Statistical Analysis Plan: J2W-MC-PYAA

A Randomized, Placebo-Controlled, Double-Blind, Sponsor Unblinded, Single Ascending Dose, Phase 1 First in Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous LY3819253 in Participants Hospitalized for COVID-19

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STATISTICAL ANALYSIS PLAN

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

ADA	Anti-drug antibody
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	AUC from time 0 to infinity
AUC(0-D29)	AUC from Day 1 to Day 29
AUC(0-tlast)	AUC from time 0 to the time of the last quantifiable concentration
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CSR	Clinical Study Report
CT	Cycle time
CV	Coefficient of variation
DAIDS	Division of Allergy and Infectious Diseases
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ISAC	Independent safety assessment committee
IV	Intravenous
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
NEWS2	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SD	Standard deviation
SoA	Schedule of assessments
SpO2	Saturation of peripheral oxygen
TE ADA	Treatment-emergent ADAs
TE ADA+	Positive treatment-emergent ADAs
TFLs	Tables, Figures, and Listings
T_{max}	Time to reach C_{max}
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 09 May 2020) and Protocol Amendment (a) (final version dated 01 June 2020).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical, PK, and PD analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1   Primary Objective

The primary objective of this study is to characterize the safety and tolerability of LY3819253 after intravenous (IV) infusion.

4.2   Secondary Objectives

The secondary objectives of this study are:

- To characterize the PK of LY3819253 after IV infusion.
- To characterize the PD of LY3819253 after IV infusion.

4.3   Exploratory Objective

The exploratory objectives of this study are:

- To characterize the participant's clinical status.

- Characterize the pharmacodynamics of LY3819253 after intravenous infusion.
- Characterize emergence of viral resistance to LY3819253.

5. STUDY ENDPOINTS

5.1 Primary Endpoint

- Safety assessments such as adverse events (AEs) and serious AEs (SAEs).

5.2 Secondary Endpoints

- LY3819253 mean concentration on Day 29.
- Change from baseline in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load (Days 7, 11, 15, and 22).
- SARS-CoV-2 viral load area under the concentration versus time curve (AUC).
- Time to SARS-CoV-2 clearance.

5.3 Exploratory Endpoints

- Duration (days) of hospitalization.
- Proportion (percentage) of participants admitted to intensive care unit (ICU).
- Proportion (percentage) of participants requiring mechanical ventilation.
- Score using the National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO) ordinal scale or live discharge from hospital at pre-specified time points.
- National Early Warning Score (NEWS2) score at pre-specified time points.
- Proportion (percentage) of participants with at least a 2-point improvement on the NIAID and WHO ordinal scale or live discharge from hospital at pre-specified time points.
- NEWS2 score at pre-specified time points.
- Proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15.
- Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, 22).
- Emergence of viral resistance to LY3819253 from baseline to Day 29.

6. STUDY DESIGN

Study PYAA is a Phase 1, double-blind, sponsor unblinded, randomized, placebo-controlled, single-ascending dose study in participants hospitalized for COVID-19.

