity. The cumulative incidence and 95% confidence intervals by treatment group will be computed and at Days 7, 14, 28 and Day 60. A figure with the cumulative incidence curves will be provided.

7.5.2.2 Time from randomization to death

The KM estimates of death will be plotted over time. The hazard ratio and its 95% CI for the treatment comparison will be derived from a stratified Cox regression model with treatment as the

sole covariate. The nominal p-value will be based on the stratified log-rank test. Stratification variables in these analyses are age-group, and remdesivir-use stratification factor, and baseline severity (clinical evaluation ordinal scale). Ties will be handled using Breslow's methodology. Subjects who do not experience death will be censored at the earlier of the date of end of study (Day 60), or last-contact date (for subjects who withdraw consent to be followed up or are lost to follow-up).

7.5.2.3 Proportion of patients alive and free of respiratory failure on Day 28

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 Clinical Status Scale meet the definition of alive and free of respiratory failure.

The proportion of patients free of respiratory failure in states 4-8 on Day 28 will be compared between the treatment groups using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by age group (<60, ≥60) and remdesivir use stratification factors and baseline severity based on the MITT population.

The numerator will present the number of subjects in the specified state of the Ordinal 8-point Clinical Status Scale on Day 28±3.

The nominal p-value will be presented. Within treatment group proportions and 95% CIs will be presented. The OR along with its 2-sided 95% CI and the absolute treatment difference in proportions with its 95% CI will be presented.

7.5.2.4 Proportion of patients alive and returned to room air on Day 28

The proportion of patients alive and returned to room air by Day 28 will be compared between the treatment groups using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by age group (<60, ≥60) and remdesivir use stratification factors and baseline severity based on the MITT population.

The numerator will present the number of patients on room air as indicated on the oxygen supplementation CRF at Day 28, with no death date prior to or on Day 28. Subjects with missing oxygen type in the Day 28 day range (Day 25-31) will be considered as not returned to room air.

The nominal p-value will be presented. Within treatment group proportions and 95% CIs will be presented. The OR along with its 2-sided 95% CI and the absolute treatment difference in proportions with its 95% CI will be presented.

7.5.2.5 Proportion of patients alive and discharged from the hospital by Day 28

The proportion of patients alive and discharged from the hospital by Day 28 will be compared between the treatment groups. using the Cochran-Mantel-Haenszel (CMH) Chi-Square test, stratified by age group (<60, ≥60) and remdesivir use stratification factors and baseline severity based on the MITT population.

The numerator will present the number of subjects with a hospitalization discharge date recorded on the hospitalization-log CRF prior to or on Day 28 with no death date prior to or on Day 28. Subjects with missing discharge date on the hospitalization_log CRF 28 will be considered as hospitalized.

The nominal p-value will be presented. Within treatment group proportions and 95% CIs will be presented. The OR along with its 2-sided 95% CI and the absolute treatment difference in proportions with its 95% CI will be presented.

Length of hospitalization will be defined as the number of days from the day of randomization to the date of discharge, measured in days.

- The number of subjects discharged, mean length of hospitalization, standard error, median, min, max by treatment group will be presented for the subgroup of subjects with hospital discharge prior to or on Day 28.

