Statistical Analysis Plan

Title Page

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Antiviral Activity of BLD-2660 in Hospitalized Participants with Recently Diagnosed COVID-19 Compared to Standard of Care Treatment
Protocol Number:	B-2660-204
Study Drug:	BLD-2660
Study Indications	Coronavirus disease 2019 (COVID-19)
Sponsor Name:	Blade Therapeutics, Inc.
Legal Registered Address:	442 Littlefield Avenue, South San Francisco, CA 94080, United States
Regulatory Agency Identifier Number(s):	IND: 149130
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Signature Page

Approvals:

Prepared by: Sponsor

Name Statistician:	DocuSigned by: Brian Mangal 9811C4E60EB14C1...	10/26/2020
	Brian Mangal, MSc.	Date: (dd/mmm/yyyy)
	Statistical Consultant	

Approved by: Sponsor	DocuSigned by: Masoud Mokhtarani F03303C7FB6F465...	10/26/2020
Name:	Masoud Mokhtarani, MD	Date: (dd/mmm/yyyy)
Title:	Cheif Medical Officer	

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Version History

This Statistical Analysis Plan (SAP) for study B-2660-204 is based on the protocol version 3.0 amendment 2.0, dated May 8th, 2020.

SAP Version	*Approval Date*	*Change*	*Rationale*
1.0	*30 August 2020*	*Not Applicable*	*Original version*
2.0	*08 October 2020*	*Subjects who die or withdraw prior to observing clinical improvement should be censored at Day 28 instead of date of death or withdrawal*	*Implemented change at the request of FDA. FDA reviewed version 1.0 and provided comments on 22 September, 2020*
		All modeling was clarified to indicate that all covariates would be entered into the model at the beginning and the stepwise selection procedure would be used to assess inclusion of these covariates.	
		For all models, corticosteroid use (yes vs no) was added as a potential covariate to include in the stepwise model selection process.	
		In the analysis of the exploratory endpoint of proportion of subjects who are SARS-CoV-2 virus free at Day 10/EOT or hospital discharge, whichever is sooner, subjects who die/withdraw from the study prior to Day 10/discharge will be classified as a non-responder instead of using their last known value.	

		For Poisson Regression models, if overdispersion exists, a negative binomial model will be used and a model where the option to adjust the standard errors using the scale parameter will not be run.	
		Removed a number of secondary and exploratory efficacy analyses	*Based on the DSMB recommendation to not expand the study, a number of efficacy analyses were removed to preserve capital*
3.0	*22 October 2020*	*Added additional details on how to derive Fi02 values based on oxygen flow rates.* *Changed IL-6 sub-group analysis from > ULN to > median,*	*eCRFs collected flow rate or Fi02. Additional details on how to derive Fi02 were needed for programming.* *IL-6 values do not have normal ranges*

1. Introduction

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analysis. This SAP should be used in conjunction with the protocol. If there are any discrepancies between the protocol and SAP, this SAP will prevail. Any deviations from this SAP that are implemented in the final analysis will be documented with sound clinical and statistical rationale in the Clinical Study Report (CSR). In the event of any changes to the primary endpoints or analyses, these changes will be documented through a protocol amendment, consistent with ICH E9.

A separate document contains the table, figure and listing specifications and any example programming codes.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate clinical benefit of BLD-2660 in hospitalized adults with recently diagnosed SARS-CoV-2 infection	• Time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first
• To evaluate improvement in oxygenation in hospitalized adults with COVID-19 treated with BLD-2660	• Change from baseline to Day 10 or hospital discharge, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
Secondary	
• To evaluate the safety and tolerability of BLD-2660 in the same population	• Incidence of TEAEs and serious adverse events (SAEs)
• To evaluate improvement in Biomarkers	• Change from baseline to Days 10/EOT, 14, 21 and 28 in serum calprotectin
• Additional efficacy outcomes	• Time to hospital discharge readiness • Proportion of participants reporting each 6-point ordinal scale of the clinical status outcome assessment Change from baseline to Days 10/EOT, 14, 21 and 28 in IL-6 and D-dimer

Objectives	Endpoints
Exploratory	
• Other efficacy outcomes	• Proportion of participants who require mechanical ventilation after study entry •
• To evaluate antiviral activity of BLD-2660 in the same population	• Change from baseline in SARS-CoV-2 viral load at Days 5, 10/EOT, 14, and 28
• Other safety outcomes	• Clinically relevant changes from baseline in electrocardiogram (ECG), and clinical laboratory values at each post baseline time point • Proportion of participants with clinically significant drug-related troponin elevations that have repeat elevation upon confirmatory testing as adjudicated by the DMC while continuing study drug during the 10-day treatment period
• To assess population pharmacokinetics (PK) characteristics of BLD-2660	• BLD-2660 plasma concentrations

1.2. Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled multicenter study designed to evaluate BLD-2660 as add-on to standard of care (SOC) therapy in hospitalized participants with recently diagnosed COVID-19 compared to SOC treatment.

