MASTER STATISTICAL ANALYSIS PLAN

MASTER PROTOCOL: COV-01 (COMMUNITY)

INDUSTRY ALLIANCE PLATFORM TRIAL TO ASSESS THE EFFICACY AND SAFETY OF MULTIPLE CANDIDATE AGENTS FOR THE TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

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MASTER STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Master Statistical Analysis Plan (SAP) Amendment v1.0 (dated 23Apr2021) for master protocol COV-01

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Upon review of this document, the undersigned approves this version of the master SAP, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
Final, v1.0	18Nov2020	PPD	Not Applicable – First Version
Amendment 1 v1.0	23Apr2021	PPD	Updated Master Protocol version on which the Master SAP is based from version 3, dated 22-Oct-2020, to version 4, dated 16-Apr-2021. Updated definition of the data cut-off date for the Interim, Primary and Final Analyses of a sub-protocol in order to prevent potential inadvertent unblinding of patients randomized to the placebo plus SoC treatment group of another subprotocol included in the shared placebo plus SoC control arm of the sub-protocol of interest; Clarified that the 'concurrent' definition for selection of the concurrent placebo plus SoC patients for the control arm of a sub-protocol will be assessed on a site-by-site basis rather than across all sites; Updated definition of the safety analysis set so that patients randomized to the placebo arm of sub-protocol X selected for the shared placebo plus SoC control arm of sub-protocol Y who started taking subprotocol Y candidate agent for another indication after baseline will be presented under the shared placebo plus SoC control arm for sub-protocol Y safety analysis; Clarified that data collected during a discharge visit will also be mapped using time window for the by-visit summaries;

			Added summaries further broken down by sub-protocol for the shared placebo plus SoC control arm to Sections 9 to 12; Added a tipping point sensitivity analysis for the primary efficacy endpoint; For each key secondary efficacy endpoint, removed the last observation carried forward (LOCF) sensitivity analysis as well as sensitivity analysis based on observed data (when applicable), and added a multiple imputation sensitivity analysis; Clarified that the 95% two-sided confidence interval (CI) obtained from a logistic regression model will be the 95% two-sided Wald CI; Added subgroup analyses by time since hospital admission at Study Day 1 (≤ 5 days or > 5 days) for the primary and key secondary efficacy endpoints. For each subprotocol, added separate summaries for patients randomized to the placebo plus SoC treatment group of the concerned sub-protocol for the prior and concomitant medications summaries as well as all safety summaries; Added risk difference and associated 95% two-sided Wald CI for the treatment comparison of the overall incidence of serious treatment-emergent adverse events (TEAEs) and overall incidence of adverse events of special interest (when applicable for a sub-protocol); Added summary of most common (5%) non-serious adverse events (AEs)

TABLE OF CONTENTS

1. INTRODUCTION

This master statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol COV-01 (COMMUNITY). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This master SAP is based on amendment 4 of the master protocol, dated 16-Apr-2021.

Presentation and analysis of efficacy and safety data specific to the sub-protocols as well as to the pharmacokinetic (PK) and pharmacodynamic (PD) endpoints will be described in separate sub-protocol SAPs.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate time to confirmed clinical recovery.

2.2. KEY SECONDARY OBJECTIVES

The key secondary objectives are:

- To evaluate oxygen-free recovery;
- To evaluate improvement or being fit-for-discharge;
- To evaluate all-cause mortality.

2.3. OTHER SECONDARY OBJECTIVES

The other secondary objectives are:

- To evaluate the distribution across categories on the 8-point ordinal scale, and the worst outcome;
- To evaluate intensive care unit (ICU) days;
- To evaluate invasive mechanical ventilator days;

- To evaluate clinical recovery;
- To evaluate sustained clinical recovery;
- To evaluate the safety of candidate agents as add-on therapy to standard of care (SoC) in patients with COVID-19.

2.4. EXPLORATORY OBJECTIVES

CCI

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

Coronavirus disease 2019 (COVID-19) Multiple Agents and Modulators Unified Industry Members Trial (COMMUNITY) is an adaptive, randomized, placebo-controlled platform study designed to rapidly evaluate candidate agents in the treatment of COVID-19. The study will include hospitalized adult patients (≥18 years of age) who have infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, as confirmed by laboratory tests and/or point of care tests. For inclusion, patients will need to be hospitalized with a clinical status of Grade 2 (hospitalized, on invasive mechanical ventilation or ECMO) to Grade 5 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]), as defined by an 8-point ordinal scale for clinical severity (refer to Section 16.1.1).

This study aims to identify efficacious candidate agents for treatment of COVID-19. The candidate agents may include, but will not be limited to, antivirals, vascular agents or immunomodulatory agents. Each sub-protocol will specify a single candidate agent or a combination of candidate agents to be administered.

The Master Protocol outlines the overall design of the study, including the population, inclusion and exclusion criteria, randomization scheme, primary, secondary, and exploratory endpoints, study design, statistical methodology, and planned analyses that are common for all candidate agents to be tested. The Master Protocol is structured such that multiple candidate agents from different pharmaceutical companies can be evaluated simultaneously. The plan is to add candidate agents as they are identified and/or to remove therapies based on results of interim analyses (IAs; e.g., due to futility or if they are considered unsafe). The shared placebo control group for a candidate agent will include only patients randomized during the same period in which the candidate agent is opened for enrollment (refer to Section 4.5). Patients will be randomized equally to either the candidate agent plus SoC or placebo plus SoC in a double-blind fashion. Patients who are randomized to placebo plus SoC will be subsequently randomized equally to a matching placebo corresponding to an available candidate agent whose sub-protocol the patient qualified for (i.e., a 2-stage randomization). Each patient in the placebo plus SoC group will receive one type of placebo. Therefore, patients may be aware of which sub-protocol they were randomized to but not whether they will receive active agent or placebo investigational product. The comparator group of a candidate agent will include patients randomized to any matching placebo for a candidate agent available at the time of randomization for that agent (refer to Section 4.5).

Patients will be screened on Day -1 (the day before the first dose of study treatment [candidate agent plus SoC or

placebo plus SoC] is scheduled) or Day 1 and will remain in the hospital from Day 1 until discharge. All patients will receive SoC treatment, either with blinded candidate agent or matching blinded placebo. The SoC will be based on appropriate local written guidelines in place at the site at the time of treatment in the study; the SoC may change during the course of the study as new information about treating COVID-19 becomes available. Dosing with the study treatment (as an add-on to SoC) will commence on Day 1. Patients will be assessed daily while hospitalized. If they are discharged from the hospital prior to Day 15, they will have study visits at Days 15 and 29 as an outpatient by telemedicine. The last day of primary assessments will be Day 29. An end-of-study visit will be conducted on Day 60 (± 4 days) via telemedicine (unless the patient is still hospitalized in which case it would be conducted in person).

Sub-protocols will outline the scientific rationale, additional eligibility criteria (if necessary), treatment dose and regimen, statistical analysis populations, and other specifics unique to each candidate agent. The sub-protocols may define adverse events of special interest (AESIs) and can include PK and/or PD assessments that are appropriate for the specific candidate agent. In order to enroll, a patient must meet all entry criteria for both the Master Protocol and at least one active sub-protocol.

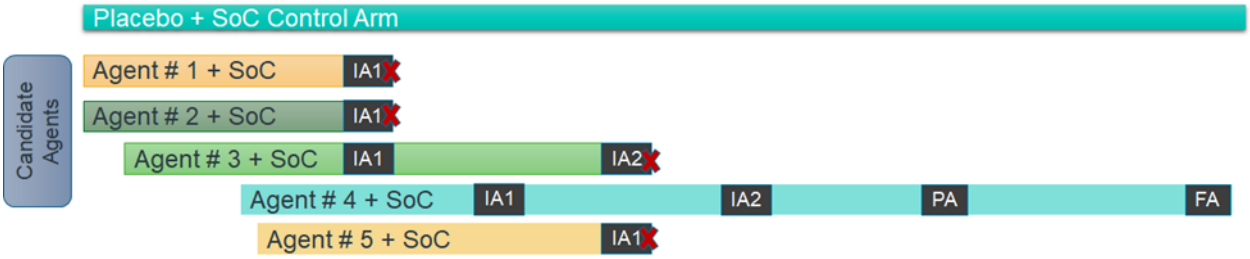
The study will evaluate the candidate agents as an add-on to the SoC to assess safety and efficacy. IAs may be performed for each candidate agent to evaluate futility for candidate agents.

Patients will be stratified at randomization by baseline clinical severity of 2 on the 8-point ordinal scale (yes/no) and remdesivir use at baseline (yes/no).

Enrollment of patients will be continuous throughout the study for each candidate agent until the total number of planned patients for that agent is enrolled or until futility criteria is met at an IA, or if the agent is considered unsafe.

In addition, centers may elect to participate in separate Investigator-initiated studies collecting additional data on patients, as their resources permit.

Figure 1 Study Schema (with hypothetical example)



FA=final analysis; IA=interim analysis; PA = primary analysis; SoC=standard of care. '×' indicates that futility boundary has been met.

Note: IA1 and IA2 will be planned at information fractions of approximately 25% and 55% of expected number of recoveries i.e., after approximately 123 and 270 patients have met the primary endpoint of confirmed clinical recovery on a particular candidate agent plus SoC and placebo plus SoC, respectively.

Note: PA will occur after approximately 350 patients have been randomized to an active agent plus SoC and have had the opportunity to complete the Day 29 visit.

Note: FA will occur after all patients randomized to that agent plus SoC and the concurrent placebo plus SoC controls have had the opportunity to complete the Day 60 visit.

Note: In the above example, Agents #1, #2, and #5 met the futility boundary at IA1, while Agent #3 met the futility boundary at IA2, and so those agents could be discontinued in the study due to futility.

Note: Patients who are randomized to placebo plus SoC will be subsequently randomized equally to a matching placebo corresponding to an available agent whose sub-protocol the patient qualified for (i.e., a 2-stage randomization).

3.2. SCHEDULE OF ACTIVITIES

An example of a schedule of activities can be found in Section 1.3 of the Master Protocol. Each sub-protocol may have its own schedule of activities.

3.3. CHANGES TO PLANNED ANALYSES FROM MASTER PROTOCOL

- The 'average ordinal scale for clinical severity score over Day 1 to Day 29' other secondary efficacy endpoint is updated to 'average ordinal scale for clinical severity score over Day 2 to Day 29' since Day 1 is the baseline value.

4. PLANNED ANALYSES

The following analyses will be performed for each sub-protocol:

- Independent data monitoring committee (IDMC) safety analyses;
- IAs for futility reviewed by the IDMC;
- Primary analysis;
- Final analysis.

4.1. IDMC SAFETY ANALYSES

An IDMC will monitor ongoing data to ensure patient well-being and safety as well as study integrity. The IDMC will be asked to make recommendations to the joint steering committee (JSC) regarding early termination or modification of the evaluation of a candidate agent.

The JSC will evaluate the IDMC recommendation(s) to make decisions on the candidate agent(s) within the study, and it will provide guidance, advice, and recommendations to the program on relevant clinical issues related to the strategy, implementation, and conduct of the study.

Unless otherwise indicated, definitions and derivations for the IDMC safety analyses will be based on those required for the primary analysis contained in this SAP (refers to Section 4.3). The data cut-off for the first IDMC safety meeting will be 4 weeks after the first patient is randomized into any sub-protocol. Thereafter, the data-cut will be

approximately every 4 weeks. Each sub-protocol other than the one to which the very first patient was randomized to will start to be included in the monthly IDMC safety meetings 4 weeks after the first patient is randomized into the sub-protocol. Safety outputs will be based on the safety analysis set (refer to Section 5.2).

The CCI Biostatistics study team will remain blinded to the IDMC safety analysis results. Once the programs have been produced and validated by the CCI Biostatistics study team in a blinded fashion, these programs will be sent to CCI Unblinded statistician, independent from the study team, who will apply the randomization schedule and provide the IDMC members with a set of unblinded outputs. The list of the unblinded personnel (i.e., CCI Unblinded Biostatistics team members as well as recipients of the unblinded results sent by CCI Unblinded Biostatistician) will be documented in the Unblinding Plan, which will be finalized before the data cut-off for the first IDMC safety analysis.

Refer to the IDMC Charter for more details about the IDMC composition, responsibilities, meeting frequency, list of outputs to be provided, etc.

4.2. INTERIM ANALYSES

Each candidate agent will be evaluated for futility at up to two IAs. For sub-studies under the master protocol, an IA will take place after:

- The appropriate number of primary efficacy endpoint events has occurred (refer to Section 16.5);
- Sponsor authorization of this SAP;
- Sponsor authorization of the analysis sets (refer to Section 5.3);
- Interim or final database lock of each sub-protocol contributing to the shared control group of the candidate agent, as appropriate;
- Interim database lock of the concerned candidate agent (refer to Data Management [DM] Interim Database Lock Plan).