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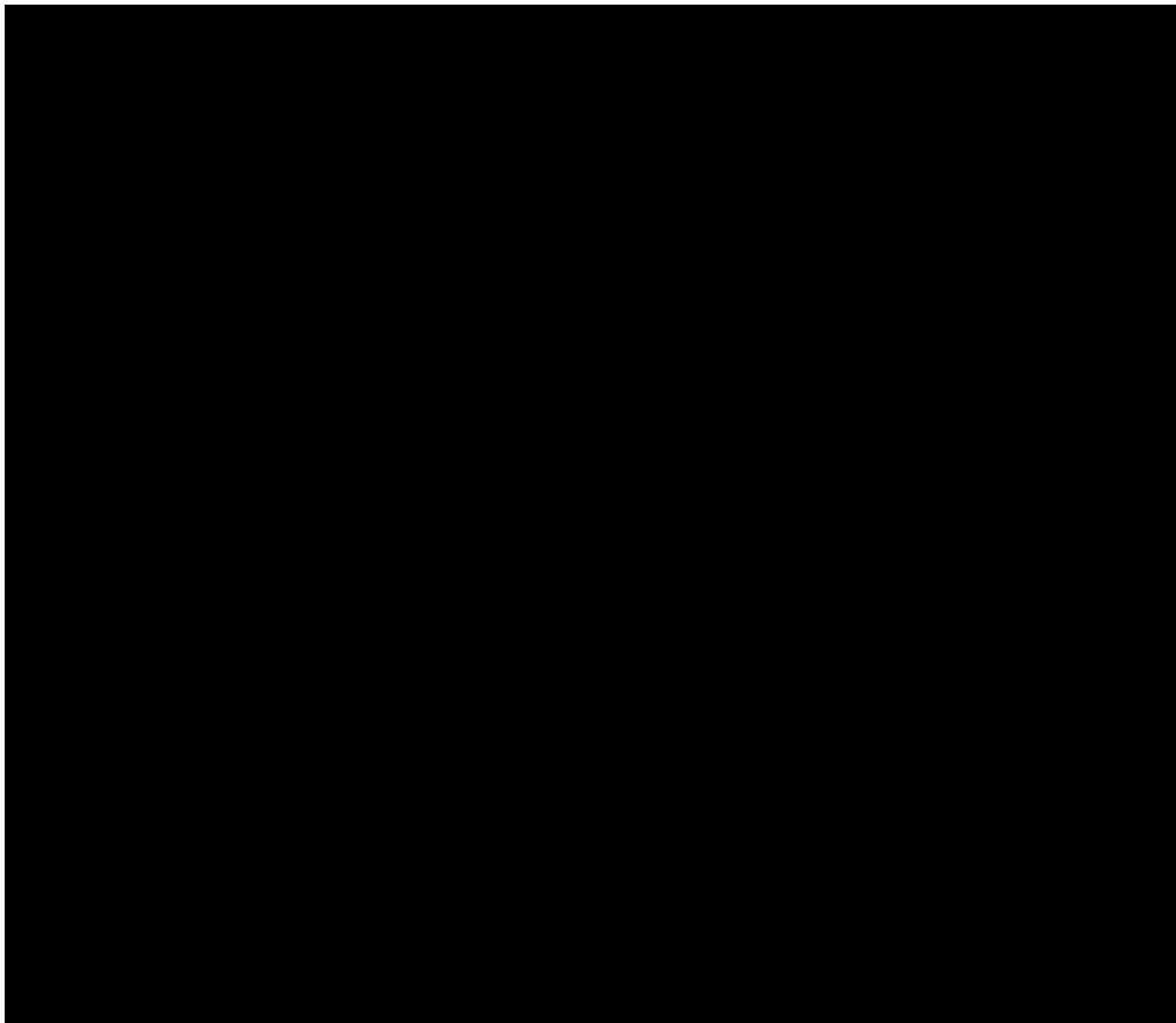