The study will include a Screening period, a Treatment period, and a Follow-up period.

After signing informed consent form (ICF), potential candidates who are hospitalized for confirmed infection with SARS-CoV-2 will undergo additional screening procedures.

On Day 1, eligible participants will be randomized in 2:1 ratio to one of 2 treatment groups, active or control, as shown in Table 1. Randomization will be stratified by remdesivir at study entry. All participants will receive study drug in combination with SOC over 10 days (through Day 10/end of treatment) or until hospital discharge, if sooner. Participants will be followed for at least 18 days after the last dose of study drug on Days 14, 21 and 28. Participants will be contacted 60 days post-study to collect information on mortality and forced vital capacity (FVC).

Table 1: Treatment Groups

Treatment Group	Dose Level, Schedule and Route of administration	Number of participants
Active	BLD-2660 900 mg twice per day (BID), oral + SOC	80
Control	Matching placebo, BID, oral + SOC	40

For each participant, the study duration for each study period is expected to last as follows:

Study Period	Duration
Screening period	Up to 3 days
Treatment period	10 days
Treatment Follow-up period	18 days
Post study follow-up period	32 days

Interim analyses are planned when approximately 25%, 50% and 75% of participants have completed the study for the purpose of reviewing safety data and for the purpose of early stopping for efficacy or futility. At the 50% interim analyses, the sample size may be increased.

The final analysis will occur once the last participant enrolled completes the end of study follow-up visit. Data from the post study follow-up visit regarding FVC will be included in the final databased after the final analysis has been completed.

2. Statistical Hypotheses

Two primary statistical hypotheses will be tested. The study will be declared a success if either of the hypotheses are statistically significant. As this is a phase 2 study, no adjustment for multiplicity will be made for having two co-primary hypotheses.

Hypothesis 1: Will evaluate clinical benefit in hospitalized adult participants with recent SARS-CoV-2 infection. The primary endpoint is time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first. The null and alternative hypotheses are:

- H_0 (null): Hazard Ratio (BLD2660/Placebo) ≥ 1, indicating that treatment does not reduce the time to recovery compared to placebo control

- H_1 (alternative): Hazard Ratio (BLD2660/Placebo) < 1, indicating that treatment does reduce the time to recovery compared to placebo control

Hypothesis 2: Will evaluate improvement in oxygenation in hospitalized adult participants with recent SARS-CoV-2 infection at the time of discharge, or Day 10, if they are still hospitalized. The primary endpoint is the change from baseline to Day 10 or hospital discharge if sooner in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2). The null and alternative hypotheses are:

- H_0 (null): Mean Treatment Difference (BLD2660 minus Placebo) ≤ 0, indicating that treatment does not improve the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) at the time of discharge or Day 10 if they are still hospitalized, compared to placebo control

- H_1 (alternative): Mean Treatment Difference (BLD2660 minus Placebo) > 0, indicating that treatment does improve the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) at the time of discharge or Day 10 if they are still hospitalized, compared to placebo control

3. Sample Size Determination

Time to clinical improvement

A randomized, double-blind, placebo-control study evaluating remdesivir in 1063 hospitalized participants with COVID-19 reported 606 recoveries, with a median time to recovery of 11 days and 15 days in the remdesivir and placebo groups, respectively (remdesivir package insert). Recovery was defined as the first day on which the participant satisfies one of the following 3 categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities (https://clinicaltrials.gov/ct2/show/NCT04280705).

Assuming the median time to clinical improvement, defined as no longer requiring oxygen support or hospital discharge whichever occurs first, will be 12-15 days in the placebo group, and that at least 75 of the planned 120 participants enrolled meet the clinically improved criteria, the study will have at least 80% power to detect a 50% reduction in the time to clinical improvement, (i.e., hazard ratio[BLD2660/Placebo] of 0.5) with a two-sided 5% significance level.

The total number of events (d) is estimated based on the following formula

$$d = \frac{(z_{\alpha/2} + z_{\beta})^2}{\pi(1-\pi)\theta^2}$$

where $z_{\alpha/2}$ and z_{β} are the value from a standard normal distribution, π is the proportion of participants randomized to control, $1-\pi$ is the proportion of participants randomized to active and θ is the inverse of the log hazard ratio, as we are modeling improvement. The total number of participants is then calculated as the number of events divided by the probability of observing the event during the study. For this study $\alpha = 5\%$, $\beta=20\%$, $\pi=1/3$ and $\theta=1/\log(0.5)$ and the probability of observing an event is 0.60.

Change from baseline to Day 10 or hospital discharge if sooner in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2).