The data cut-off date will be the date when approximately the required number of events is reached for an IA (refer to Section 16.5.1) and the last patient having the event is from the sub-protocol of interest for the IA, because if the last patient with an event is from a sub-protocol other than the one of interest, the patient's treatment arm will automatically be unblinded since those patients can only be included in the shared placebo plus SoC control arm of the sub-protocol of interest. Efficacy outputs will be based on the full analysis set (FAS; refer to Section 5.1) and

include data from patients who have had the opportunity to complete the Day 29 study visit or discontinued from study before or on the IA data cut-off date, whichever occur first, while safety outputs will be based on the safety analysis set (refer to Section 5.2) and include all data included in the database at the time of the interim database lock.

Unless otherwise specified, definitions and derivations for the IAs will be based on those required for the primary analysis contained in this SAP (refers to Section 4.3).

As for the IDMC safety analyses, results of each IA will be reviewed by the IDMC. The IDMC will be asked to make recommendations to the JSC regarding early termination of the evaluation of a candidate agent due to futility based on pre-defined stopping rules (refer to Section 16.5.1).

The JSC will evaluate the IDMC recommendation(s) to make decisions on the candidate agent(s) within the study, and it will provide guidance, advice, and recommendations to the program on relevant clinical issues related to the strategy, implementation, and conduct of the study.

Due to the shared placebo plus SoC treatment arm, both the CCI Biostatistics study team and CCI Unblinded statistician, independent from the study team, will be involved in the monitoring of the overall number of patients having met the primary endpoint of confirmed clinical recovery through Day 29, without re-hospitalization through Day 29 (refer to Section 16.1.1), across a particular candidate agent plus SoC and its contemporaneous shared placebo plus SoC treatment arms to confirm the timing of each IA. Once the programs have been produced and validated by the CCI Biostatistics study team in a blinded fashion, these programs will be sent to CCI Unblinded statistician who will apply the randomization schedule and inform CCI Blinded statistician of the overall number of patients having the event (n) and overall number of patients included in the analysis (N). No results by treatment arm will be generated by the programs and no information by treatment arm will be shared with CCI Blinded statistician (refer to the Unblinding Plan for the list of the unblinded personnel i.e. CCI Unblinded statistician, etc.).

The CCI Biostatistics study team will remain blinded to the IA results. Once the programs have been produced and validated by the CCI Biostatistics study team in a blinded fashion, these programs will be sent to CCI Unblinded statistician, independent from the study team, who will apply the randomization schedule and provide the IDMC members with a set of unblinded outputs. The list of the unblinded personnel (i.e. CCI Unblinded Biostatistics team members as well as recipients of the unblinded results sent by CCI Unblinded Biostatistician) will be documented in the Unblinding Plan, which will be finalized before the data cut-off for the first IDMC safety analysis.

Refer to the IDMC Charter for more details about the IDMC composition, responsibilities, meeting frequency, list of outputs to be provided, etc.

4.3. PRIMARY ANALYSIS

The primary analysis for a candidate agent will take place after:

- Approximately 350 patients have been randomized to the candidate agent plus SoC active arm of the sub-protocol of interest and approximately 350 patients have been randomized to the shared placebo plus SoC control arm of the sub-protocol of interest (refer to Section 4.5), and last patient randomized into one of these two arms is from the sub-protocol of interest, because if the last randomized patient is from a sub-protocol other than the one of interest, the patient's treatment arm will automatically be unblinded since those patients can only be included in the shared placebo plus SoC control arm of the sub-protocol of interest;
- The last patient randomized to that candidate agent plus SoC treatment arm or its concurrent shared placebo plus SoC control arm have had the opportunity to complete the Day 29 study visit or discontinued from study before or on the Day 29 study visit;
- Sponsor authorization of this SAP;
- Sponsor authorization of the analysis sets (refer to Section 5.3);
- Interim or final database lock of each sub-protocol contributing to the shared control group of the candidate agent, as applicable;
- Interim database lock of the concerned candidate agent database (refer to DM Interim Database Lock Plan).

The data cut-off date will be the date the last patient completed the Day 29 study visit or discontinued from the study before or on the Day 29 study visit, whichever occurs first.

With the following exception, all planned analyses identified in this SAP will be performed by CCI Biostatistics at the time of the primary analysis of a sub-protocol. The exception is the summary and analysis of the secondary efficacy endpoint incidence of sustained clinical recovery as confirmed by Day 60 (refer to Section 16.2.1.9) which will be performed at the time of the final analysis of a sub-protocol (refer to Section 4.4).

For each sub-protocol, additional outputs to be produced at the time of the primary analysis may be specified in sub-protocol SAPs.

The CCI Biostatistics study team will remain blinded to the results of the primary analysis. Once the programs have been produced and validated by the CCI Biostatistics study team in a blinded fashion, these programs will be sent to CCI Unblinded statistician, independent from the study team, who will apply the randomization schedule and provide to a pre-identified and limited number of people within the Sponsor of the concerned sub-protocol with a set of unblinded outputs. The list of the unblinded personnel (i.e., CCI Unblinded Biostatistics team members as well as recipients of the unblinded results sent by CCI Unblinded Biostatistician) will be documented in the Unblinding Plan, which will be finalized before the data cut-off for the first IDMC safety analysis.

4.4. FINAL ANALYSIS

The final analysis for a candidate agent will take place after:

- Approximately 350 patients have been randomized to the active arm of the sub-protocol of interest and approximately 350 patients have been randomized to the shared placebo plus SoC control arm of the sub-protocol of interest (refer to Section 4.5), and last patient randomized into one of these two treatment arms is from the sub-protocol of interest, because if the last randomized patient is from a sub-protocol other than the one of interest, the patient's treatment arm will automatically be unblinded since those patients can only be included in the shared placebo plus SoC control arm of the sub-protocol of interest;
- The last patient randomized to that candidate agent plus SoC treatment arm and its concurrent shared placebo plus SoC control arm (refer to Section 4.5) have had the opportunity to complete the Day 60 visit or discontinued from the study,
- Sponsor authorization of this SAP,
- Interim or final database lock of each sub-protocol contributing to the shared control group of the candidate agent, as applicable;
- Final database lock of the concerned candidate agent.

Unless otherwise specified, definitions and derivations for the final analysis will be based on those required for the primary analysis contained in this SAP (refer to Section 4.3). The outputs to be produced at the time of the final analysis of a sub-protocol are:

- Summary of patient disposition (refer to Section 9.1);

- Summary of protocol deviations (refer to Section 9.2)
- Summary of concomitant medications (refer to Section 13);
- Summary and analysis of the incidence of sustained clinical recovery as confirmed by Day 60 (other secondary efficacy endpoint; refer to Section 16.2.3.1);
- Summary of all-cause mortality through Day 60 (additional efficacy endpoint; refer to Section 16.4.3);
- All summaries planned for the AEs (refer to Section 17.1).

For each sub-protocol, additional outputs to be produced at the time of the final analysis may be specified in sub-protocol SAPs.

The CCI Biostatistics study team will remain blinded to the results of the final analysis of each subprotocol with the exception of the final analysis of the last sub-protocol reaching this milestone. Once the programs have been produced and validated by the CCI Biostatistics study team in a blinded fashion, these programs will be sent to CCI Unblinded statistician, independent from the study team, who will apply the randomization schedule and provide to a pre-identified and limited number of people within the Sponsor of the concerned sub-protocol with a set of unblinded outputs. The list of the unblinded personnel (i.e., CCI Unblinded Biostatistics team members as well as recipients of the unblinded results sent by CCI Unblinded Biostatistician) will be documented in the Unblinding Plan, which will be finalized before the data cut-off for the first IDMC safety analysis.

4.5. SELECTION OF THE CONTROL ARM FOR AN ANALYSIS

The subset of the placebo plus SoC group, regardless of which sub-protocol the placebo patient belongs, enrolled concurrently to an active agent with matching inclusion/exclusion criteria will serve as the control arm for the analysis of a candidate agent. An exception to this definition is that if a sub-protocol X is not open at a site for screening, the concurrent placebo from other active sub-protocol(s) at that site will not be eligible for inclusion in the control arm for sub-protocol X. This is because patient's eligibility for sub-protocol X cannot be determined without sub-protocol consent and obtaining consent for a sub-protocol is not possible until that sub-protocol is opened at a site for screening. It is to be noted that a patient randomized to the placebo arm of sub-protocol X taking the candidate agent of sub-protocol Y for another approved indication (based on data collected on the *Concomitant Medications* page of the eCRF) at the time of randomization will not be eligible for the control arm of the sub-protocol Y.

For each sub-protocol and each site, 'concurrently' is defined as the period starting on the date the site was opened

for screening for the sub-protocol and ending on the date of the last patient randomized into that sub-protocol for an interim, primary, and final analyses. For IDMC safety analyses, the date of the data cut-off will be used in lieu of the date of the last patient randomized into the sub-protocol.

5. ANALYSIS SETS

For purposes of analysis, the analysis sets in this section are defined for all sub-protocols. Specific additional analysis sets may be defined in sub-protocols or their corresponding sub-protocol SAPs.

5.1. FULL ANALYSIS SET

For each sub-protocol, the full analysis set (FAS) will contain all patients who were randomized to the sub-protocol candidate agent plus SoC arm as well as all patients who were randomized to any placebo plus SoC arm included in the control arm of the candidate agent (refer to Section 4.5).

For displays and analyses based on FAS, patients will be classified according to randomized treatment.

5.2. SAFETY ANALYSIS SET

For each sub-protocol, the safety analysis set will contain all patients included in the FAS (refer to Section 5.1) who took at least one dose study drug. If there is any doubt whether a patient was treated or not, he/she will be assumed treated with the study drug for the purposes of analysis.

For analyses and displays based on the safety analysis set, patients will be classified according to the actual treatment received (based on data captured on the interactive web response system [IWRS]). That is, a patient randomized to a placebo plus SoC arm who received at least one dose of the candidate agent during the course of the study will be classified under the candidate agent plus SoC arm and a patient randomized to the candidate agent plus SoC arm who never received the candidate agent will be classified under the control arm.

If a patient randomized to the placebo arm of sub-protocol X is selected for the control arm of sub-protocol Y (refer to Section 4.5) and begins taking the candidate agent of sub-protocol Y for another approved indication after randomization as a concomitant medication (based on data captured on the *Concomitant Medications* page of the eCRF), this patient will still be presented under the control arm of sub-protocol Y for summaries based on the safety analysis set and a listing of all AEs will be provided for such patients, if they exist.

5.3. PROCESS FOR ANALYSIS SET ASSIGNMENT

The analysis sets that will be used to summarize, analyze, and list the data collected during the course of this study are all defined based on objective criteria only. That is, none of the analysis set definitions included in this SAP contains subjective criteria (e.g., major protocol deviation potentially having an impact on the efficacy data). Hence, the authorization of this SAP will also stand for the agreement and authorization of the inclusion/exclusion of each patient in each of these analysis sets.

If analysis sets defined in a sub-protocol SAP involve subjective criteria, the process for analysis set assignment prior to interim, primary or final database locks will be detailed in the sub-protocol SAPs.

6. GENERAL CONSIDERATIONS

6.1. STUDY DAY

Study day will be calculated from the day of the first dose of the study drug for patients who received at least one dose of study drug and from the day of randomization for randomized patients who were never dosed, and will be used to show start/stop day of assessments and events.

Study day will be computed as follows:

- Study Day = (Date of interest –Date of first dose of study drug/randomization, as appropriate) + 1 if the date of interest is on or after the date of first dose of study drug/randomization, as appropriate;
- Study Day = (Date of interest – Date of first dose of study drug/randomization, as appropriate) if the date of interest is prior to the date of first dose of study drug/randomization, as appropriate.

Based on these formula, Study Day 1 will be the day of the first dose of the study drug for patients who received at least one dose of study drug and the day of randomization for randomized patients who were never dosed.

In the situation where the date of interest is partial or missing, Study Day and any corresponding durations will be considered as missing in the analyses and the date of interest will be presented as partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled measurements) taken prior to the first dose of study drug for patients who received at least one dose of study drug and as the last non-missing measurement (including unscheduled measurements) taken prior to randomization for randomized patients who were never dosed. In the case where the last non-missing measurement and first dose of study drug/randomization dates coincide, time will be considered. If time is not collected, missing or unknown, measurements taken on the same day of the first dose, or same day as randomization for subjects not dosed, will be considered as the baseline measurement unless the assessment was scheduled to be collected post-first dose/post-randomization in the master/sub-protocol (refer to Section 3.2).

For adverse events (AEs) commencing on the date of the first dose of study drug/randomization, time of onset of the AE will be considered when determining if the event was pre-baseline (not treatment-emergent) or post-baseline (treatment-emergent). Medications that are ongoing or commencing on the date of the first dose of study drug/randomization will be considered as concomitant medications (refer to Section 13) . Partial or completely missing AE and medication dates will be handled as described in Appendix 1.