The study will comprise up to 4 dose cohorts. Cohorts 1-3 will compromise at least 8 participants:
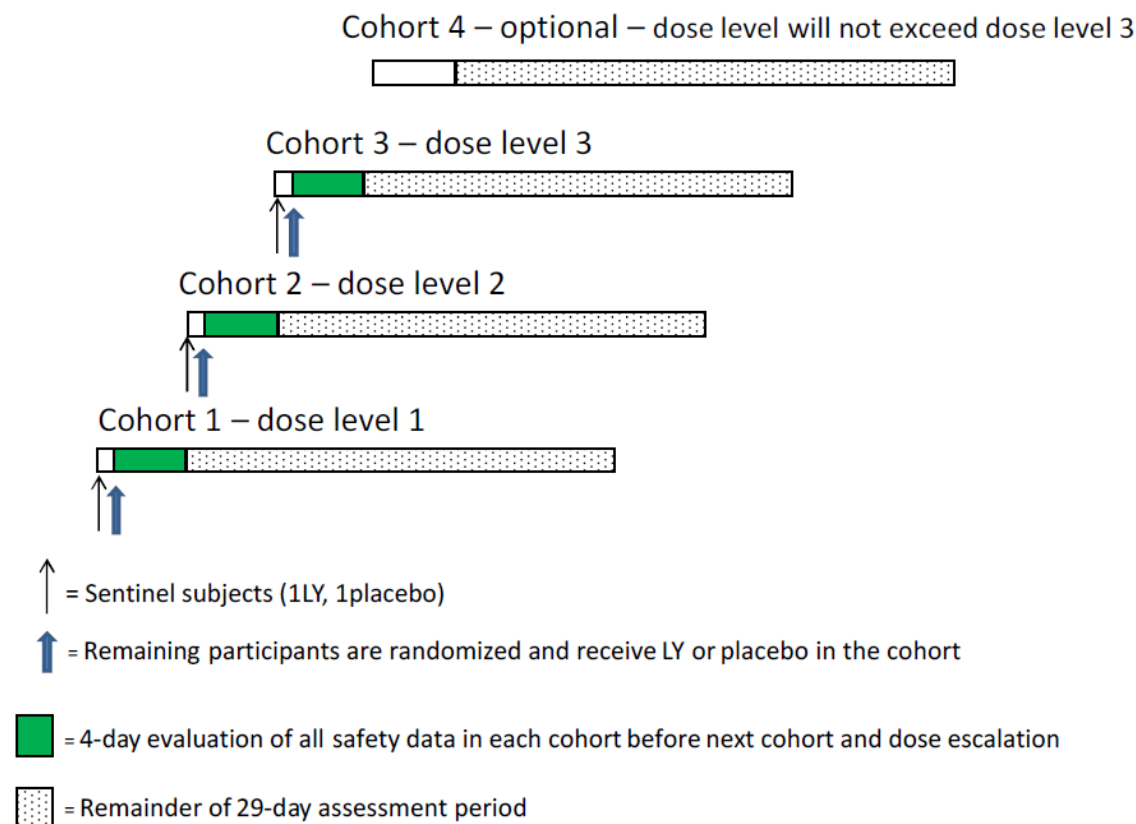
- 6 randomized to LY3819253 and
- 2 randomized to placebo.

Sentinel dosing will be used in any dose cohort that represents a dose increase from the preceding cohort. The first 2 participants in each cohort will be randomized 1:1 to LY3819253 and placebo.

Safety and tolerability will be reviewed for sentinel participants up to 24 hours after dosing. The investigator and the Lilly sponsor team are responsible for determining if safety and tolerability is acceptable to continue with dosing subsequent participants. Subsequent participants will be randomized to the remaining treatment allocations, 5 to LY3819253 and 1 to placebo.

The decision to dose the next cohort will be made when all participants from the previous cohort have been dosed and safety data is assessed for at least 4 days after the IV infusion by the investigator(s) and Lilly sponsor team in consultation with an independent safety assessment committee (ISAC).

Cohort 4 may be initiated, at the discretion of the sponsor team, if more data is needed to inform

Cohort 4 – optional – dose level will not exceed dose level 3

Cohort 3 – dose level 3

Cohort 2 – dose level 2

Cohort 1 – dose level 1

↑ = Sentinel subjects (1LY, 1placebo)

⬆ = Remaining participants are randomized and receive LY or placebo in the cohort

🟩 = 4-day evaluation of all safety data in each cohort before next cohort and dose escalation

▢ = Remainder of 29-day assessment period

Abbreviations: LY = Lilly study intervention

the dose of LY3819253.

Figure 1 - Sequential single ascending dose schema of study J2W-MC-PYAA

7. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Cohort	Study Treatment Name*	Treatment order in TFL
All	Pooled placebo IV	1
1	700 mg LY3819253 IV	2
2	2800 mg LY3819253 IV	3
3	7000 mg LY3819253 IV	4
4 (optional)	TBD mg LY3819253 IV	5

Abbreviations: IV = intravenous; TBD = to be determined.
* Planned doses presented - the actual dose administered will be displayed in the TFLs.

8. SAMPLE SIZE JUSTIFICATION

For Cohorts 1-3, approximately 24 participants will be randomized to receive one of three dose levels of LY3819253 or placebo. Additional participants may be required to ensure a minimum of 8 participants in each cohort complete 7 days of study assessments. Up to a maximum of 3 additional participants per cohort may be added.

Participant viral loads over time were simulated using a representative PK/PD model to enable a Monte Carlo assessment of the power of the trial to detect a 30% treatment difference in mean AUC (28 day) of viral load. This assessment revealed greater than 90% probability of meeting the following Bayesian critical success factor:

$$Pr \left((\text{mean AUC}_{PL} - \text{mean AUC}_{LY}) / \text{mean AUC}_{PL} > 0.3 \right) > 0.60$$

PL = placebo, LY = LY3819253

Additionally, the anticipated 6 participants per treatment provides greater than 80% probability (within each treatment arm) of observing safety events of reasonable prevalence (that is, at least 25%) to support the primary objective of safety assessment.