A prospective observational cohort study of non-intubated moderate to severe ARDS participants (Ding, 2020) reported the partial pressure of oxygen (PaO_2)/FiO_2 ratio for 10 participants, which gave a mean and standard deviation of 147 ± 46 mm Hg. Converting to a $Sp0_2/FiO_2$ ratio gives a mean and standard deviation of 192 ± 39 using the equation reported by Rice et al. (2007) (Rice, 2007).

Assuming a standard deviation of 40 in the SpO_2/FiO_2 ratio, a sample size of 120 participants (80 active, vs 40 control) will provide approximately 90% power to detect a treatment difference in the SpO_2/FiO_2 ratio of 25 or greater, based on a two-sample t-test with a two-sided 5% significance level.

The total number of participants (N) is estimated based on the following formula

$$N = \frac{(z_{\alpha/2} + z_{\beta})^2}{\pi(1-\pi)\theta^2}$$

where $z_{\alpha/2}$ and z_{β} are the value from a standard normal distribution, π is the proportion of participants randomized to control, $1-\pi$ is the proportion of participants randomized to active and θ is the standardized effect size we wish to detect. For this study $\alpha = 5\%$, $\beta=10\%$, $\pi=1/3$ and $\theta=0.625$ (i.e., 25/40).

4. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All randomized participants
Full Analysis Set (FAS)	All randomized participants who receive at least one dose of study drug. This population will be used for all efficacy analyses
Modified Intent to Treat (MITT)	All randomized participants who receive at least one dose of study drug and one post baseline assessment of the SpO_2/FiO_2 ratio. This population will be used for the primary and secondary endpoints related to improvement in SpO_2/FiO_2 ratio.
Per Protocol Analysis Set (PP)	All randomized participants who receive at least 6 doses of study drug without any major protocol violations that would impact the assessment of the primary efficacy endpoints. This population will be used for efficacy analyses of the primary efficacy endpoints
Safety Analysis Set	All enrolled participants who receive any study drug
PK Analysis Set	All enrolled participants who receive any study drug and have plasma concentration data

5. Statistical Analyses

5.1. General Considerations

The following is a list of general reporting conventions:

- Percentages will be based on the number of participants in the analysis set unless otherwise indicated.
- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form of n (%).
- Percentages will be reported to 1 decimal place.
- Continuous data will be summarized using the mean, standard deviation (SD), median, minimum, 25th and 75th percentiles, maximum, and number of participants with data.
- Means and medians will be reported at 1 more significant digit than the precision of the data. Standard deviations and confidence intervals will be reported at 2 more significant digits than the precision of the data. Quartiles, minima and maxima will be reported to the same level of precision as the original observations.
- The median will be reported as the average of the 2 middle numbers if the dataset contains even numbers.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5, then round down; if ≥ 5, then round up.
- All p-values will be 1-sided and reported to 3 decimal places (e.g., 0.XXX). Values < 0.001 will be reported as < 0.001.

If departures from these general conventions are present in the specific evaluations sections of this SAP, then those conventions will take precedence over these general conventions.

5.2. Visit Windows

The following table outlines the analysis visits that data will be mapped to for analysis of efficacy, safety and pharmacodynamics data collected during the study. If after mapping, multiple data points share the same analysis visit, the data point closest to the expected study visit will be used. If there is a tie, the earlier of the visits will be used.

Study Visit	**Analysis Visit**	**Analysis Window**
Screening	Screening	0
Baseline	Baseline	0
Days 1 – 9	Days 1 – 9	0

Day 10	Day 10	± 1 day
Day 14	Day 14	± 2 day
Day 21	Day 21	± 3 day
Day 28/EOS	Day 28	± 3 day
Post Study Visit	Day 88	± 10 day

If Baseline is missing then screening data should be mapped to baseline for analysis purposes.

5.3. Missing Data, Outliers, and Pooling

5.3.1. Missing Data

As the rules for imputation of missing data will differ by endpoint, details on imputation rules for missing data are provided with the description of the endpoint and analytical methods for analysis.

5.3.2. Outliers

All reported values will be included in the analyses.

5.3.3. Pooling

Based on the total sample size of the study, and the anticipated number of sites, participants will be pooled across all sites, for all analyses.

5.4. Participant Disposition

A clear accounting of disposition, including the numbers and percentages of participants screened, randomized, completed treatment and completed post treatment follow-up and completed post study follow-up, will be reported overall and by treatment group. In addition, the primary reasons for early discontinuation of study intervention during the treatment period and early study discontinuation will be reported overall and by treatment group. A graphical representation of participant disposition, by treatment group, will be produced using a CONSORT flow diagram.

A summary of the number of participants included in each analysis set (i.e., FAS, MITT, PP, Safety, PK) will be provided overall and by treatment group. Participants could be excluded from an analysis set for more than one reason. All participants excluded from an analysis set will be listed with the reason(s) for exclusion.