6.3. UNSCHEDULED VISITS, RETESTS, DISCHARGE, AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled visits will not be included in by-visit summaries but might contribute to the baseline timepoint (refer to Section 6.2) and/or worst/maximum/minimum post-baseline value, where required (e.g., shift table).

In case of a retest when retest is defined as having a blood sample tested twice, the latest available measurement for that blood sample will be used for the by-visit summaries. In case of a retest when retest is defined as having two blood samples collected on the same day, results from the last blood sample will be used for the by-visit summaries.

Refer to Section 6.4 for the conventions to map discharge and early termination data to protocol-defined visit windows. Discharge and early termination data might also contribute to the worst/maximum/minimum post-baseline value, where required (e.g. shift table).

Listings will include all scheduled, unscheduled, retest, discharge, and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Discharge and early termination data will be mapped based on the scheduled Study Day of each scheduled visit with adjusted protocol-defined visit window, as specified in the appropriate sub-protocol schedule of activities (refer to Section 3.2).

If discharge or early termination data are mapped to a scheduled visit for which data from the scheduled visit are also available (i.e., non-missing), the data collected at the scheduled visit will be used in the by-visit summaries. If discharge or early termination data are mapped to a scheduled visit for which data from the scheduled visit are not available (i.e., missing), data from the discharge or early termination visit will be used in the by-visit summaries, as applicable.

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

- Change from baseline = Observed value at post-baseline visit – Baseline value

Percent change from baseline will be calculated as:

- Percent change from baseline = (Change from baseline / Baseline value) * 100

7. STATISTICAL CONSIDERATIONS

For continuous data, descriptive statistics (i.e., n [number of patients with available data], mean, standard deviation [SD], minimum, 25th percentile (Q1), median, 75th percentile (Q3), and maximum values) will be presented by treatment arm and visit, when applicable.

For categorical data, the number and percentage of patients in each category will be presented by treatment arm and visit, when applicable.

7.1. SAMPLE SIZE CALCULATION

A total of up to 350 patients are planned to be randomized to each candidate agent plus SoC. Simultaneously, patients will be randomized to placebo plus SoC throughout the course of the study. The subset of shared placebo

plus SoC treatment arm, regardless of which sub-protocol the placebo belongs, enrolled concurrently to an active agent with matching inclusion/exclusion criteria will serve as comparator (refer to Section 4.5). The primary efficacy endpoint to compare selected treatment plus SoC to placebo plus SoC included in the control arm will be the time to confirmed clinical recovery through Day 29 i.e., fit for discharged (defined by achieving a score of 6, 7 or 8 on the 8-point ordinal scale for clinical severity status), without re-hospitalization through Day 29 (refer to Section 16.1.1).

Assuming a median time to confirmed clinical recovery of 11 days for patients randomized to a candidate agent plus SoC arm compared with 15 days for those randomized to its concurrent placebo plus SoC arm, 350 patients are needed per arm in order to observe 490 confirmed clinical recovery events between the 2 treatment arms being compared at the primary analysis of a sub-protocol. This sample size will provide approximately 88% power to detect a hazard ratio (HR) of 1.364 for the occurrence of the confirmed clinical recovery events, when comparing each candidate agent plus SoC with their concurrent placebo plus SoC arm, at a one-sided significance level of 0.025.

This sample size will provide the following information about the key secondary efficacy endpoints:

- Assuming the oxygen-free recovery rate at Day 29 is 65% for the concurrent placebo plus SoC arm of a candidate agent, a sample size of 350 patients per arm will provide approximately 80% power to detect a 9.7% absolute increase in the proportion of patients who have oxygen-free recovery at Day 29 in the candidate agent plus SoC arm;

- Assuming 70% of patients randomized to the concurrent placebo plus SoC arm of a candidate agent achieve at least 2-point improvement from baseline on the 8-point ordinal scale or are fit for discharge at Day 29, 350 patients per arm will provide approximately 80% power to detect a 9.2% absolute increase in this proportion with a candidate agent plus SoC arm at Day 29;

- Assuming the all-cause mortality rate through Day 29 is 15% for the concurrent placebo plus SoC arm of a candidate agent, a sample size of 350 patients per arm will provide 80% power to detect an absolute reduction of 6.75% (8.25% rate for the candidate agent plus SoC arm) in the mortality rate by Day 29. Assuming a mortality rate of 15% for the concurrent placebo plus SoC arm of a candidate agent and 19% for the candidate agent plus SoC arm (i.e., an adverse treatment effect of 4%) with a sample size of 350 per arm, the chance to observe a decrease in the mortality rate of at least 1% with a candidate agent plus SoC arm compared to its concurrent placebo plus SoC arm is approximately 4%.

The sample size calculation was performed using EAST 6.5.

For a sub-protocol where the primary analysis population is a subset of the randomized population, the sample size may be adjusted as applicable to power the designated primary analysis population as appropriate.

Each candidate agent may be evaluated for futility at up to two IAs (refer to Section 16.5).

7.2. MISSING DATA

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.2, and 16.3.2 of this SAP.

Missing safety data will not be imputed. Partially or completely missing AE and medication dates will be handled as described in Appendix 1.

7.3. STATISTICAL TESTS

Unless otherwise specified, all statistical tests will be conducted at the two-sided 0.05 significance level at the primary analysis. Confidence Intervals (CIs) will be two-sided with 95% coverage, unless otherwise specified.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment to control the family-wise type I error over the two IAs and the primary analysis of a candidate agent is needed as both IAs will be for futility only (refer to Section 16.5).

At the time of the primary analysis of each candidate agent, the primary efficacy endpoint will be tested at the 0.05 alpha level. Then, a hierarchical testing procedure will be used to test the three key secondary hypotheses (refer to Section 16.2.3.1). With this approach when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The hierarchical testing procedure will be implemented in the following order:

1. Primary endpoint: Time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29 (refer to Sections 16.1.1 and 16.1.3);
2. Key Secondary endpoint: Incidence of oxygen-free recovery at Day 29 (refer to Sections 16.2.1.1 and 16.2.3.1);
3. Key secondary endpoint: Incidence of ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29 (refer to Sections 16.2.1.2 and 16.2.3.1);

4. Key secondary endpoint: Incidence of all-cause mortality through Day 29 (refer to Sections 16.2.1.3 and 16.2.3.1).

In the hierarchical testing procedure, the formal testing can be performed for a step only when the statistical significance is declared for all the endpoints tested in the previous steps. If the testing sequence is stopped at a particular step, only nominal p-value will be provided for the remaining endpoints in the testing sequence.

Only nominal p-values will be provided for the non-key secondary endpoints and no statistical inference will be performed for the CCI [redacted] and safety endpoints.

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers. For each sub-protocol, data from all patients included in the candidate agent plus SoC arm will be pooled together in the analyses of the sub-protocol, regardless of the patient's centers. Similarly, data from all patients included in the control arm of the candidate agent will be pooled together in the analyses of the sub-protocol, regardless of the patient's centers.

Statistical analyses will be adjusted for the countries. Subgroup analyses by country might be performed for the primary and key secondary efficacy endpoints (refer to Sections 7.7, 16.1.5, and 16.2.5).

If data are too sparse for at least one country (i.e., less than 10% of FAS patients, regardless of the treatment arm), countries will be pooled into regions based on geographical area (e.g., North America, Latin America, Western Europe, Eastern Europe, and Rest of the World). In that case, statistical analyses will be adjusted for regions instead of countries.

For each sub-protocol, determination of the countries or regions to be included in the statistical models will be finalized in a blinded fashion before a sub-protocol database lock for an IA or Primary Analysis (refer to Sections 4.2 and 4.3) based on emerging data.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The analyses will be adjusted for the following covariates and factors. For details of their inclusion in the models, refer to Sections 16.1.3, 16.2.3, and 16.3.3.

- Baseline value of the concerned endpoint, when applicable;

- Baseline clinical severity score of 2 randomization strata (yes or no), as captured on the IWRS;
- Remdesivir at baseline randomization strata (yes or no), as captured on the IWRS;
- Country (or region; refer to Section 7.5).

Sensitivity analyses replacing the randomization strata as captured in IWRS by the randomization strata as derived based on the data captured on the electronic case report form (eCRF) might be performed if at least 10% of the patients are mis-stratified at the time of randomization for a stratification variable (refer to Section 16.1.4) i.e.,

- Baseline clinical severity score of 2 (yes or no) as captured on the *Ordinal Scale for Clinical Severity* page of the eCRF;
- Remdesivir use at baseline (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (i.e., medications that were taken by a patient on the day the patient was randomized to a sub-protocol).

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as supplementary analyses for the primary and key secondary efficacy endpoints as stated in Sections 16.1.5 and 16.2.5, respectively.

The subgroups are:

- Age (years) at informed consent (≥ 18 - ≤ 49, ≥ 50 - ≤ 64; ≥ 65 - ≤ 84 or ≥ 85);
- Sex (male or female);
- Race (White, Black or African American or Other);
- Ethnicity (Hispanic or Latino or not Hispanic or Latino);
- Country (or region; refer to Section 7.5);
- Obesity co-morbidity at screening (BMI < 30 kg/m^2 or BMI ≥ 30 kg/m^2);
- Diabetes co-morbidity at screening (yes or no);
- Cardiovascular disease co-morbidity at screening (yes or no);
- Hypertension co-morbidity at screening (yes or no);

- Chronic lung disease co-morbidity at screening (yes or no);
- Chronic liver disease co-morbidity at screening (yes or no);
- Kidney disease co-morbidity at screening (yes or no);
- Immunosuppressive/Immunocompromise disorder co-morbidity at screening (yes or no);
- Time since hospital admission (≤ 5 days or > 5 days; refer to Section 11.1);
- Baseline clinical severity score of 2 randomization strata (yes or no) as captured on the IWRS;
- Disease severity at baseline (2, 3, 4, or 5) based on the ordinal scale for clinical severity as captured on the *Ordinal Scale for Clinical Severity* page on the eCRF;
- Disease severity score of 2, 3 or 4 (yes or no) at baseline based on the ordinal scale for clinical severity as captured on the *Ordinal Scale for Clinical Severity* page on the eCRF
- Remdesivir use at baseline randomization strata (yes or no) as captured on the IWRS;
- Concomitant use of remdesivir at any time during the period of the endpoint of interest (yes or no) based on collected on the *Concomitant Medications* page of the eCRF (for concomitant use definition, refer to Section 13). The concomitant use of remdesivir at any time during the period of the endpoint of interest in the 'yes' subgroup will be further broken down by duration of concomitant use of remdesivir, where the duration of concomitant use categories (e.g., < x days or ≥ x days) will be determined in a blinded fashion based on emerging data before the interim database lock of a candidate agent primary analysis;
- Dexamethasone use at baseline (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (i.e., medications that were being taken by a patient on the day the patient was randomized to a sub-protocol);
- Concomitant use of dexamethasone at any time during the period of the endpoint of interest (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (for concomitant use definition, refer to Section 13). The concomitantly use dexamethasone at any time during the period of the endpoint of interest 'yes' subgroup will be further broken down by duration of concomitant use of dexamethasone, where the duration of concomitant use categories (e.g., < x days or ≥ x days) will be determined in a blinded fashion based on emerging data before the interim database lock of a candidate agent primary analysis.

For age subgroups, if data are too sparse for the '≥ 18 - ≤ 49' or '≥ 50 - ≤ 64' subgroups (i.e., less than 10% of FAS

patients, regardless of the treatment arm), these two subgroups will be pooled together into a '≥ 18 - ≤ 64' subgroup. Similarly, if data are too sparse for the '≥ 65 - ≤ 84 or '≥ 85' subgroups, these two subgroups will be pooled together in a '≥ 65' subgroup. If even after pooled two subgroups, the resulting '≥ 18 - ≤ 64' or '≥ 65' subgroup is still less than 10% of FAS patients, regardless of the treatment arm, only descriptive statistics will be provided for the concerned subgroup.

For race subgroups, if data are too sparse for the 'Black or African American' or 'Other' subgroups (i.e., less than 10% of FAS patients, regardless of the treatment arm), the 'Black or African American' and 'Other' subgroups will be pooled together into a 'Non-White' subgroup. If even after having pooled these two subgroups the number of patients in the resulting 'Non-White' subgroup is still less than 10% of FAS patients, regardless of the treatment arm, only descriptive statistics will be provided for the 'Non-White' subgroup.

For the disease severity at baseline subgroups, if data are too sparse for the subgroups of patients with a disease severity at baseline of 3 or 4 (i.e., less than 10% of FAS patients, regardless of the treatment arm), these two subgroups will be pooled together. If data are too sparse for the subgroup of patients with a disease severity at baseline of 2, pooled 3/4 (if applicable) or 5, only descriptive statistics will be provided for the concerned subgroups. That is, the subgroup of patients with a disease severity at baseline of 2 or 5 will not be pooled with any other subgroup.