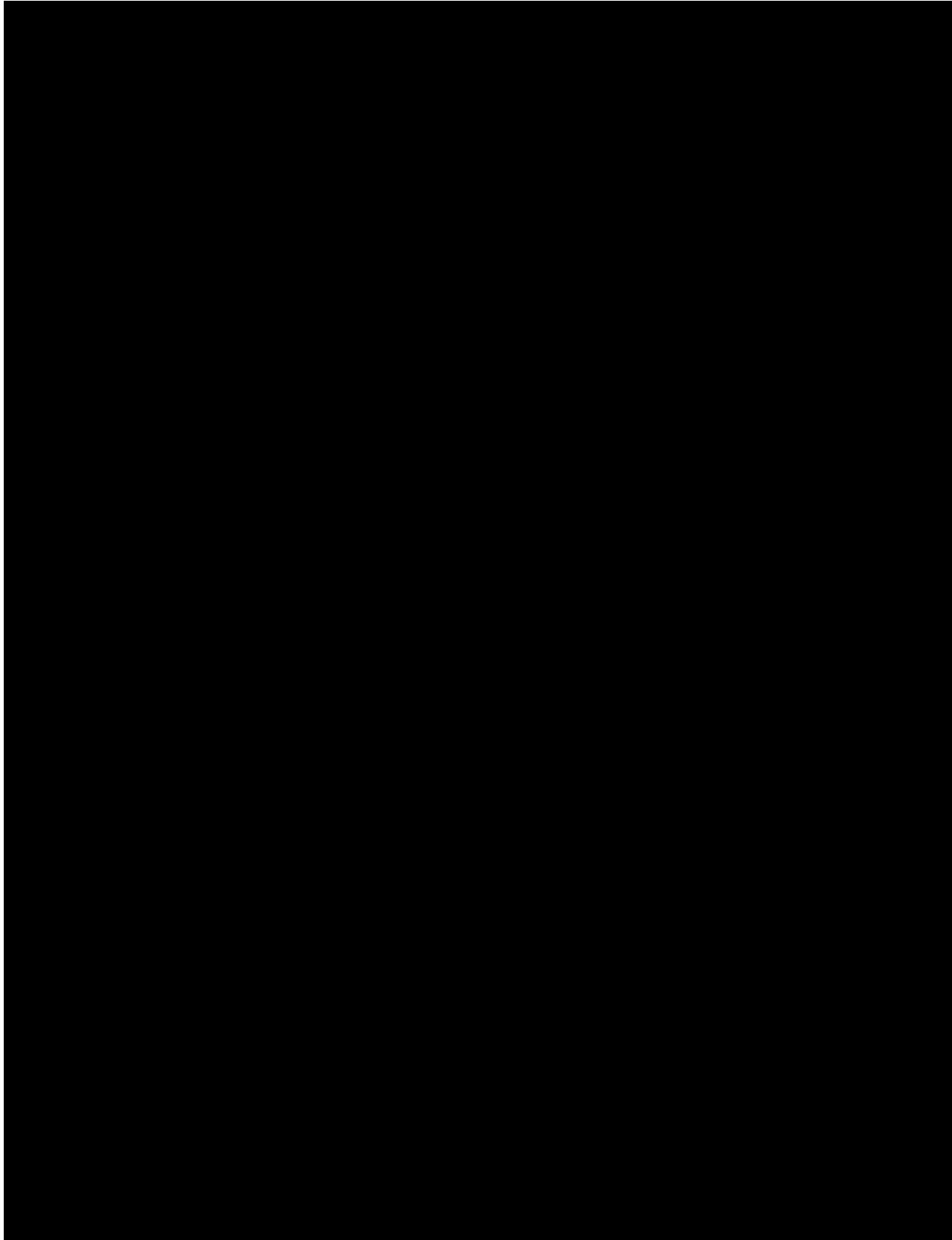
7.6   Safety