A tabular summary of all major protocol violations will be provided by treatment group and overall. Major protocol violations will be classified as follows:

- Violations of inclusion and exclusion criteria
- Receiving the wrong study intervention
- Non-compliance with study intervention. A participant is defined as non-compliant if the participant took < 80% of the study intervention.
- Taking a prohibited medication
- Other

As participants can report multiple protocol violations, they will be included for each observed violation (i.e., these categories will not be mutually exclusive).

5.5. Primary Endpoint(s) Analysis

5.5.1. Definition of Endpoint(s)

Time to Clinical Improvement

Time to clinical improvement will be derived as the earliest date of either not requiring oxygen support or hospital discharge, minus the date of randomization. Participants who die or withdraw from the study prior to observing clinical improvement will be censored on day 28. Participants will be censored on day 28, if clinical improvement has not been observed by this time point. If a participant discontinues study drug early, they will still be assessed for this endpoint until one of the above criteria (i.e., clinical improvement, death/withdrawal, day 28 visit without clinical improvement) is met.

Change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO2/FiO2)

SpO2 and FiO2 will be collected twice daily while a participant is in hospital. The average of the twice daily SpO2/FiO2 ratio will be used for all derivations. If only a single ratio is collected, that single ratio for that day will be used. Once discharged, only a single ratio will be used in the derivations. Participants who are discharged prior to day 10, will have their end of treatment assessment, mapped to day 10.

The SpO2 value will be recorded on the eCRF. To derive the FiO2 value, oxygen flow rate as collected on the eCRF will be converted to FiO2 using the following table.

Method	O2 Flow rate (l/min)	Estimated FiO2 (%)
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask (Simple Mask)	5	40
	6-7	50
	7-8	60
Face mask with reservoir (non-rebreather face mask)	<6	Follow nasal cannula
	6	60
	7	70
	8	80
	9	90
	10	95
	>10	100
Venturi Mask	4	28
	6	31
	8	40
	10	50

The change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO2/FiO2) will be derived by taking the SpO2/FiO2 ratio at the earlier of day 10 or hospital discharge and subtracting the baseline SpO2/FiO2 ratio. Missing data will be assumed to be missing at random and this endpoint will be analyzed using likelihood-based methods, therefore missing data will be maintained as missing.

5.5.2. Main Analytical Approach

Time to Clinical Improvement

Time to clinical improvement will be presented by treatment group, using the Kaplan-Meier estimator. A Cox proportional hazards model with treatment, remdesivir strata (yes/no) and age (years) as covariates will be used to estimate the hazard ratio and compare treatment groups. Additional covariate's (i.e., Country (USA, Brazil), Chloroquine or hydroxychloroquine use (yes vs no), HIV anti-viral drug use (yes vs no), corticosteroid use (yes vs no) and azithromycin use (yes vs no)) may also be included if these are found to influence the treatment effect, based on observing p-value of < 0.05 for the covariate, after adjusting for the others in the model. The

stepwise selection procedure will be used to assess the additional covariates. In addition, the log rank test and stratified log rank test, with remdesivir as the strata, will be provided. The primary analysis will be conducted using the FAS.

Change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO2/FiO2)

The primary efficacy endpoint of change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO2/FiO2) will be analyzed using a mixed model for repeated measures (MMRM). The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The model will contain treatment, time and the treatment by time interaction as fixed effects and baseline score, age (years), corticosteroid use (yes vs no) and remdesivir strata as covariates. If age and/or corticosteroid use are not significant at the 5% level, they will be removed from the model. As the follow-up visit schedule for each participant will be variable, the following timepoints will be used; Day 1, Day 2, Day 3, Day 4, Day 5 and Day 10/Discharge. Additional time points (e.g., Days 6-9) may be included if most participants are not discharged prior to Day 10.. An unstructured covariance matrix will be assumed to model the within-participant errors. This variance-covariance matrix will be estimated across treatment groups. However, if there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be examined (heterogeneous Toeplitz structure, Compound Symmetry) and the one with the best fit as determined by the Akaike information criteria (AIC) (i.e., smallest AIC value) will be used. The least squares means (LS-means) for each treatment, LS-means treatment difference and corresponding confidence interval (CI) for the LS-means difference and p-value for the treatment difference, will be reported at the Day10/Discharge timepoint.

The primary analysis will be conducted using the FAS.

5.5.3. Sensitivity Analysis

Time to Clinical Improvement

The following sensitivity analyses will be conducted:

1) The primary analysis will be repeated for the PP analysis set.

Change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO2/FiO2)

The following sensitivity analyses will be conducted:

1) The primary analysis will be repeated for the MITT analysis set.
2) The primary analysis will be repeated for the PP analysis set.