For any other subgroups, if data are too sparse (i.e., less than 10% of FAS patients for a subgroup, regardless of the treatment arm), only descriptive statistics will be provided for the concerned subgroups.

Additional subgroups might be defined based on emerging data to explore the impact of medical therapy in COVID-19 with proven efficacy (e.g., vaccine use, other evolving SoC, etc.). The decision to add such subgroups and their definition will be taken in a blinded fashion before the interim database lock of a candidate agent primary analysis based on data captured on the *Concomitant Medications* page of the eCRF.

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

8. OUTPUT PRESENTATIONS

Appendix 2 shows conventions for presentation of data in outputs.

The table, figure, and listing (TFL) shells provided with this SAP describe the presentations for each sub-protocol in accordance with this master SAP and therefore, the format and content of the summary tables, figures, and listings to be provided by CCI [redacted] Biostatistics. If a sub-protocol has additional endpoints or analyses, additional TFL shells will be provided with the sub-protocol SAP.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Number and percentages of patients treated, ongoing on study drug, who completed/ discontinued early from treatment (including reason for withdrawal), ongoing in study, and who completed/discontinued early from the study (including reason for withdrawal) will be provided overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol. It is to be noted that the number and percentage of patients ongoing on study drug and ongoing in study will be excluded from the summary at the time of the final analysis.

In addition, a Kaplan-Meier curve (product-limit estimate) of time to discontinuation from study, in days, for each treatment arm will be provided along with a summary of the associated statistics including, the 25th, 50th (median), and 75th percentiles, and their corresponding two-sided 95% CIs. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol. Patients who are ongoing in the study at the time of an analysis will be censored at the date of the last contact before or on the date of the data cut-off for the analysis and patients who completed the study will be censored at study completion. The standard errors (SEs) will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation

Number of patients included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol.

Listings for randomization schemes/codes and disposition data will be provided separately.

9.1.1. DERIVATIONS

- Time to discontinuation from study (days) = (Date of study discontinuation – Date of Study Day 1 [refer to Section 6.1]) + 1

Date of study discontinuation will be captured on the *Disposition* page of the eCRF.

Patients who are ongoing in the study at the time of an analysis will be censored at the date of the last contact before or on the date of the data cut-off for the analysis and patients who completed the study will be censored at study completion.

9.2. PROTOCOL DEVIATIONS

All protocol deviations (critical, major, and minor) will be recorded in the clinical trial management system (CTMS) protocol deviations log for the duration of the study (refer to the Protocol Deviations Management Plan for the definition of critical, major, and minor protocol deviations). Site-level identified protocol deviations will be replicated for all patients ongoing in the study at the site at the time of the protocol deviation and presented in the summary outputs as patient-level protocol deviation.

Number and percentage of patients with critical and major protocol deviations will be provided overall and by treatment arm based on the FAS for each category of protocol deviations specified in the Protocol Deviations Management Plan. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol.

A listing of all protocol deviations (critical, major, and minor) will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – in integers, calculated relative to date of consent:
    - As a continuous variable;
    - As a categorical variable (≥ 18 - ≤ 49, ≥ 50 - ≤ 64, ≥ 65 - ≤ 84, or ≥ 85);
- Sex (male or female);

- Childbearing potential for female patients only (yes or no) and reasons if not of childbearing potential;
- Race:
    - American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, multiple, not reported, or unknown;
    - White, Black or African American, others, not reported, or unknown;
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, or unknown);
- Country;
- Region (if applicable, refer to Section 7.5);
- Height (cm);
- Weight (kg);
- Body Mass Index (BMI) (kg/m^2);

Demographic and other baseline characteristics will be summarized overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol. No statistical testing will be carried out for any demographic or other baseline characteristic.

Demographic and other baseline characteristics data will be listed.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as follows:

- BMI (kg/ m^2) = Weight (kg)/ [Height (m)^2]

11. DISEASE HISTORY

The following disease history endpoints will be summarized overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol.

- Time since onset of first COVID-19 symptom(s) (days) – calculated relative to Study Day 1 (refer to Section

6.1)

- Time since COVID-19 diagnosis (days) – calculated relative to Study Day 1;
- Time since hospital admission (days) – calculated relative to Study Day 1;
- Patients on supplemental oxygen at Study Day 1 (yes or no);
- Type of supplemental oxygen only for patients receiving supplemental oxygen at Study Day 1;
- Time since start of supplemental oxygen (days) - calculated relative to Study Day 1 only for patients on supplemental oxygen at Study Day 1;
- Patients receiving ICU/high dependency unit (HDU)-level care at Study Day 1 (yes or no);
- Time since start of ICU/HDU-level care (days) – calculated relative to Study Day 1 only for patients receiving ICU/HDU-level care at Study Day 1;
- Patients on invasive mechanical ventilation at Study Day 1 (yes or no);
- Type of invasive mechanical ventilation at Study Day 1 only for patients on invasive mechanical ventilation at Study Day 1;
- Time since start of invasive mechanical ventilation (days) – calculated relative to Study Day 1 only for patients on invasive mechanical ventilation at Study Day 1;
- Patients diagnosed with acute respiratory distress syndrome (ARDS; yes or no);
- Time since ARDS diagnosis (days) – calculated related to Study Day 1 only for patients diagnosed with ARDS;
- Patients with or without each of the following COVID-19 symptoms at screening. For each symptom, patients with the symptom will be further broken down by severity (mild, moderate, severe, or unknown):
    - Cough;
    - Fever;
    - Myalgia;
    - Diarrhea;
    - Dyspnea;

- Fatigue/malaise;
- Loss of appetite;
- Loss of smell;
- Loss of taste.

- Baseline clinical severity score (2, 3, 4, or 5, as well as 2 or 3/4/5) as captured on the *Ordinal Scale for Clinical Severity* page of the eCRF;
- NEWS2 total score at baseline;
- Oxygen saturation (SpO_2; %) at baseline;
- Fraction of Inspired Oxygen (FiO_2; %) at baseline.

All disease history characteristics will be listed.

11.1. DERIVATIONS

Time since events, in days, will be calculated as follows:

- Time since onset of first COVID-19 symptom(s) (days) = (Date of Study Day 1 [refer to Section 6.1] – Date of onset of first COVID-19 symptom[s]); date of onset of COVID-19 symptoms as captured on the *Medical History* page of the eCRF;
- Time since COVID-19 diagnosis (days) = (Date of Study Day 1 - Date of COVID-19 diagnosis); date of COVID-19 diagnosis as captured on the *Medical History* page of the eCRF;
- Time since hospital admission (days) = (Date of Study Day 1 – Date of hospital admission); where date of hospital admission will be the earliest date of hospital admission captured on the *Hospitalization* page of the eCRF;
- Time since start of supplemental oxygen (days) = (Date of Study Day 1 – Date of start of supplemental oxygen) if patient is already on supplemental oxygen at Study Day 1; where the date of start of supplemental oxygen will be earliest date of start of supplemental oxygen as captured on the *Supplemental Oxygen and Mechanical Ventilation* page of the eCRF. That is, time since start of supplemental oxygen will not be computed for patients not on supplemental oxygen at Study Day 1;

- Time since start of ICU/HDU-level care (days) = (Date of Study Day 1 – Date of start of ICU/HDU-level care) if patient is already receiving ICU/HDU-level care at Study Day 1; where the date of start of ICU/HDU-level care will be the earliest date of start of ICU/HDU-level care captured on the *Hospitalization* page of the eCRF; That is, time since start of ICU/HDU-level care will not be computed for patients not receiving ICU/HDU-level care at Study Day 1;

- Time since start of invasive mechanical ventilation (days) = (Date of Study Day 1 – Date of start of invasive mechanical ventilation) if patient is already on invasive mechanical ventilation at Study Day 1; where the date of start of invasive mechanical ventilation will be the earliest date of start of invasive mechanical ventilation captured on the *Supplemental Oxygen and Mechanical Ventilation* page of the eCRF. That is, time since start of invasive mechanical ventilation will not be computed for patients not on invasive mechanical ventilation at Study Day 1.

- Time since ARDS diagnosis (days) = (Date of Study Day 1 – Date of ARDS diagnosis) if patient was diagnosed with ARDS at screening; where the date of start of ARDS diagnosis as captured on the *Medical History* of the eCRF. That is, time since ARDS will not be computed for patients not already diagnosed with ARDS at screening.

12. MEDICAL HISTORY

Medical history is defined as any medical conditions/diseases that started and stopped before screening as well as any medical conditions/diseases that started before screening AND were ongoing at the time of screening.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or later and will be summarized by System Organ Class and PT overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol. A patient having more than one medical condition/disease within the same System Organ Class or PT will be counted only once for that System Organ Class or PT. In the summary, System Organ Classes will be sorted in alphabetical order and within each System Organ Class, PTs will be sorted in decreasing order of total frequency.

Additionally, for each of the following COVID-19 comorbidities, the number and percentage of patients, as captured on the *Medical History* page of the eCRF, will be reported overall and by treatment arm based on the FAS. The control arm of a candidate agent (refer to Section 4.5) will be further broken down by sub-protocol.

- Any comorbidity, defined as having any of the comorbidities listed below;

- Obesity (refer to Sections 7.7 and 10.1);
- Diabetes;
- Cardiovascular disease;
- Hypertension;
- Chronic lung disease;
- Chronic liver disease;
- Kidney disease;
- Immunosuppressive/immunodeficiency disorder.

13. PRIOR AND CONCOMITANT MEDICATIONS

All medications collected on the *Concomitant Medications* page of the eCRF will be classified as either:

- Prior medications, defined as any medication that started and stopped prior to the date of Study Day 1 (refer to Section 6.1);

or

- Concomitant medications, defined as:
    - Any medication that started before the date of Study Day 1 AND ended on or after the date of Study Day 1, or were ongoing at that time;
    - Any medication that started on or after the date of Study Day 1.

Partially or completely missing medication start and stop dates will be handled as described in Appendix 1.

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version September 2020 B3 or later.

Concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by treatment arm based on the FAS. A patient having more than one medication within the same ATC level 2 or preferred drug name will be counted only once for that ATC level 2 or preferred drug name. Further,

for each sub-protocol, separate summaries will also be presented for patients randomized to the sub-protocol placebo plus SoC treatment group.

Additionally, the number and percentages of patients receiving following medications of interest will be summarized overall and by treatment arm based on the FAS. For each sub-protocol, summaries will also be presented for the subset of patients randomized to the Placebo to the candidate agent plus SoC treatment group of the sub-protocol.

- Remdesivir use at baseline (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (i.e., medications that were being taken by a patient on the day the patient was randomized to a sub-protocol);
- Concomitant use of remdesivir at any time during the period of the analysis being performed (yes or no; refer to Section 7.7);
- Dexamethasone use at baseline (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (i.e., medications that were being taken by a patient on the day the patient was randomized to a sub-protocol);
- Concomitant use of dexamethasone at any time during the period of the analysis being performed (yes or no; refer to Section 7.7);
- Steroid use at baseline (yes or no) based on data collected on the *Concomitant Medications* page of the eCRF (i.e., medications that were being taken by a patient on the day the patient was randomized to a sub-protocol);
- Concomitant steroid use at any time during the period of the analysis being performed (yes or no; refer to Section 7.7).

All medications (prior and concomitant) will be listed.

14. EXPOSURE TO STUDY DRUG

Each candidate agent included within the study will have a sub-protocol that will provide details of that treatment, including route and mode of administration, dose, dosage regimen, and duration of treatment. The derivations for study drug exposure as well as summaries and analyses of exposure are therefore not covered in this master protocol SAP but will be covered in the SAP for each sub-protocol.

15. COMPLIANCE WITH STUDY DRUG

Similar to study drug exposure, derivations of compliance to study drug as well as summaries and analyses of study drug compliance, are not covered in this master protocol SAP, but will be covered in the SAP for each sub-protocol.

16. EFFICACY ENDPOINTS

Unless otherwise indicated, all efficacy summaries and figures will be presented by treatment arm and visit, when appropriate, based on the FAS. Listings will be provided for all efficacy data.

16.1. PRIMARY EFFICACY

Unless otherwise indicated, all efficacy summaries and analyses will be presented based on the FAS.

16.1.1. TIME TO CONFIRMED CLINICAL RECOVERY THROUGH DAY 29, WITHOUT RE-HOSPITALIZATION THROUGH DAY 29

The primary efficacy endpoint is the time to confirmed clinical recovery through Day 29, i.e., fit for discharge (defined by achieving a score of 6, 7, or 8 on the 8-point ordinal scale for clinical severity), without being re-hospitalized through Day 29.