For the optional Cohort 4, up to 100 participants may be randomized in an approximate 1:1 ratio to receive either LY3819253 or placebo. The overall numbers of participants randomized to LY3819253 and placebo in this study will provide 60% power to detect a reduction in the rate of clinical worsening from 22% to 9% (one-sided alpha=0.05). Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15.

A participant is only allowed to receive one IV infusion in one cohort.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Entered" population will consist of all participants who sign the informed consent form.

The "Safety" population will consist of all participants randomly assigned and who received study intervention (either placebo or LY3819253). Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all randomized participants who received study intervention (LY3819253) and have at least one evaluable PK sample. Participants will be analyzed according to the intervention they actually received.

The "Pharmacodynamic" population will consist of all randomized participants who received study intervention (either placebo or LY3819253) and provided at least one post-baseline measure for the relevant endpoint. Participants will be analyzed according to the intervention they actually received.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

10.   STATISTICAL METHODOLOGY

10.1   General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and N; for log-normal data (e.g. the PK parameters: AUCs and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical and ordinal data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

10.2   Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, body mass index and saturation of peripheral oxygen (SpO2) will be summarized and listed. All other demographic variables will be listed only. Additional clinic meaningful parameters may be added if deemed necessary.

10.3   Pharmacokinetic Assessment

10.3.1   Pharmacokinetic Analysis

PK analysis will be the responsibility of the Eli Lilly PK/PD group prior to database lock.

PK parameter estimates for LY3819253 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be geometric mean of concentration on Day 29. Other noncompartmental parameters, such as half-life, AUC from time 0 to infinity (AUC[0-∞]), AUC from time 0 to Day 29 (AUC[0-D29]), $C_{max,}$ clearance, and volume of distribution may be reported.

Additional population PK model-based analyses may be performed.

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of LY3819253 will be used to determine the following PK parameters, when possible:

Parameter	Units[a]	Definition
AUC(0-D29)	µg.h/mL	Area under the concentration versus time curve from time zero to time t, where t is Day 29
AUC(0-t_{last})	µg.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	µg.h/mL	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
t_{last}		Time of the last observed drug concentration
C_{max}	µg/mL	Maximum observed drug concentration
C_{D29}	µg/mL	Observed drug concentration on Day 29
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V_z	L	Volume of distribution during the terminal phase
V_{ss}	L	Volume of distribution at steady state

[a] Units of source LY3819253 serum concentration data will be ng/mL, to one decimal place.

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and time of maximum observed drug concentration (t_{max}) will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive serum concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{\frac{1}{2}}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{\frac{1}{2}}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{\frac{1}{2}}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last quantifiable drug concentration will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Serum concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

  - o The compound is non-endogenous.

  - o The samples are from the initial dose period for a patient or from a subsequent dose period following a suitable wash-out period.

  - o The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

10.3.2   Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment using descriptive statistics.

The PK parameter estimates will be evaluated to delineate dose proportionality. Log-transformed C_{max}, and AUC(0-∞) of LY3819253 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals. Results of the dose proportionality analysis will be plotted.

The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality.

Example SAS code for the analysis:

```
proc mixed data=pk;
  model log_pk = log_dose / alpha=0.1 cl solution residual ddfm=kr2;
  estimate '700 mg'  intercept 1 log_dose 2.87506126 / alpha=0.1 cl; /*Log of 700 */
  estimate '2800 mg' intercept 1 log_dose 3.44715803 / alpha=0.1 cl; /*Log of 2800 */
  estimate '7000 mg' intercept 1 log_dose 3.84509804 / alpha=0.1 cl; /*Log of 7000 */
  estimate '2800 mg - 250 mg'    log_dose 0.97003679 / alpha=0.1 cl; /*Difference in
  log values of 7000 and 700 */
  ods output solutionf=est;
  ods output estimates=estims;
run;
```

10.4   Pharmacodynamic Assessment

10.4.1   Pharmacodynamic Analysis

The PD endpoints for this study are:

- Change from baseline in SARS-CoV-2 viral load (Days 7, 11, 15 and 22)
- Viral load AUC (Day 1 to 29)
- Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, 22)
- Time to SARS-CoV-2 clearance
- Viral resistance to LY3819253 (from baseline to Day 29)

Viral clearance is defined as two consecutive negative SARS-CoV-2 values from the nasopharyngeal swabs. When deriving clearance, any missing data from the nasopharyngeal swabs will be set to positive. Time to SARS-CoV-2 clearance is defined as the earliest timepoint of the two.