All summaries of safety parameters will be provided by treatment group. All safety assessments will be included in the summary tables presented for the cumulative study period if the onset date is on or after Day 1 and up to and including Day 60 of the study.

For analysis by time-point the day ranges are specified in Section 8.4. Presentations will be provided by treatment group for the as-treated analysis population.

7.6.1   Adverse Events

All AEs are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the latest approved version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Listings and summaries will be based on the resulting SOCs and PTs.

AEs during the Study Period will be included in the frequency tabulations if they occur on or after Day 1 and up to Day 60 of the study. These AE summaries will be based on proportions, which represent the number of subjects experiencing the AEs based on the As-treated analysis population.

The following summaries will be provided:
- AEs (including clinical and laboratory AEs):
  - All AEs
  - Most frequently reported AEs (reported in at least 5% of subjects in any group)
  - AEs by Intensity (mild, moderate, or severe)
  - All SAEs

- AEs related to study drug:
  - All AEs related to study drug
  - Most common (reported in 2% of subjects or more in any group)
  - AEs by Intensity
  - All SAEs related to study drug

All reported AEs (including those that occur more than 60 days after the dose of study medication) will be listed.
.

7.6.2   Deaths

All deaths recorded on any study status pages, the clinical status page, death data page, the AE page, or SAE page (with a death date, or cause of death, or outcome or SAE categorization present) of the CRF will be reported. All Adverse events with the outcome of death reported during the study will be listed. A listing of the data collected on the death data page will be provided.

7.6.3   AEs of Special Interest

The proportion (%) of participants with AEs of special interest will be provided by treatment group. AEs of special interest are infections, malignancies, autoimmune disorders and infusion reactions.

- AEs of infections are all AEs within the SOC 'infections and infestations'. Summaries of AEs and SAEs of infection are included as part of the tables identified in section 7.6.1.
- AEs of malignancies are all events in the MedDRA Maintenance and Support Services Organization (MSSO) malignancies Structured MedDRA Query (SMQ)
- Pre-specified MedDRA codes of autoimmune disorders events of interest for abatacept will identify events of interest for autoimmune disorders.
- Pre-specified MedDRA codes of peri-infusional AEs of interest for abatacept will identify events in the summary of infusion AEs that occur within the first 24 hours after the start of infusion.

7.6.4   Subgroup Analyses

The subgroups of interest for analyses of the frequencies of AEs by SOC and PT during the cumulative period are:
- age-subgroup (<60, ≥60 years)
- gender
- race

If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis. Only subgroups consisting of 5 or more subjects in each treatment group will be considered.

7.6.5   Clinical Laboratory Evaluations

Day ranges for analysis time points of laboratory evaluations are defined in Table 8.4-2.
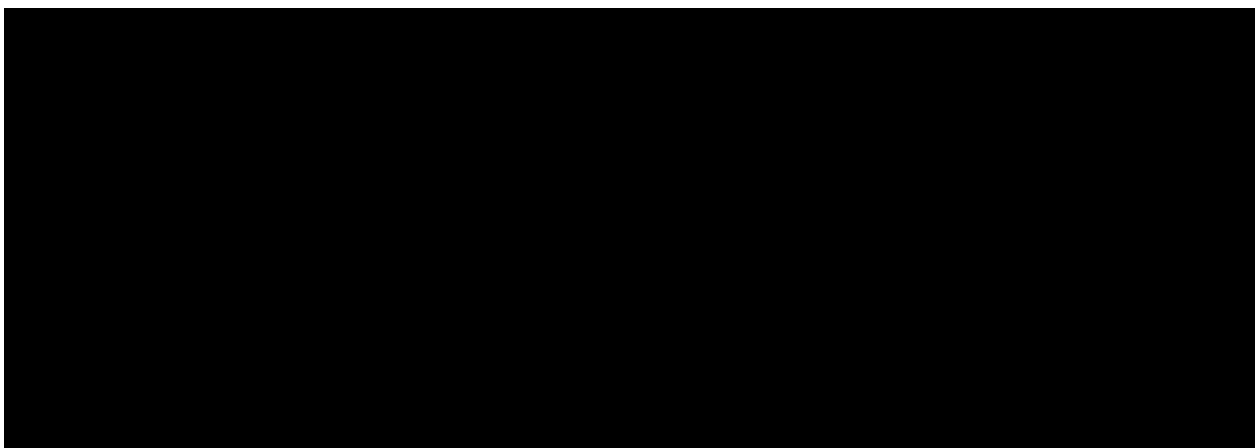
7.6.5.2 Marked Laboratory Abnormalities

Laboratory abnormalities will be reported using the as-treated analysis population for the double-blind treatment period and for the cumulative study period. Laboratory measurements will be included in the analysis for the cumulative period if the measurement date is after first dose date up to 60 days post dose date.

Laboratory abnormalities are identified using a pre-defined set of marked abnormality criteria. The criteria will be listed in the study report.