It is to be noted that:

- The re-hospitalization-free requirement does not apply to patients who achieved an ordinal scale score of 6 that were never discharged from the hospital before Day 29. For such patients, the re-hospitalization-free requirement is superseded by not having a subsequent worsening on the ordinal scale score (i.e., a score < 6 on the ordinal scale for clinical severity) that would remain until Day 29;
- Patients achieving a score of 7 on the ordinal scale for clinical severity discharged to hospice care will be considered as not fit for discharge in the analysis.

The ordinal scale for clinical severity is as follows:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive 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 limitations on activities.

Time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, will be measured in days from the date of Study Day 1 (refer to Section 6.1):

- Time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29 (days) = (Date of event – Date of Study Day) + 1

Refer to Section 6.1 for the definition of Study Day 1.

The following algorithm will be followed to determine if a patient met the event (i.e., confirmed clinical recovery through Day 29, without rehospitalization through Day 29) or should be censored:

1. First, the patient's alive status by Day 29 will be verified as per data collected on the *Death Details* page of the eCRF. If the patient died before or on Day 29, he/she will be censored at Day 29. If the patient has not died by Day 29, then go to step 2;
2. Second, the patient's study discontinuation status by Day 29 will be verified as per data collected on the *Disposition* page of the eCRF. If the patient discontinued from the study before or on Day 29, he/she will be censored at date of discontinuation from study. If the patient was still ongoing in the study at Day 29, then go to step 3;
3. Last, it will be verified if a patient had a score of 6, 7 or 8 on the 8-point ordinal scale (as captured on the *Ordinal Scale for Clinical Severity* page of the eCRF) before or on Day 29:
    a. For patients who had a score of 6 on the 8-point ordinal scale and were never discharged from the hospital before Day 29, it will be checked if patient worsened on the 8-point ordinal scale (i.e., had a score < 6) before or on Day 29:
        i. If so (i.e., patient worsened) and patient never subsequently re-reached a score of 6 before or on Day 29, the patient will be censored at Day 29;
        ii. If so (i.e., patient worsened) but patient subsequently re-reached a score of 6 before or on

Day 29, the patient will be considered as having the event and the date of the event will be the earliest date on which the patient re-reached a score of 6;

iii. If not (i.e., patient did not worsen), the patient will be considered as having the event and the date of the event will be the earliest date on which the patient had a score of 6 before or on Day 29;

b. For patients who had a score of 7 on the 8-point ordinal scale, it will first be verified if patient was discharged to hospice care as per data captured on the *Hospitalization* page of the eCRF.

i. If so (i.e., patient was discharged to hospice care), the patient will be considered as not fit for discharge and will be censored at Day 29;

ii. If not (i.e., patient was discharged, but not to hospice care), then go to step c.

c. For patients who had a score of 7 (discharged, but not to hospice care) or 8 on the 8-point ordinal scale, it will be verified if patient was re-hospitalized before or on Day 29 as per data captured on the *Hospitalization* page of the eCRF. To do so, it will be checked if a patient had at least one record where the hospitalization start date is after the earliest date on which the patient had a score of 7 or 8 but before or on Day 29.

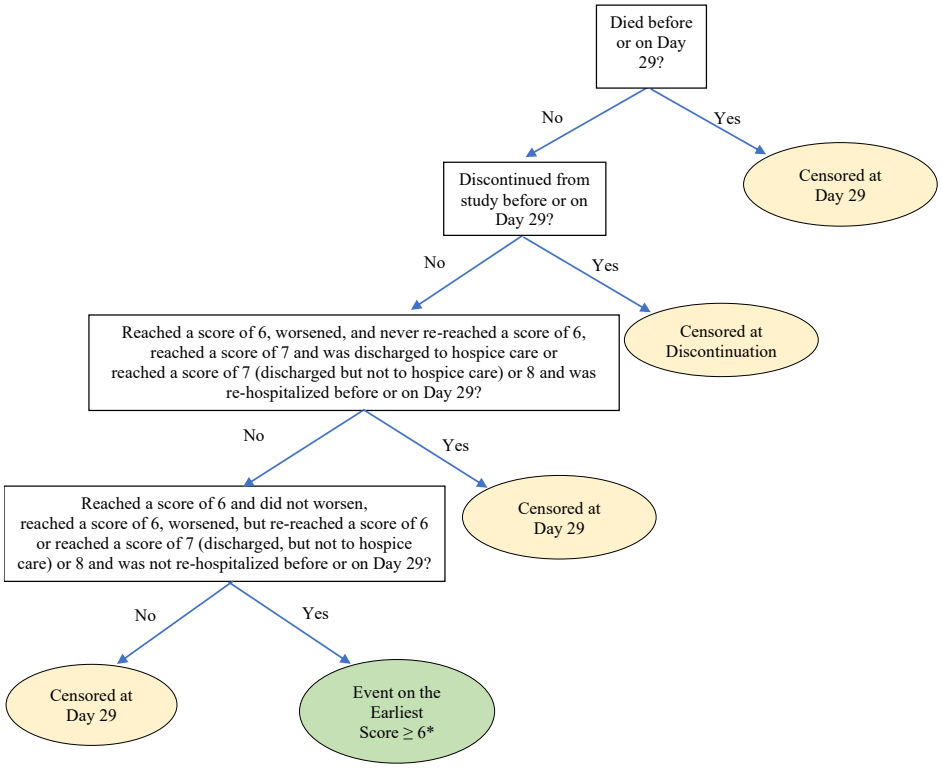
i. If so (i.e., patient was re-hospitalized), the patient will be censored at Day 29;

ii. If not (i.e., patient was not re-hospitalized), the patient will be considered as having the event and the date of the event will be the earliest date on which patient had a score ≥ 6 before or on Day 29;

d. Patients who never had a score of 6, 7 or 8 on the 8-point ordinal scale, did not discontinue from the study or died before or on Day 29 will be censored at Day 29

Refer to Figure 2 for a schematic of the primary endpoint determination of date of event and censoring.

Figure 2 Schematic of Determination of Primary Efficacy Endpoint Date of Event or Censoring



* For patients who had a score of 6, worsened, ***re-***reached a score of 6, and were never discharged from the hospital before or on Day 29, earliest date on which the patient ***re-***reached a score of 6.

16.1.2. Missing Data Imputation Method for Primary Efficacy Endpoint

For the time to confirmed clinical recovery (days) through Day 29, without re-hospitalization through Day 29, missing ordinal scale for clinical severity scores and missing hospitalization data will not be imputed before applying the censoring rules for the main analysis of the primary efficacy endpoint (refer to Section 16.1.1).

16.1.3. Main Analysis of Primary Efficacy Endpoint

For the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, as defined in Section 16.1.1, the number and percentage of patients with and without the event will be presented by randomized treatment arm. For patients who did not meet the event, the main reason for censoring (refer to Section 16.1.1) will be summarized similarly.

Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the time to confirmed clinical recovery though Day 29, without re-hospitalization through Day 29. Kaplan-Meier estimate of the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, in days, will be provided at the 25th, 50th (median), and 75th percentiles time along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation. Kaplan-Meier estimates of the probability of having the event will also be provided at Day 29 along with the number of patients with the event and the number of patients at risk at that time.

The difference between a candidate agent plus SoC arm and its control arm will be compared using a stratified log-rank test. The stratification factor will be the baseline clinical severity of 2 on the 8-point ordinal scale (yes or no) stratification variable, remdesivir use at baseline (yes or no) stratification variable, both as captured on the IWRS, and country (region; refer to Section 7.5). The p-value associated with the stratified log-rank test statistic will be provided and compared at the two-sided 0.05 alpha level at the time of the primary analysis of a candidate agent. The p-value will also be compared to the specified boundaries at the IAs for futility in order to serve as guidance for the IDMC to make recommendations based on the totality of available information at the time of the IAs (refer to Section 16.5).

Additionally, a Cox proportional hazards model will be performed including the baseline clinical severity of 2 on the 8-point ordinal scale (yes or no) stratification variable, remdesivir use at baseline (yes or no) stratification variable, both as captured on the IWRS, country (region), and treatment arm as factors. Ties will be handled using the exact

method. The HR (candidate agent plus SoC vs. placebo plus SoC) and corresponding two-sided 95% CI will be provided.

For the methods to control the overall alpha level of a sub-protocol at the two-sided 0.05 level, refer to Section 7.4.

16.1.4. SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

The following sensitivity analyses to the main analysis of the primary efficacy endpoint will be performed:

- **Sensitivity to stratification variables**: The main analysis to the primary efficacy endpoint (refer to Section 16.1.3) may be repeated but stratification variables as derived based on the eCRF data (refer to Section 7.6) will be included in the model instead of the stratification variables as captured on the IWRS. This analysis will be performed only if at least 10% of patients are mis-stratified at the time of randomization for a stratification variable;

- **Sensitivity to censoring assumptions #1**: The main analysis of the primary efficacy endpoint will be repeated but patients who discontinued early from the study before or on Day 29 will be censored at Day 29;

- **Sensitivity to censoring assumptions #2**: The main analysis of the primary efficacy endpoint will be repeated but, for patients who discontinued early from the study before or on Day 29, the last patients' known event status will be carried forward to Day 29 before applying the censoring rules for the main analysis of the primary efficacy endpoint (refer to Section 16.1.1).

- **Sensitivity to censoring assumptions #3**: The primary analysis assumes that censoring is at random (CAR) for patients who discontinued early from the study before or on Day 29 (refer to Section 16.1.3). For this sensitivity analysis, the time to event (refer to Section 16.1.1) will be imputed only for these patients using a model that assumes censoring not at random (CNAR). The model will assume that these patients would have hazard following discontinuation from study that is reduced by some factor delta (δ) compared with hazard of remaining patients in their group who have similar key baseline characteristics (Lipkovich et al, 2016), where reduced hazard rate indicates a longer time to event (confirmed clinical recovery through Day 29, without re-hospitalization through Day 29). In order to stress-test the assumption of CAR with an assumption that is less favorable to a candidate agent plus SoC treatment arm, a $\delta < 1$ will be used for the candidate agent plus SoC treatment arm while a $\delta = 1$ will be used for the concurrent shared placebo plus SoC control arm as $\delta = 1$, which corresponds to the CAR assumption.

  Multiple imputation method using covariates-adjusted and delta-adjusted piecewise exponential survival model

as suggested in Lipkovich et al, 2016, will be used as the imputation method separately for each treatment arm. For each sub-protocol, the prior distribution and pieces used in this covariates-adjusted and delta-adjusted piecewise exponential survival model will be determined in a blinded fashion prior to the DBL for a sub-protocol Primary Analysis. The model will include the baseline clinical severity of 2 on the 8-point ordinal scale stratification variable (yes or no), remdesivir use at baseline stratification variable (yes or no), both as captured on the IWRS, and country (region; refer to Section 7.5) as covariates.

If the imputed event time exceeds Day 29, the patient will be censored at Day 29. Multiple imputation (MI) method will be used where 100 imputed datasets will be generated using above model and a seed of 2102.

Each of the multiply-imputed datasets will then be analyzed using the same stratified log-rank test and Cox regression model as for the main analysis to the primary efficacy endpoint (refer to Section 16.1.3). The survival distribution quartiles (25th, 50th [median], and 75th percentiles), log-rank statistics, and hazard ratios will be combined as suggested in Moscovici and Ratitch, 2017. The combined statistics and p-value associated with the combined log-rank statistic will be presented.

A tipping point analysis will be implemented where the above described MI will first be performed using a δ = 0.95 for the candidate agent plus SoC treatment arm and then repeated but decreasing the δ-adjustment applied to the candidate agent plus SoC treatment arm gradually by reduction of 0.05 (i.e., 0.95, 0.90, 0.85, etc.) until the study conclusion is not significant anymore. For each of these analyses, the δ used for the concurrent shared placebo plus SoC control arm will always remain 1. The δ when the study conclusion becomes non-significant will be referred to as the tipping point.

Additional sensitivity analyses might be specified in the sub-protocol SAPs.

16.1.5. SUPPLEMENTARY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

The following supplementary analyses to the main analysis of the primary efficacy endpoint will be performed:

- The main analysis to the primary efficacy endpoint will be repeated (refer to Section 16.1.3) but without country (region; refer to Section 7.5) included as stratification variable;
- The main analysis of the primary efficacy endpoint will be repeated but without the requirement for follow-up confirmation. That is, for this analysis, patients will be considered as having met the event as soon as they reach a score of 6, 7 or 8 on the 8-point ordinal scale, regardless of if they subsequently worsened or were re-hospitalized before or on Day 29, exception of patients with a score of 7 discharged to hospice care who will

still be considered as not having the event;

- The main analysis of the primary efficacy endpoint will be repeated for each subgroup defined in Section 7.7. For subgroups corresponding to one of the factors included in the main model, the corresponding factor will be excluded from the model. For example, the remdesivir use at baseline (yes/no) stratification variable as captured on the IWRS will not be included in the model for the analysis of the patients who received remdesivir at randomization as captured on the IWRS subgroup, and analysis of the patients who did not receive remdesivir at randomization as captured on the IWRS subgroup.