Depending on the amount of missing data, additional sensitivity analyses may be needed. If these are needed, they will be documented in the CSR.

5.5.4. Supplementary Analyses

None.

5.6. Secondary Endpoint(s) Analysis

5.6.1. Key/Confirmatory Secondary Endpoint(s)

Change from baseline in serum calprotectin

Both the observed value and the change from baseline value will be summarized. Participants who are discharged prior to day 10, will have their end of treatment assessment, mapped to day 10.

To compare the change from baseline over time a MMRM model will be used. Missing data will be assumed to be missing at random and maintained as missing. The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The model will include baseline value as a covariate, treatment, visit and visit-by-treatment interaction terms as categorical fixed effects, and participant as a random effect. An unstructured covariance matrix will be assumed to model the within-participant errors. This variance-covariance matrix will be estimated across treatment groups. However, if there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be examined (heterogeneous Toeplitz structure, Compound Symmetry) and the one with the best fit as determined by the Akaike information criteria (AIC) (i.e., smallest AIC value) will be used. The least squares means (LS-means) for each treatment, LS-means treatment difference and corresponding confidence interval (CI) for the LS-means difference and p-value for the treatment difference, will be reported at each visit. For each parameter, a plot of the LS-means (and 95% CI), over time and by treatment group, will be produced.

5.6.1.1. Sensitivity Analysis

None

5.6.1.2. Supplementary Analyses

None

5.6.2. Supportive Secondary Endpoint(s)

Time to hospital discharge readiness

Time to hospital discharge readiness will be derived as the date of discharge readiness minus the date of randomization. Participants who die/withdraw from the study, prior to discharge, will be censored at day 28. Participants still not ready for hospital discharge at day 28 will be censored at day 28. This endpoint will be analyzed using the same approach as the primary endpoint of time to clinical improvement.

Proportion of participants reporting each 6-point ordinal scale of the clinical status outcome assessment at Days 10/EOT, 14, 21 and 28

The frequency and proportion of participants reporting each score will be reported by treatment group. Participants who are discharged prior to day 10, will have their end of treatment assessment, mapped to day 10. The difference in distributions will be compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) test with Modified ridit scores and stratified by Country (USA, Brazil), age (<= 65 vs > 65), corticosteroid use (yes vs no) and remdesivir use (yes vs no).

5.7. Tertiary/Exploratory Endpoint(s) Analysis

The following exploratory endpoints will be analyzed using the FAS without adjustment for multiplicity.

Proportion of participants requiring mechanical ventilation after study entry

The frequency and proportion of participants will be reported by treatment group. The difference between treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test stratified by Country (USA, Brazil), age (<= 65 vs > 65), corticosteroid use (yes vs no) and remdesivir strata (yes, no). The common risk difference and two-sided 95% stratified Newcombe confidence interval will be reported. The strata will be weighted using Mantel-Haenszel weights.

Change from baseline in SARS-CoV-2 viral load at Days 10/EOT, 14, 21 and 28

The change from baseline to each of days 5, 10, 14, 21 and 28 in the SARS-CoV-2 viral load will be derived by taking the SARS-CoV-2 viral load at the post baseline timepoint (i.e., Days 10, 14, 21 and 28) and subtracting the baseline SARS-CoV-2 viral load. Participants who are discharged prior to day 10, will have their end of treatment assessment, mapped to day 10. Missing data will be assumed to be missing at random and this endpoint will be analyzed using likelihood-based methods, therefore missing data will be maintained as missing. The change from baseline to each of days 5, 10, 14, 21 and 28 in the SARS-CoV-2 viral load will be

analyzed using a mixed model for repeated measures (MMRM) approach as outlined for the co-primary endpoint of change from baseline in SpO2/FiO2 ratio. The data may be log transformed prior to analysis if the assumptions of normality are violated. For values below the limit of quantification, half the value between 0 and the limit of quantification will be used. This analysis will only be conducted for patients who are positive at baseline based on PCR testing.

5.8. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Missing data will be maintained as missing, unless otherwise specified. All safety analyses will be descriptive in nature.

5.8.1. Extent of Exposure

Duration of study drug exposure, defined as the number of days between the date of first dose following randomization and the date of the last dose, will be summarized by treatment group.

Duration will be calculated as date of last dose – date of first dose + 1.

In addition, the number and proportion of participants with study drug exposure of 0-3, 4, 5, 6, 7 and 8-10 days will be summarized by treatment group

5.8.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs that occur on or after the date of first dose of study intervention will be considered Treatment Emergent Adverse Events (TEAEs), and will be summarized using frequency counts and percentages, with the number of participants in the safety set used as the denominator.