7.6.5.3 Changes from baseline in safety laboratory parameters

Laboratory measurements and corresponding change from baseline values will be summarized (mean baseline with standard deviation, mean post-baseline with standard deviation, mean change from baseline with standard error and 95% CI for change from baseline) by time point and treatment group during the cumulative study period and laboratory test. Subjects who have laboratory measures at baseline and corresponding measure at the given timepoint will be included in the laboratory analyte assessment. Note that not all subjects have laboratory determinations for all analytes at all visits, and therefore the sample size may vary from analyte to analyte at each time point. The 95% CI for the change from baseline within the treatment arm will be constructed based on the t-statistic.

Visit windows for these summaries are provided in Section 8.4.

The following laboratory parameters as defined in the protocol will be summarized:

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

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

This subset of labs should be obtained on a weekly basis whenever possible during the on treatment period (Day 1, 8, 15, 22 and 28). They include: ███████████████████████ ███████████████████ WBC (total leukocyte count), including differential.
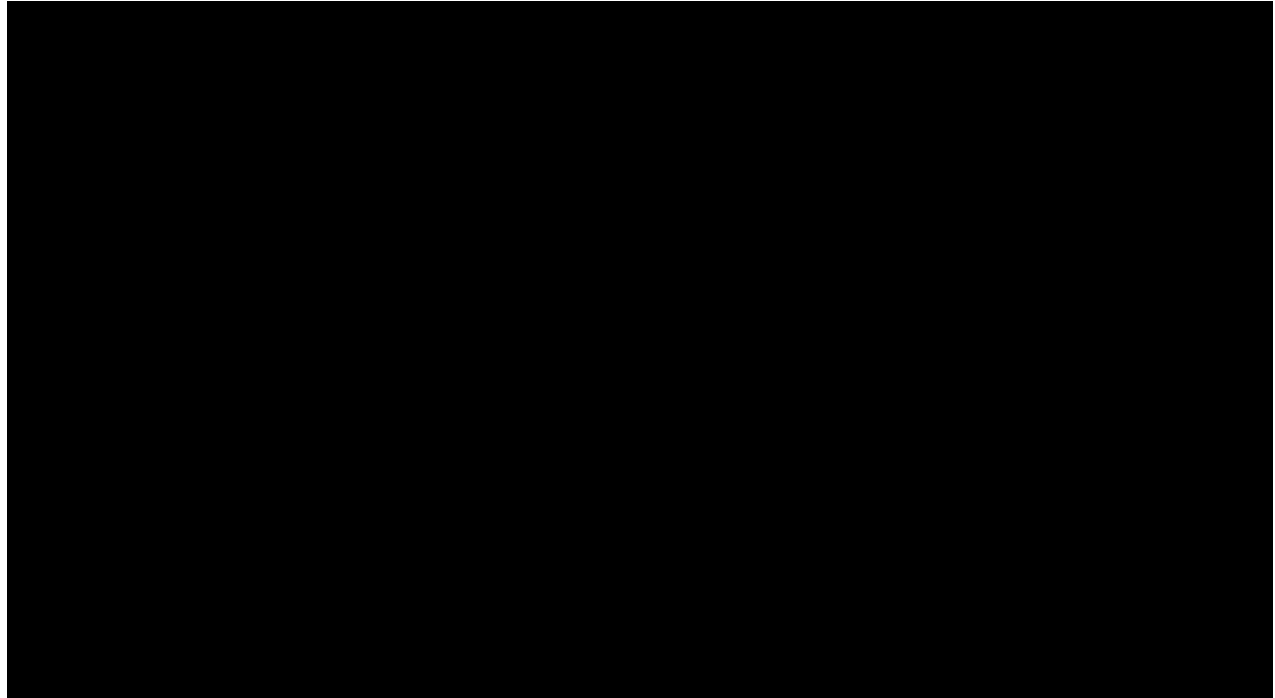
8 CONVENTIONS

8.1 Baseline Measures

For each subject, the baseline value of a parameter is defined as:

- if time of the measurement is available: the last assessment of that parameter prior to the start time of the drug infusion on Day 1 (for example FiO2).
- otherwise: the last assessment of that parameter prior to or on Day 1 (for example: min SeBP on Day 1 for change from baseline in SeBP).
- for vital signs, all values on Day1 are baseline values.