16.2. SECONDARY EFFICACY

16.2.1. SECONDARY EFFICACY ENDPOINTS

16.2.1.1. Incidence of Patients with Oxygen-Free Recovery at Day 29

The first key secondary efficacy endpoint is the incidence of patients with oxygen-free recovery at Day 29, defined as the proportion of patients who were alive, discharged, and not receiving supplemental oxygen at Day 29.

1. The alive status of a patient at Day 29 (yes or no) will be determined as follows based on data captured on the *Death Details* page of the eCRF: patients who died before or on Day 29 will be considered as not being alive at Day 29 while patients without any data captured on this page of the eCRF before or on Day 29 but with some data captured on any other page of the eCRF on or after Day 29 will be considered to be alive at Day 29;

2. The patient's discharge status (yes or no) at Day 29 will be established as follows based on data collected on the *Ordinal Scale for Clinical Severity* page of the eCRF: a patient will be considered as being discharged at Day 29 if 1) their ordinal scale score is 7 at Day 29 and patient was not discharged to hospice care or 2) their ordinal scale score is 8 at Day 29. Discharge to hospice care status will be verified based on data collected on the *Hospitalization* page of the eCRF. To do so, the outcome of the hospitalization record with the latest stop date before or on Day 29 will be examined. The hospitalization outcome of that record should not be 'Home: Hospice Care' or 'Hospice Medical Facility' for a patient with an ordinal scale score of 7 at Day 29 to be considered as discharged at that time. Patients who discontinued early from study before Day 29 will be considered as having a missing discharged status at Day 29;

3. The patient's oxygen-free status (yes or no) at Day 29 will be determined as follows: data collected on the

Supplemental Oxygen and Mechanical Ventilation page of the eCRF will be examined to verify if the patient has a record where the start date of supplemental oxygen/mechanical ventilation is before or on Day 29 and stop date of supplemental oxygen/mechanical ventilation is after Day 29* or is ongoing at Day 29. Patients without such record will be considered as being oxygen-free at Day 29 while patient with such record will be considered as being not oxygen-free at Day 29. Patients who discontinued early from study before Day 29 will be considered as having a missing oxygen-free status at Day 29.

* That is, patients who stopped receiving supplemental oxygen/mechanical ventilation on Day 29 will be considered as being oxygen-free at Day 29.

All three criteria (alive, discharged, and not receiving supplemental oxygen at Day 29) must be fulfilled for a patient to be considered as having an oxygen-free recovery at Day 29. That is, as soon as a patient does not fulfill at least one of the three criteria, he/she will be considered as not having an oxygen-free recovery at Day 29, regardless of the status of the other criteria. Should the status of one of the three criteria be missing while the two other criteria are fulfilled or missing, patients' oxygen-free recovery at Day 29 will be considered as missing.

Scenario	Alive at Day 29 (as per step 1)	Discharge at Day 29 (as per step 2)	Oxygen-free at Day 29 (as per step 3)	Oxygen-free Recovery at Day 29
1	Alive	Yes	Yes	Yes
2	Dead	Yes, No, Missing	Yes, No, Missing	No
3	Alive, Dead, Missing	No	Yes, No, Missing	No
4	Alive, Dead, Missing	Yes, No, Missing	No	No
5	Missing	Yes, Missing	Yes, Missing	Missing
6	Alive, Missing	Missing	Yes, Missing	Missing
7	Alive, Missing	Yes, Missing	Missing	Missing

Refer to Section 16.2.2.1 for handling of missing oxygen-free recovery at Day 29 status.

16.2.1.2. Incidence of Patients with ≥ 2-point Improvement from Baseline or Fit for Discharge on the Ordinal Scale at Day 29

The second key secondary efficacy endpoint is the incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the 8-point ordinal scale for clinical severity (refer to Section 16.1.1) at Day 29, where fit for discharge is defined as having a score of 6, 7 or 8 on the ordinal scale for clinical severity. Patients with an ordinal scale score of 7 must not have been discharged to hospice care to be considered as fit for discharge.

By endpoint definition, patients with an ordinal scale score of 6, 7 (but not discharged to hospice care) or 8 at Day 29 will be considered as having met the event (yes) at Day 29, regardless of their change from baseline in ordinal

scale score, while patients with a score of 7 discharged to hospice care will be considered as not having met the event, also regardless of their change from baseline in ordinal scale score. For patients hospitalized and not considered as fit for discharge at Day 29 i.e., patients with an ordinal scale score < 6, the '≥ 2-point improvement from baseline' requirement (yes or no) will be established based on the patient's change from baseline in the ordinal scale at Day 29, where change from baseline will be computed as defined in Section 6.5.

Refer to Section 16.2.2.1 for handling of missing ≥ 2-point improvement from baseline or fit for discharge on the 8-point ordinal scale for clinical severity status.

16.2.1.3. Incidence of All-Cause Mortality through Day 29

The third key secondary efficacy endpoint is the incidence of all-cause mortality through Day 29, defined as the proportion of patients having died due to any cause before or on Day 29. Patients' alive/death status by Day 29 will be determined based on data captured on the *Death Details* page of the eCRF. If a patient does not have any data captured on the *Death Details* page of the eCRF by Day 29 but his/her 'subject status' captured on the *Contact* page of the eCRF at Day 29 is alive or he/she had some data captured on any other page of the eCRF on or after Day 29, he/she will be considered alive on Day 29.

Refer to Section 16.2.2.1 for handling of missing alive/death through Day 29 status.

16.2.1.4. Distribution of Patients across the Categories of the 8-point Ordinal Scale for Clinical Severity at Days 8, 15, and 29

An 'other secondary efficacy endpoint' is the distribution of patients across the categories of the 8-point ordinal scale for clinical severity at Days 8, 15, and 29 i.e., the proportion of patients in each category of the 8-point ordinal scale for clinical severity at Days 8, 15, and 29. It is to be noted that patients with a score of 7 discharged to hospice care will be pooled with patients with a score of 1 (death) for this 'other secondary efficacy endpoint'.

Refer to Section 16.1.1 for the description of the 8-point ordinal scale and to Section 16.2.2.1 for handling of missing ordinal scale scores.

16.2.1.5. Worst Post-Baseline Score on 8-point Ordinal Scale from Baseline to Day 29

An 'other secondary efficacy endpoint' is the worst post-baseline score (lower scores are worse) through Day 29 in the 8-point ordinal scale (refer to Section 16.1.1), derived from all scores recorded after baseline up to and including Day 29. It is to be noted that patients with a score of 7 discharged to hospice care will be considered as having a

score of 1 (death) instead of a score of 7 for this 'other secondary efficacy endpoint.

Refer to Section 16.2.2.2 for handling of missing ordinal scale scores.

16.2.1.6. Number of ICU Days from Day 1 through Day 29

An 'other secondary efficacy endpoint' is the number of ICU days from Day 1 through Day 29. This endpoint will be considered as an ordinal endpoint.

For each patient, the number of ICU days from Day 1 through Day 29 will be derived based on the sum of the duration of any episodes of ICU admission between Day 1 and Day 29, inclusively, for patients who were alive on Day 29. Episodes of ICU admission will be identified based on data recorded on the *Hospitalization* page of the eCRF, where *Hospitalization Status* is recorded as *ICU/HDU*. For patients who were discharged to hospice care or died before or on Day 29, the number of ICU days from Day 1 through Day 29 will be set to 30 (worst possible scenario).

The duration, in days, of an episode of ICU admission will be derived as follows:

- Duration of an episode of ICU admission (days) = (Date of ICU discharge – Date of ICU admission) + 1

If the start date of an episode of ICU admission is prior to Day 1, it will be set to the date of Study Day 1 (refer to Section 6.1) when deriving ICU duration for that episode.

If an episode of ICU admission is ongoing at Day 29 or at the time of analysis, the stop date of the admission will be set to the minimum of:

- The start date of any subsequent ICU admission;
- Day 29;
- The data cut-off date for the analysis.

If there are any overlapping dates of ICU admission, a Day will only be counted once when deriving the overall number of ICU days for a patient. For example, if a patient has a record where the start and stop Study Days of the ICU/HDU admission are Day 3 and Day 10, respectively, and another record where the start and stop Study Days of ICU/HDU admission are Day 9 and Day 12, respectively, Days 9 and 10 will be counted only once in the overall number of ICU days for that patient.

Refer to Section 16.2.2.2 for handling of missing number of ICU days from Day 1 through Day 29.

16.2.1.7. Number of Invasive Mechanical Ventilator Days from Day 1 through Day 29

For each patient, the 'other secondary efficacy endpoint' of the number of invasive mechanical ventilator days from Day 1 through Day 29, inclusively, will be considered as an ordinal endpoint and derived similarly to the number of ICU days from Day 1 through Day 29 (refer to Section 16.2.1.6) but using the data collected on the *Supplemental Oxygen and Mechanical Ventilation* page of the eCRF where *Type of supplemental oxygen* is recorded as *Invasive Mechanical Ventilation*.

Refer to Section 16.2.2.2 for handling of missing number of invasive mechanical ventilation days from Day 1 through Day 29.

16.2.1.8. Incidence of Patients with Clinical Recovery by Days 8, 15, and 29

An 'other secondary efficacy endpoint' is the incidence of patients with clinical recovery at Days 8, 15, and 29, defined as the proportion of patients being fit for discharge (i.e., patients achieving a score of 6, 7, or 8 on the 8-point ordinal scale for clinical severity; refer to Section 16.1.1) at Days 8, 15, and 29, respectively, as per data recorded on the *Ordinal Scale for Clinical Severity* page of the eCRF. It is to be noted that patients with a score of 7 discharged to hospice care will not be considered as being fit for discharge for this 'other secondary efficacy endpoint'.

Refer to Section 16.2.2.1 for handling of missing clinical recovery status by Days 8, 15, and 29.

16.2.1.9. Incidence of Patients with Sustained Clinical Recovery as Confirmed by Day 60 Follow-up

An 'other secondary efficacy endpoint' is the incidence of patients with sustained clinical recovery as confirmed by Day 60 follow-up, defined as the proportion of patients considered as being fit for discharge (i.e., achieving a score of 6, 7, or 8 on the 8-point ordinal scale for clinical severity) through Day 29, without re-hospitalization by Day 60 (refer to Section 16.1.1), as per the *Ordinal Scale for Clinical Severity* and *Hospitalization* pages of the eCRF. It is to be noted that patients with a score of 7 discharged to hospice care before or on Day 29 will not be considered as being fit for discharge for this 'other secondary efficacy endpoint'.

Similarly to the primary efficacy endpoint, patients achieving a score of 6 on the ordinal scale for clinical severity before or on Day 29 will be considered as having sustained clinical recovery if they have no worsening of their ordinal scale score by Day 60 (i.e., a score < 6 on the ordinal scale for clinical severity) or were discharged from the hospital after Day 29 and were not re-hospitalized by Day 60.

Refer to Section 16.2.2.1 for handling of missing sustained clinical recovery as confirmed by Day 60 status.

16.2.2. Missing Data Imputation Method for Secondary Efficacy Endpoints

16.2.2.1. Binary Endpoints

For the ***incidence of oxygen-free recovery at Day 29*** endpoint, the algorithm defined in Section 16.2.1.1 will first be applied. Then, patients with a missing oxygen-free recovery status at Day 29 will considered as not having met the event for this key secondary efficacy endpoint.

For the ***incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29*** endpoint (refer to Section 16.2.1.2), patients with a missing ordinal scale score at Day 29 due to patient's death, discontinuation from study before or on Day 29 or for any other reason (with the following exception) will be considered as not having met the event at Day 29 for that key secondary endpoint. The only exception is for patients with a missing ordinal scale score at Day 29 for which the latest non-missing ordinal scale score before Day 29 was 7 (but not discharge to hospice care) or 8. These patients will be assumed to be fit for discharge at Day 29 and so, as having met the event.

For the ***incidence of all-cause mortality through Day 29*** endpoint (refer to Section 16.2.1.3), patients with an unknown alive/death status at Day 29 due to discontinuation from study for a reason other than death or missing data will be considered as alive in the analysis, exception of patients for who the last-missing ordinal scale score was 7 and that have been discharged to hospice care before discontinuing from study before Day 29. These patients will be considered as dead at Day 29 for the main analysis of this key secondary efficacy endpoint.

For the ***clinical recovery by Day 8*** endpoint (refer to Section 16.2.1.8), any patient who died before or on Day 8, discontinued from study before or on Day 8 or with missing clinical recovery status at Day 8 will be considered as not having clinical recovery by Day 8. Missing ***clinical recovery by Days 15 and 29*** will be handled similarly.