Summaries of TEAEs will be presented by treatment group, and overall, using the MedDRA level hierarchy (system organ class and preferred term) as follows:

- Overall TEAEs (i.e., regardless of intensity or relationship to treatment)
- TEAEs by NCI CTCAE intensity grade (Grade 1, 2, 3, 4, 5)
- TEAEs by relationship to study medication (related, not related)
- TEAEs leading to permanent discontinuation of study medication (i.e., action taken is drug withdrawn)
- TEAEs leading to permanent discontinuation of study medication (i.e., action taken is drug withdrawn) by relationship to study medication
- Serious TEAEs (SAEs)
- SAEs by relationship to study medication (related, not related)

Unless otherwise specified, at each level of summarization a participant will be counted once if they reported one or more events at that level of summarization. If more than one occurrence of an event is reported, the event of the worst intensity or the worst-case relationship assessment will be summarized.

In the case of an incomplete AE start date, determining if an AE is treatment emergent will be based on the following rules. If the day is missing and the month and year of an onset date are provided and on or after the date of randomization, the following rules will be applied.

- If month/year of the onset date is on or after the month/year of randomization, the AE will be considered treatment emergent.
- If month/year of the onset date is equal to the month/year of randomization, and the end date is present, the end date will be used to determine when the AE started. If the end date is on or after randomization, the AE will be considered treatment emergent; otherwise, if the AE stopped before randomization, then it will not be considered treatment emergent.
- If month/year of the onset date is equal to the month/year of randomization, and the end date is a partial date, the AE will be considered treatment emergent.
- If, despite implementing the above conventions, the onset date of the AE cannot be placed before, on, or after randomization, then the event will be considered treatment emergent.

5.8.3. Safety Labs

This study will be using local labs instead of central labs. Descriptive summary statistics of the observed values and change from baseline values for hematology, chemistry and urinalysis data at screening, baseline and each post-baseline visit (i.e., Day 5/Discharge, Day 10/Discharge, 14, 21 and 28) will be presented by treatment group. Boxplots will be used to display the distribution of the observed values over time, by treatment group.

Participants with clinically significant values for any safety labs are to be reported as an AE and therefore clinically significant laboratory findings will be interpreted from the AE summaries.

A listing of participants with clinically significant drug-related troponin elevations that have repeat elevation upon confirmatory testing as adjudicated by the DMC while continuing study drug during the 10-day treatment period will be provided.

5.8.4. Vital Sigs

Descriptive summary statistics of the observed values for blood pressure (systolic and diastolic), heart rate, temperature and respiratory rate data collected at screening, baseline and post-baseline visits will be presented by treatment group. As temperature is collected twice daily while a participant is hospitalized, the average of the daily measurements will be used. Boxplots will be

used to display the distribution of the observed values over time, using all post baseline assessments, by treatment group.

Participants with clinically significant values for any vital signs are to be reported as an AE and therefore clinically significant vital sign findings will be interpreted from the AE summaries.

5.8.5. 12-Lead ECG

Descriptive summary statistics of the observed values for 12-lead ECG data at screening, baseline and each post-baseline visit (i.e., Day 5/Discharge, Day 10/Discharge, 14, 21 and 28) will be presented by treatment group. Boxplots will be used to display the distribution of the observed values over time, by treatment group.

Participants with clinically significant values for any 12-lead ECG findings are to be reported as an AE and therefore clinically significant 12-lead ECG findings will be interpreted from the AE summaries.

5.8.6. Physical Exam

A complete physical exam is planned for screening and day 10. A limited physical exam is planned for baseline, day 5, 14, 21 and 28.

At each time point, findings that are both abnormal and clinically significant will be summarized using frequency counts and percentages, with the number of participants in the safety set used as the denominator.

5.9. Other Analyses

5.9.1. Pharmacokinetic Analyses

BLD-2660 plasma concentrations collected on Day 5 pre-dose and 1-2 hours post dose will be summarized using descriptive statistics, by time point.

Pharmacokinetic parameters may be estimated using a population PK approach. Details of this analysis will be provided in a separate analysis plan.

5.9.2. Pharmacodynamic Analyses

The following pharmacodynamic parameters will be summarized using descriptive statistics, by time point and treatment group:

- IL-6
- D-Dimer

Both the observed value and the change from baseline value will be summarized. Participants who are discharged prior to day 10, will have their end of treatment assessment, mapped to day 10.

To compare the change in these parameters over time a MMRM model will be used. Missing data will be assumed to be missing at random and maintained as missing. The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The model will include baseline value as a covariate, treatment, visit and visit-by-treatment interaction terms as categorical fixed effects, and participant as a random effect. An unstructured covariance matrix will be assumed to model the within-participant errors. This variance-covariance matrix will be estimated across treatment groups. However, if there is a convergence problem with the unstructured covariance matrix, then alternative covariance structures will be examined (heterogeneous Toeplitz structure, Compound Symmetry) and the one with the best fit as determined by the Akaike information criteria (AIC) (i.e., smallest AIC value) will be used. The least squares means (LS-means) for each treatment, LS-means treatment difference and corresponding confidence interval (CI) for the LS-means difference and p-value for the treatment difference, will be reported at each visit. For each parameter, a plot of the LS-means (and 95% CI), over time and by treatment group, will be produced.