If these two negative values are followed by a subsequent positive value, this measurement will be flagged and considered for evaluation of viral mutation or resistance.

10.4.2 Pharmacodynamic Statistical Methodology

SARS-CoV-2 viral load

SARS-CoV-2 viral load will be measured using the cycle time (CT) from a polymerase chain reaction (PCR) assay. Higher CT values indicate a lower viral load.

SARS-CoV-2 viral load, including changes from baseline, will be summarized and plotted by treatment, and listed. Baseline is defined as the Day 1 predose assessment. Overlaying individual profiles of SARS-CoV-2 viral load data will also be presented graphically over time.

Changes from baseline in SARS-CoV-2 viral load data will be statistically analyzed using a mixed model for repeated measures (MMRM). The model will contain baseline as a covariate, treatment, day and treatment-by-day interaction as fixed effects, and subject as a random effect. The unstructured covariance matrix will be selected initially; if this analysis fails to converge another covariance structure will be selected based on AIC and BIC values. The least square (LS) means and treatment differences (LY3819253 minus pooled placebo at each dose level) will be calculated and presented with their corresponding 90% confidence intervals (CIs). All available data will be used in the analysis.

An example of the SAS code that will be used is as follows:

```
proc mixed data=xxx;
class trtmnt subject day;
model chg = base trtmnt day trtmnt*day / alpha=0.1 cl ddfm=kr2;
repeated day / subject=subject type=un;
lsmeans trtmnt*day / alpha=0.1 cl pdiff ;
ods output lsmeans=lsm01  diffs=diff01;
run;
```

where chg is the change from baseline, base is the baseline in SARS-CoV-2 viral load data, day is the study day, and trtmnt is the treatment used in the comparison.

A Bayesian linear mixed effect model will be fitted to evaluate the critical success factor by Lilly statistics group with the model listed below:

$$y_{ijk} = \mu + \alpha \times base + \alpha_i + \beta_k + (\alpha\beta)_{ik} + \varepsilon_{ij} + \varepsilon_{ijk}$$

Where y_{ijk}: the change from baseline for treatment i, subject j at day k

μ: a constant common to all observations

α: a fixed coefficient on the covariate baseline viral load

α_i: a parameter corresponding to treatment i

β_k: a parameter corresponding to day k

$(αβ)_{ik}$: an interaction parameter corresponding to treatment i and day k

$ε_{ij}$, $ε_{ijk}$: random error for between and within subject variability

prior $μ$, $α$, $α_i$, $β_k$, $(αβ)_{ik} \sim N(0, 100)$

$ε_{ij} \sim N(0, σ_1)$, $ε_{ijk} \sim N(0, σ_2)$

$σ_1, σ_2 \sim uniform(0, 100)$ or $igamma(0.01, 0.01)$

the posterior of the following quantity will be assessed:

$pr(Δ_{anyLYdose} - Δ_{placebo} < -0.3) > 0.6$ *at Day 7, 11, 15, and 22 in log base 10 scale.*

SARS-CoV-2 viral load AUC

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC(0-D29) will be summarized and plotted by treatment and listed.

Additionally, AUC(0-D29) data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect and baseline viral load as a covariate. The least square (LS) means and treatment differences (LY3819253 minus pooled placebo at each dose level) will be calculated and presented with their corresponding 90% confidence intervals (CIs). All available data will be used in the analysis.

An example of the SAS code that will be used is as follows:

```
proc mixed data=xxx;
class trtmnt;
model AUC = base trtmnt / alpha=0.1 cl ddfm=kr2;
lsmeans trtmnt / alpha=0.1 cl pdiff;
ods output lsmeans=lsm01;
ods output diffs=diff01;
run;
```

where AUC is the AUC(0-D29) data, trtmnt is the treatment used in the comparison, and base is the baseline viral load.

Similar Bayesian model listed in Section 10.4.2 by removing the day, interaction, and within subject error term will be applied for AUC measure analysis.

SARS-CoV-2 clearance

The proportion of patients that achieve SARS-CoV-2 clearance will be summarized by treatment in frequency tables, and listed.

In addition, the number of patients that achieve SARS-Cov-2 clearance will be analyzed using a Chi-square test to compare LY3819253 versus pooled placebo at each dose level, if there are sufficient data available.