Day 1 is the day of the study-drug infusion, except for the subjects randomized who were never treated. For those subjects Day 1 is the day of randomization only.

8.2 Missing Measurements

For listings of efficacy measures, missing values will be represented as missing. Unless otherwise specified, for analyses involving binary endpoints a missing responder value due to discontinuation or for other reasons will be imputed as a non- responder.

8.3 Missing, Unknown or Partial Dates

The BMS-188667 safety guidelines[8] for conventions relating to the handling of missing or partial dates and the determination of appropriate default values in such cases (in particular, for concomitant medication dose start-dates and end-dates and AE onset dates) will be utilized. All of these applicable rules regarding missing, unknown or partial dates also apply to efficacy data.

8.4   Day Ranges for Analysis Timepoints

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Therefore, the designation of visits during the study period will be based on the day of evaluation relative to the Day 1 of the trial rather than the nominal visit recorded in the case report form (CRF). Tables below define visit windows to be used. If a subject has more than one visit where a measurement is recorded within a window, the measurement closest to the target day will be used. In case of two visits being equally distant from the target day, the later measurement will be used in analyses. Exception to these rules applies to immunogenicity. For this, the least favorable value (toward a positive response) in the window will be used.

Table 8.4-1:   Day Ranges for Analyses (Clinical Outcome Scale, Vital Signs, FI02)

Visit	Target Day	Day Ranges
Day 1	1	1
Day 2- 28 (Daily)*	2-28 (Daily)	
Day 7	7	2-10
Day 7 (if Daily till Day 7)**	7	7-10
Day 14	14	11-17
Day 21	21	18-24
Day 28	28	25-31
Day 28(if Daily till Day 28)***	28	28-31
Day 35	35	32-38
Day 42	42	39-45
Day 49	49	46-52
Day 60	60	53-65

* Only if applicable. Depending on whether the presentation of results is for weekly intervals or for daily intervals, the corresponding day ranges are to be used. For example, if daily results are presented then Day 7 is the measurement selected for analysis for that day. If a presentation is for weekly interval then for Day 7 the measurement closest to the target day in the day range 2-10 is selected for analysis.

**If for the same scale in the same presentation the summaries are daily up to Day 7 and then Day 14, 21, etc., then the Day range for Day 7 will be 7-10 with Target Day 7.

*** If for the same scale in the same presentation the summaries are daily up to Day 28 and then Day 35, 42, etc., then the Day range for Day 28 will be 28-31 with Target Day 28.

Table 8.4-2: **Day Ranges for laboratory analyses** ████████████████████
████████████████████

Visit	Target Day	Day Ranges
Day 1	1	1
Day 8	8	2-11
Day 15	15	12-18
Day 22	22	19-24
Day 28	28	25-31
Day 35	35	32-38
Day 42	42	39-45
Day 49	49	46-52
Day 60	60	53-65

9   CONTENT OF REPORTS

The topline results will include the following:

- Demography and baseline characteristics.
- Subject Disposition
- Concomitant Medications
- Primary Efficacy Endpoint Analysis
- Sensitivity Analyses and Supplemental Analysis of Primary Endpoint
- Secondary Efficacy Endpoint Analyses
- Safety Summary Table

10   DOCUMENT HISTORY

Table 10-1: **Document History**

Version Number	Author(s)	Description
1.0	████████	Original Issue

2.0	███████	• Appendix 1: Removed the following as it is not a protocol deviation: 'Subject on supplemental oxygen at randomization but with oxygen saturation < 93 documented on the oxygen supplementation form'
		• 8.1 Baseline Values: Added the following: for vital signs, all values on Day1 are baseline values.
		• ████████████████████
		• ████████████████████
		• Changed the efficacy analysis from ITT to MITT. In this double-blind trial there should be no bias introduced by the random events that happen after randomization that will prevent patients from being treated. The trigger for this change was a patient who was randomized, then found not to have COVID and therefore not treated. The patient refused being followed up. Switching from ITT to MITT will avoid that this patient is included in the analysis.
		• Added new day range to Table 8.4-1 in case presentation is daily till Day 28 and weekly thereafter
		• Changed 'Schedule of Analyses' in section 1 Background and rationale to reflect that the Day 28 endpoints will be analyzed using a first database lock for final analysis after all patients have completed the Day 28 period.