5.9.3. Subgroup Analyses

The following sub-groups will be examined for the primary endpoints. Results will be displayed in both tabular form and graphical form using a forest plot.

- Age (<=65 vs > 65)
- Gender (male vs female)
- Remdesivir Use within 24 hours of Randomization (yes vs no)
- Country (USA, Brazil)
- Corticosteroid Use (e.g., Dexamethasone) (yes vs no)
- Patients with a positive PCR test at baseline vs not positive.
- Patients with IL-6 > median at baseline vs ≤ median

5.9.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the FAS set, by treatment group and overall, using descriptive statistics. No statistical hypothesis tests will be performed.

5.9.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term for each treatment group, and overall. At each level of summarization, a participant is counted once if he/she reported one or more medical history terms at that level. No statistical hypothesis tests will be performed.

5.9.6. Concomitant Medications

Concomitant medications are those that are taken at any time after the first dose of study medication.

If the start day of a medication is missing, then if the month and year of the start date are on or after the date of randomization, the following rules will be applied:

- If month/year of the stat date is equal or after the month/year of the date of randomization, the medication will be considered concomitant;
- If month/year of the start date is equal to the month/year of the date of randomization, and the end date is present, the end date will be used to determine if the medication stopped prior to randomization or after. If the end date is after, the medication will be considered concomitant; otherwise, if the medication stopped prior, then it will be considered to be prior;
- If month/year of the start date is equal to the month/year of the date of randomization, and the end date is a partial date, the medication will be considered concomitant;
- If, despite implementing the above conventions, the start date of the medication cannot be placed before, on, or after randomization, then the medication will be considered concomitant.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by drug class (ATC Level 3) and preferred term for each treatment group. The summaries will present the number and percentage of participants using each medication by treatment group and overall. Participants may have more than one medication per drug class or preferred term. At each level of summarization, a participant is counted once if he/she reported one or more medications at that level. No statistical hypothesis tests will be performed.

5.9.7. Compliance

Compliance will be calculated and summarized by treatment group. Compliance will be calculated as 100× (total number of capsules taken / total number of capsules expected to be taken). The total number of capsules taken is recorded on the eCRF. The number of expected capsules taken will be calculated as the duration of dosing (last dose date minus first dose date, plus 1) multiplied by 12. For example, if a participant is dosed for 10 days the expected number of capsules taken is 120.

5.10. Interim Analyses

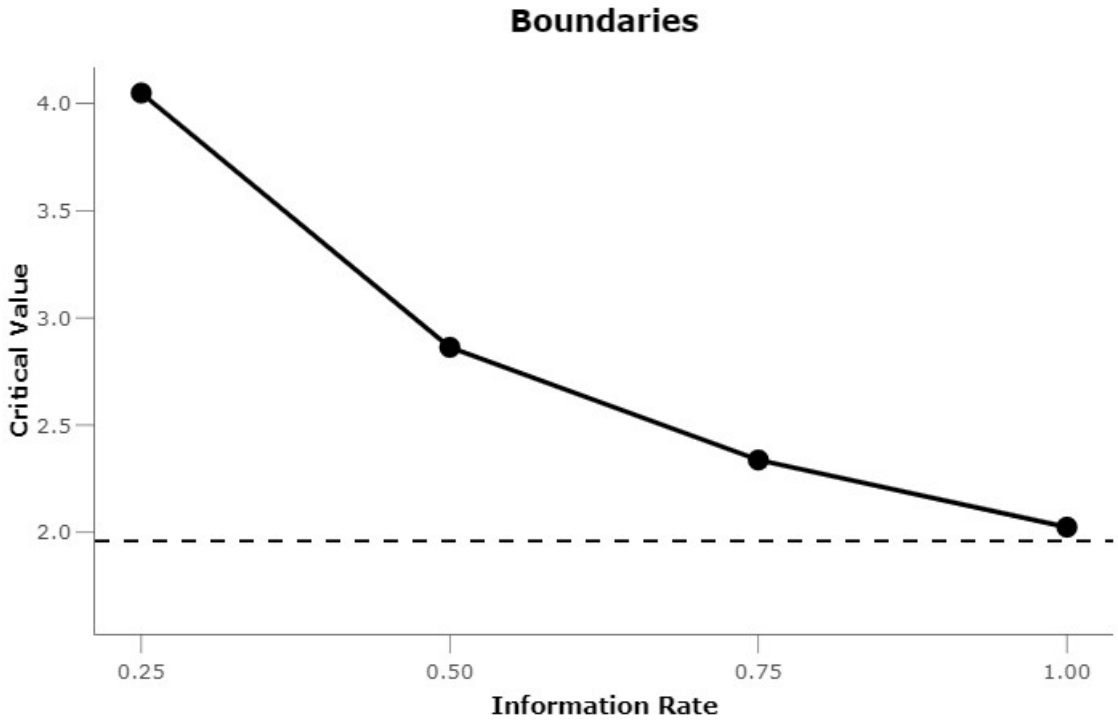
The study originally planned interim analyses at approximately 25%, 50% and 75% of participants completing the trial. Due to rapid enrollment, only a single interim analysis was conducted, at the time when enrollment had completed (and ~50% of the patients had completed the trial). This interim analysis was not used to stop the trial early for efficacy or futility, as enrollment had already completed, and occurred at a scheduled safety review by the independent