An example of the SAS code that will be used is as follows:

```
proc freq data=xxx;
weight count;
table trtmnt*clear / chisq all;
run;
```

where trtmnt is the treatment used in the comparison, clear is the SAR-CoV-2 clearance (yes/no), and count is the corresponding number of patients.

Additional analyses on viral clearance, such as logistic regression with treatment as a fixed effect, may be conducted as deemed appropriate and where sufficient data are available.

Time to SARS-CoV-2 clearance

The time to SARS-CoV-2 clearance will be summarized by treatment, and listed.

In addition, a graphical presentation of the clearance times will be provided using a Kaplan-Meier plot.

Viral Resistance to LY3819253

Participant who show signs of viral resistance will be summarized in frequency tables by treatment and listed.

PK/PD Modeling

Additional PK/PD exposure-response modeling of viral dynamics may be conducted. These analyses will be the responsibility of Eli Lilly PK/PD group.

10.5 Efficacy Assessments

10.5.1 Hospitalization and clinical events, clinical status, and environmental risk factors

All hospitalization events, procedures of special interest, and environmental risk factors will be listed.

The following data will be summarized by treatment using descriptive statistics:

- Duration of hospitalization (in days);

- Score on the NIAID ordinal scale at pre-specified time points;
- Score on the WHO ordinal scale at pre-specified time points;
- NEWS2 score at pre-specified time points.

The following data will be summarized by treatment using frequency tables:

- Proportion (percentage) of participants admitted to ICU;
- Proportion (percentage) of participants requiring mechanical ventilation;
- Proportion (percentage) of participants with at least a 2 point improvement on the NIAID scale or live discharge from hospital from baseline at any time during the study;
- Proportion (percentage) of participants with at least a 2-point improvement on the WHO ordinal scale or live discharge from hospital from baseline at any time during the study;
- Proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 15;
- Proportion (percentage) of participants with at least a 2-point worsening on the NIAID ordinal scale from baseline at any time during the study;
- Consciousness level score assessed by NEWS2;
- Severity of pre specified clinical events (fever, cough, and shortness of breath).

10.6   Safety and Tolerability Assessments

10.6.1   Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing, and that does not worsen postdose. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed.

The severity of infusion reactions will be graded using the table for assessing acute allergic reactions and events of cytokine release syndrome in protocol Section 6.1.1.2.; all other AEs will be graded for severity using the definitions of mild, moderate and severe provided in protocol Section 10.3.3. from the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

Discontinuations of study intervention and/or of study due to AEs will be listed.

10.6.2   Medical history, pre-existing conditions, and prior medication

All medical history, pre-existing conditions and prior medication data will be listed.

10.6.3   Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version Global B3 202003 / WHODD MAR20B3). Concomitant medication will be listed.

10.6.4   Chest x-ray

All chest x-ray data will be listed.

10.6.5   Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment together with changes from baseline, and listed. Baseline is defined as the Day 1 predose assessment. Additionally, clinical chemistry and hematology data outside the reference ranges will be listed and flagged on individual participant data listings.

All SARS-CoV-2 panel parameters (C-reactive protein, ferritin, D-dimer, procalcitonin, and troponin) will be summarised separately, together with changes from baseline, and listed. Baseline is defined as the Day 1 predose assessment. Additionally, SARS-CoV-2 panel data outside the reference ranges will be listed and flagged on individual participant data listings.

10.6.6   Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

10.6.7   Immunogenicity Assessments

The frequency and percentage of participants with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to LY3819253 may be evaluated only if the data from validated immunogenicity assays available.

For participants who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For participants who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of participants with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

The relationship between the presence of antibodies and PK parameters, PD response or safety to LY3819253 may also be assessed only if are the data available. These analyses will be the responsibility of Eli Lilly PK/PD group.

10.6.8 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

10.6.9 Infusion-related Reactions

Infusion-related reaction data will be listed and summarized by treatment and premedication used for infusion (if applicable) in frequency tables.

10.6.10 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.6.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11.   INTERIM ANALYSES

No interim analyses are planned. Periodic, unblinded reviews of PK, PD and safety data will occur throughout the study in addition to the scheduled dose escalation reviews.

Analyses to support these data review will be the responsibility of Eli Lilly and Company Stats and PK/PD group.

12.   CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13.   REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services.

14.   DATA PRESENTATION

14.1   Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

14.2   Missing Data

Missing data will not be displayed in listings.

14.3   Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

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