For the ***sustained clinical recovery as confirmed by Day 60*** follow-up endpoint (refer to Section 16.2.1.9), any patient who died before or on Day 60, discontinued study before Day 60 or with a missing 8-point ordinal scale score at Day 60 will be counted as not having sustained clinical recovery.

16.2.2.2. Ordinal Endpoints

Missing ***ordinal scale scores*** will be imputed as follows for the distribution of patients across the categories of the 8-point ordinal scale for clinical severity at Day 8 endpoints (refer to Section 16.2.1.4):

- Patients who died prior to Day 8 will have a score of 1 used for Day 8;
- For all other occurrences of patient with missing ordinal score at Day 8 (e.g., patients who discontinued from the study before Day 8, etc.), the last non-missing post-baseline ordinal scale score before Day 8 (included data collected at unscheduled post-baseline visits) will be used to impute the missing ordinal scale score at Day 8 exception of patients for who the last non-missing post-baseline ordinal scale score before Day 8 is 7 that were discharged to hospice care. For these patients, the missing ordinal scale score at Day 8 will be imputed to 1.

Missing ordinal scale score at Days 15 and 29 will be imputed similarly.

For the ***worst post-baseline score on the 8-point ordinal scale from baseline to Day 29*** endpoint(refer to Section 16.2.1.5), patients who have died prior to Day 29 will have their worst post-baseline ordinal scale score from Day 1 to Day 29 set to a score of 1. For patients who are alive at Day 29, no imputation of missing post-baseline ordinal scale scores will be performed. The worst post-baseline ordinal scale score will be identifying among the non-missing post-baseline ordinal scale scores (including data collected at unscheduled post-baseline visits).

For the ***number of ICU days and number of invasive mechanical ventilation days*** endpoints (refer to Sections 16.2.1.6 and 16.2.1.7, respectively), missing data will not be imputed.

16.2.3. MAIN ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

Refer to Section 7.4 for more information about the hierarchical testing procedure that will be used to test the three key secondary hypotheses. Only nominal p-values will be provided for the non-key secondary endpoints.

16.2.3.1. Binary Endpoints

For the incidence of patients with oxygen-free recovery at Day 29 (refer to Section 16.2.1.1), incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29 (refer to Section 16.2.1.2), incidence of all-cause mortality through Day 29 (refer to Section 16.2.1.3), incidence of patients with clinical recovery at Days 8, 15 and 29 (refer to Section 16.2.1.8), and incidence of patients with sustained clinical recovery as confirmed by Day 60 follow-up (refer to Section 16.2.1.9), the number and percentage of patients with and without the event will be provided by treatment arm. For the incidence of all-cause mortality, primary reason of death will also be summarized by treatment arm.

For each of these endpoints, a logistic regression will be performed to test the difference between a candidate agent plus SoC and placebo plus SoC treatment arms, including the baseline clinical severity of 2 on the 8-point ordinal

scale for clinical severity (yes or no) stratification variable, remdesivir use at baseline (yes or no) stratification variable, both as captured on the IWRS, country (region; refer to Section 7.5), and treatment arm as factors. The estimate of the relative risk (risk difference) between the two treatment arms, the corresponding two-sided 95% Wald CI, and the p-value obtained from the logistic regression model will be provided.

The odds ratio (of candidate agent plus SoC vs. placebo plus SoC) for having the event at the specified Day and its two-sided 95% CI will also be presented.

16.2.3.2. Ordinal Endpoints

For the incidence of patients in each category of the 8-point ordinal scale for clinical severity at Days 8, 15, and 29 endpoints (refer to Section 16.2.1.4), the number and percentage of patients in each ordinal scale category will be provided at each specified Day for each treatment arm and will be analyzed using a proportional odds model, including the baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity (yes or no) stratification variable, remdesivir use at baseline (yes or no) stratification variable, both as captured on the IWRS, country (region; refer to Section 7.5), and treatment arm as factors.

The odds ratio (candidate agent plus SoC vs. placebo plus SoC) of having a higher score than any given category k of the ordinal scale at Days 8, 15, and 29, their two-sided 95% CI, and associated p-value will be presented for each specified Day, where it is assumed that the odds ratio does not differ depending upon k.

The worst post-baseline score on the 8-point ordinal scale for clinical severity from randomization to Day 29 (refer to Section 16.2.1.5) and each "number of days" endpoint (refer to Sections 16.2.1.6 and 16.2.1.7) will be summarized and analyzed similarly.

Shift tables from baseline to each post-baseline day up to Day 29 as well as to the worst post-baseline score will also be provided for the 8-point ordinal scale for clinical severity.

16.2.4. Sensitivity Analyses for Secondary Efficacy Endpoints

The following sensitivity analyses to the main analysis of each key secondary efficacy endpoint will be performed. No sensitivity analyses will be performed for the non-key secondary efficacy endpoints.

- **Sensitivity to stratification variables**: The main analysis of each key secondary efficacy endpoint will be repeated but the stratification variables as derived based on the eCRF data (refer to Section 7.6) will be included in the model instead of the stratification variables as captured on the IWRS if at least 10% of patients are mis-

stratified at the time of randomization for a stratification variable.

- **Sensitivity analysis to missing data assumption #1**:
    - For the incidence of patients with oxygen-free recovery at Day 29 (refer to Section 16.2.1.1), a multiple imputation approach will be applied to impute the missing oxygen-free recovery status (yes or no) at Day 29 for subjects who discontinued from study before or on Day 29 using a logistic regression including effects for the treatment arm, baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity stratification variable (yes or no), remdesivir use at baseline stratification variable (yes or no), both as captured on the IWRS, and country (or region; refer to Section 7.5). One hundred (100) imputed datasets will be generated using a seed of 2504.

      Each imputed dataset will then be analyzed using the same model as for the main analysis of this key secondary efficacy endpoint (refer to Section 16.2.3.1).

      The relative risks and parameter estimates for the effects of the logistic regression model and their SEs will then be combined using the Rubin's rule to obtain a combined estimate of the treatment arm effect and its SE, and the associated p-value will be provided. The relative risks and odds ratios will first be log transformed and then combined to obtain a combined relative risk and combined odds ratio, and their associated 95% CI. The combined relative risk and combined odds ratio, and associated 95% CI, will be back-transformed before being displayed;

    - For the incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29 (refer to Section 16.2.1.2), the same sensitivity analysis using multiple imputation as described above as for the key secondary efficacy endpoint of incidence of patients with oxygen-free recovery at Day 29 will be performed for this key secondary efficacy endpoint, but using a seed of 1228 ;

    - For the incidence of all-cause mortality through Day 29 (refer to Section 16.2.1.3), the same sensitivity analysis using multiple imputation as described above as for the key secondary efficacy endpoint of incidence of patients with oxygen-free recovery at Day 29 will be performed for this key secondary efficacy endpoint, but using a seed of 2007.

- **Sensitivity analysis to missing data assumption #2**:
    - For the incidence of all-cause mortality through Day 29, a tipping point analysis will be performed. For patients who discontinued early from the study, all possible combinations of the number of patients

dead or alive at Day 29 will be considered and the main analysis of this key secondary efficacy endpoint will be repeated for each combination.

A dot plot will be produced with number of patients with unknown death status at Day 29 imputed to death for the shared placebo plus SoC treatment arm reported on the x-axis and number of patients with unknown death status at Day 29 imputed to death for the candidate agent plus SoC treatment arm reported on the y-axis, and distinguishing between combination that results in statistically significant treatment effect (a dot is displayed for the combination) vs. not statistically significant treatment effect (no dot is displayed for the combination). The clinical plausibility of the combinations on the boundary will be discussed in the clinical study report (CSR) to evaluate robustness of study conclusions to missing data.

16.2.5. SUPPLEMENTARY ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

The main analysis of each key secondary efficacy endpoint will be repeated for each subgroup defined in Section 7.7. For subgroups corresponding to one of the factors included in the main model, the corresponding factor will be excluded from the model. For example, the remdesivir use at baseline (yes/no) stratification variable, as captured on the IWRS, will not be included in the analysis of the patients who received remdesivir at randomization subgroup, as captured on the IWRS, and analysis of the patients who did not receive remdesivir at randomization subgroup, as captured on the IWRS.

The following supplementary analyses will also be performed for the incidence to all-cause mortality key secondary efficacy endpoint:

- For the incidence of all-cause mortality through Day 29, the time to all-cause death, in days, will be derived as follows:
    - Time to all-cause mortality (days) =

        (Date of all-cause death/Date of censoring - Date of Study Day 1 [refer to Section 6.1]) + 1.

      The date of death will be taken from data captured on the *Death Details* page of the eCRF.

      For patients who were alive on Day 29, time to all cause-mortality will be censored at Day 29. For patients with an unknown alive status at the time of the analysis due to missing data, time to all-cause mortality will be censored at the latest date on which the patient was known to be alive before or on the data cut-off date of the analysis. The last date the patient was known to be alive will be the latest date

collected on any page of the eCRF. For patients who discontinued from the study before the time of the analysis, time to all-cause mortality will be censored at the date of study discontinuation, as captured on the *Disposition* page of the eCRF.

Number and percentage of patients with and without the event will be presented by randomized treatment arm. For patients who did not meet the event, the main reason for censoring will be summarized similarly.

The incidence of all-cause mortality through Day 29 along with its two-sided 95% CI by treatment arm will then be estimated using Kaplan-Meier survival curves of the time to all-cause mortality. Kaplan-Meier survival curves by treatment arm will also be provided.

The 25th percentile, 50th percentile (median), and 75th percentile of time to all-cause mortality (days) with the corresponding two-sided 95% CIs based on the Kaplan-Meier survival curves (refer to Section 16.2.4) for each treatment arm will also be presented. The estimate of the SEs will be computed using Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982) and the other CIs will be derived from the Kaplan-Meier estimates using the log-log transformation.

A Cox proportional hazard model will be performed, including the baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity (yes or no), remdesivir use at baseline (yes or no) stratification variables, both as captured on the IWRS, country (region), and treatment arm as factors. Ties will be handled using the exact method. The hazard ratio of the candidate agent plus SoC vs. placebo plus SoC, its associated two-sided 95% CI, and p-value will be provided.

No supplementary analyses will be performed for the non-key secondary efficacy endpoints.

16.3. EXPLORATORY EFFICACY

16.3.1. EXPLORATORY EFFICACY ENDPOINTS

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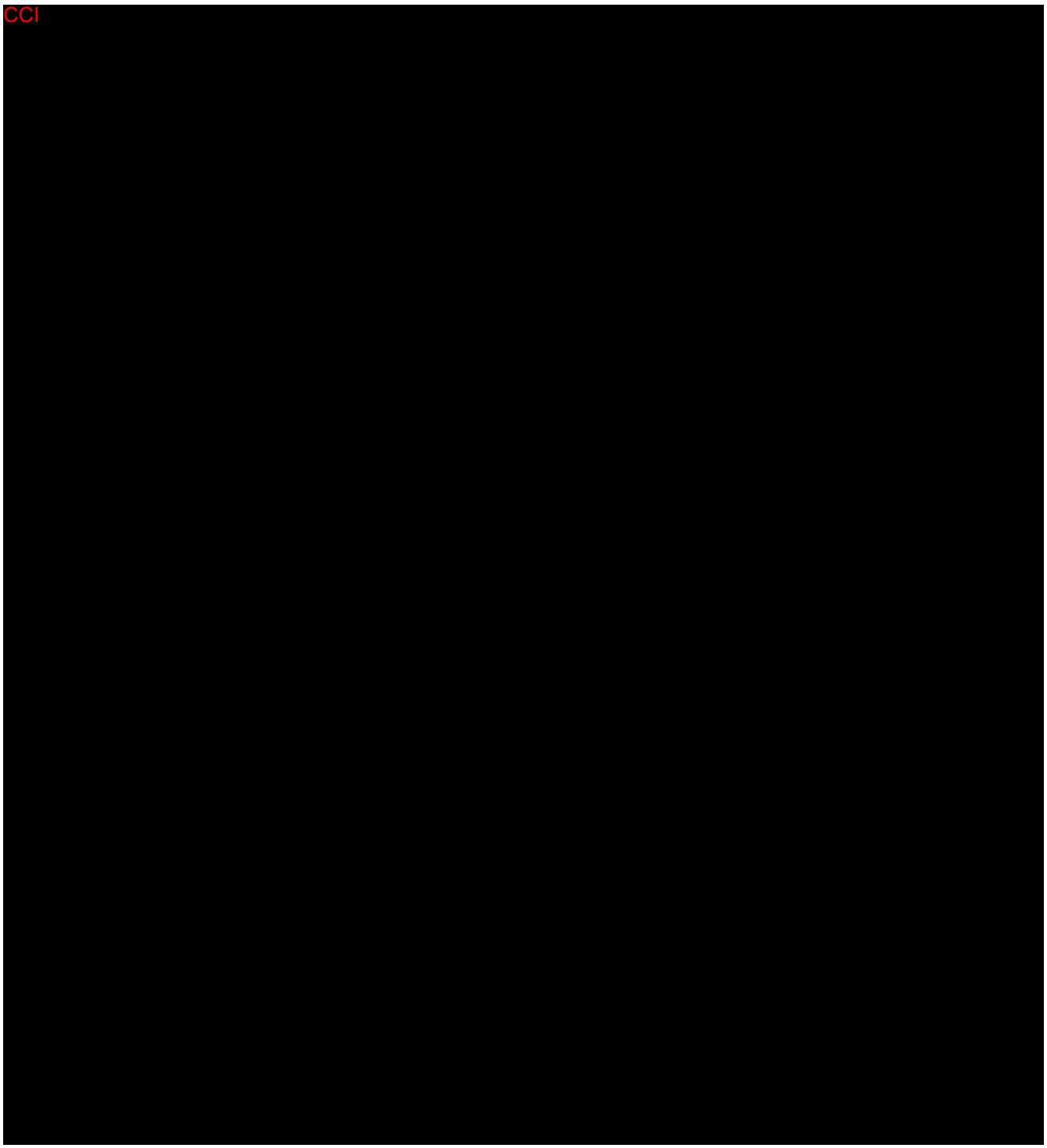