DMC. This interim was for the purpose of ensuring safety and included efficacy data to assess the risk/benefit.

After the last patient has completed their Day 10 assessment, but prior to final data base lock, an interim analysis will be conducted for the purpose of BLADE to begin Phase 3 planning. Blade plans to amend the current protocol to include a second part that would be a Phase 3 trial. As this is a COVID-19 study and there is an immediate public need for effective therapies, BLADE feels amending the protocol to adopt this second Phase 3 part of the study will significantly reduce the start-up time required to initiate the independent phase 3 (part 2 of the study) study by 4-6 months. This approach was communicated to FDA on 11-September 2020, and the sponsor did not receive any objections to this approach. The Phase 3 portion will be analyzed separately from the Phase 2 portion.

The original interim analysis plans for the Phase 2 portion of the study were as follows. An interim analysis is planned when approximately 25%, 50% and 75% of participants have completed the study for the purpose of early stopping for efficacy or futility. Based on the enrollment rates, one or more of these planned interim analyses may occur earlier in time or may not occur at all.

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor each of the primary endpoints as a guide for the DMC for an overall one-sided type-I error rate of 2.5%, for each endpoint. At the time of the planned interim analyses (when approximately 25%, 50% and 75% of participants have completed the study), the amount of information (i.e., information rate) for each primary endpoint will be different, and therefore each endpoint will have a different critical value to determine if the study should be stopped early for efficacy. For the primary endpoint of change from baseline in SpO2/FiO2 ratio the amount of information is based on the number of participants (total planned =120), and the interim analyses will occur when approximately, 30, 60, and 90 participants (information rate = .25, .5 and .75) complete the study. For the primary endpoint of time to clinical improvement the amount of information is based on the observed number of events (total planned =75) and the information rate at the time of the interim analyses will depend on the observed number of events at that time (example if there are only 15 events observed at the first planned interim, the information rate at this time point will be 15/75=0.20). The following plot provides the critical value boundaries based on the O'Brien-Fleming Lan-DeMets spending function.



Conditional power will be used as an additional guide to the DMC to assess futility. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the study given the data accumulated thus far. If the conditional power is less than 20% based on the observed effect size, for both primary endpoints, consideration will be given to stopping the study.

The conditional power for each primary endpoint will be calculated as,

$$\mathrm{CP}_{\hat{\delta}_1}(z_1, \tilde{n}_2) = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$

where z_1 is the observed Wald test statistic at the interim, n_2 -tilde is the planned sample size for stage 2, n_1 is the sample size for stage 1, and n_2 is the cumulative planned sample size (i.e., $n_2 = n_1 + n_2$ -tilde) and z_α is the value from the inverse normal distribution with α =2.5%.

At the interim analysis when approximately 50% of the participants have completed the study, a sample size re-estimation step will occur using the promising zone approach (Mehta and Pocock, 2011) and method of Chen, DeMets and Lan, based on the observed effect size at this interim analysis. The promising zone is defined as a conditional power of between 50% and 80%. If the conditional power falls into this region the sample size may be increased to raise the conditional power to 80%.

The study will not stop enrolment awaiting these DMC reviews, though the DMC may recommend temporary or permanent cessation of enrolment based on their safety reviews.

A separate unblinded statistical team will prepare the above information for the DMC to review and make recommendations to the Sponsor. The following efficacy endpoints will be summarized at each interim analysis using the FAS:

Objectives	Endpoints
Primary	
• To evaluate clinical benefit of BLD-2660 in hospitalized adults with recently diagnosed SARS-CoV-2 infection	• Time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first
• To evaluate improvement in oxygenation in hospitalized adults with COVID-19 treated with BLD-2660	• Change from baseline to Day 10 or hospital discharge, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
Secondary	
•	
• Additional efficacy outcomes	• Time to hospital discharge readiness
Exploratory	
• Other efficacy outcomes	• Proportion of participants who require mechanical ventilation after study entry •

6. References

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