Table 10-1:   **Document History**

Version Number	Author(s)	Description
	████████	• ███████████████████████████████████ ████████ • 7.7.3 Immunogenicity Analyses section was removed because immunogenicity analysis requires long-term follow-up, and the early termination of the study cuts the follow-up short. • 7.5.1 It is clarified that subjects who has discharged from hospital before Day 28 and with a normal Day 28 follow-up visit after Day 28 visit window, will be imputed as a treatment success.

APPENDIX 1   CRITERIA FOR RELEVANT PROTOCOL DEVIATIONS

Type of Participant and Target Disease Characteristics

1) Adults without confirmed virological diagnosis of SARS-CoV-2 infection (by RT-PCR) defined by missing date of confirmed disease diagnosis in CRF or subjects who did not test positive

2) Subject without documented need for supplemental oxygen prior to or at randomization according to no information on oxygen supplementation form prior to or at randomization

3) Subject requiring mechanical ventilation at screening or at randomization as documented using either the 8-point ordinal scale and/or oxygen supplementation form

4) Subject with no X-ray, computerized tomography [CT], or high-resolution CT [HRCT] prior to or at randomization

Incorrect dosing or study treatment assignment

5) Subjects randomized to Abatacept who were treated with placebo or subjects randomized to placebo who were treated with Abatacept

Use of prohibited concomitant medication from Day 1 to Day 28

Not applicable

Subjects not withdrawn for treatment and/or study despite having met specified criteria for withdrawal

Not applicable

Subjects who did not receive, or received incorrectly, an important study procedure:

6) Subjects with missing survival status at Day 28 (+-3).

APPENDIX 2   CONVERSION TABLES FOR SUPPLEMENTAL OXYGEN REQUIREMENTS

The convention for conversion of supplemental oxygen to establish the FiO2 will follow the following rules[910]. Please note, FiO2 can be reported as the fraction of or percentage of inspired oxygen. Care must be taken to use the same units.

The following modalities should be captured with specific FiO2 values due to their design:

1) Room air, the FiO2 will be 0.21.
2) 100% non-rebreather mask, the FiO2 will be 1.0.
3) High flow nasal cannula, when reported in FiO2.
4) High flow oxygen mask with venturi valves (i.e. venturi mask). They range from 0.24 to 0.60.
5) Invasive mechanical ventilation.

The challenge is for patients receiving supplemental oxygen by nasal cannula or mask. Here one cannot know the "exact" FiO2 and must estimate the FiO2. Factors like respiratory rate, tidal volume, and extent of mouth breathing can alter the FiO2. Oxygen flow rates may be reported in liters per minute [LPM]. High flow nasal cannula is sometimes reported in flow rate so the following conversion rate estimates will be adopted as convention.].)[11].

6) Low flow nasal cannula using oxygen delivery rates of 1 to 6 LPM increases FiO2 about 0.04 with each increase of 1 LPM. 1 LPM: 0.25, 2 LPM: 0.29, 3 LPM: 0.33, 4 LPM: 0.37, 5 LPM: 0.41, 6 LPM 0.45.
7) High flow nasal cannula, when reported in 6–15 LPM increases FiO2 about 0.025 with each increase of 1 LPM. 6 LPM: 0.49, 7 LPM: 0.515, 8 LPM: 0.54, 9 LPM: 0.565, 10 LPM: 0.585, 11 LPM 0.61, 12 LPM: 0.635, 13 LPM 0.66, 14 LPM: 0.685, 15 LPM 0.72.
8) Simple mask with oxygen flow rates between 6 and 12 LPM. 6 LPM: 0.35, 7 LPM: 0.39, 8 LPM: 0.43, 9 LPM: 0.47, 10 LPM: 0.50, 11 LPM: 0.55, 12 LPM: 0.60.

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