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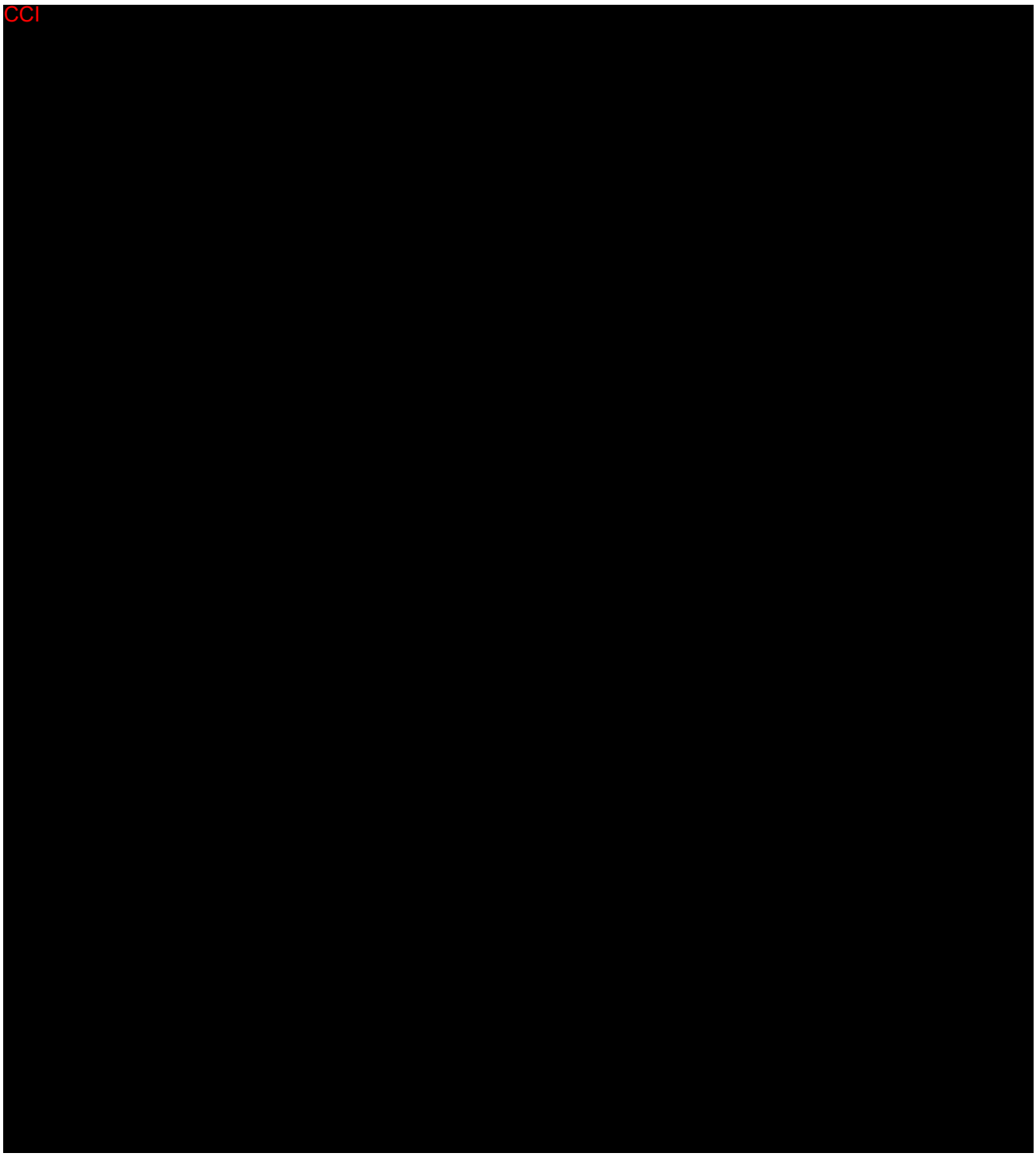

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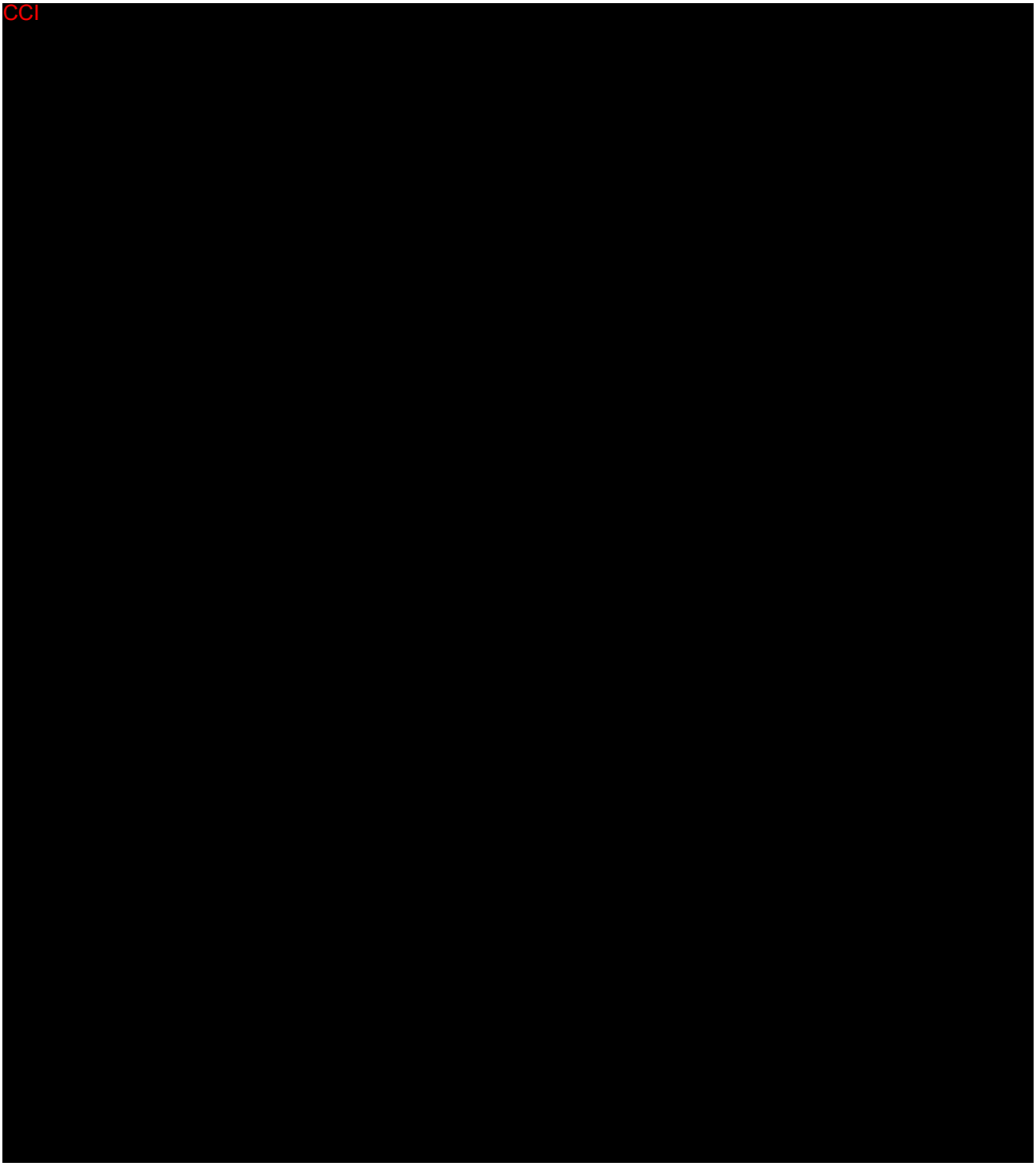

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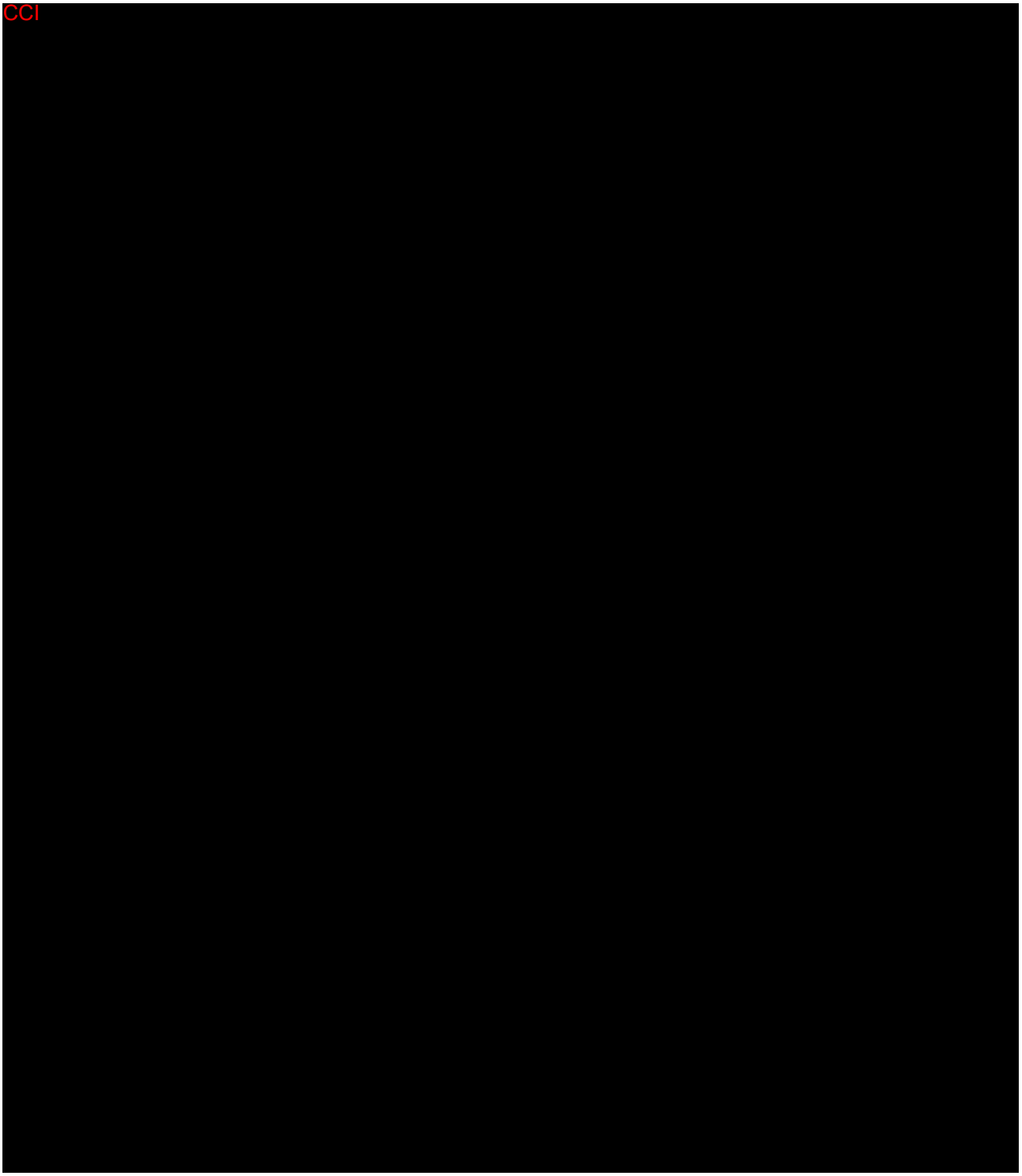

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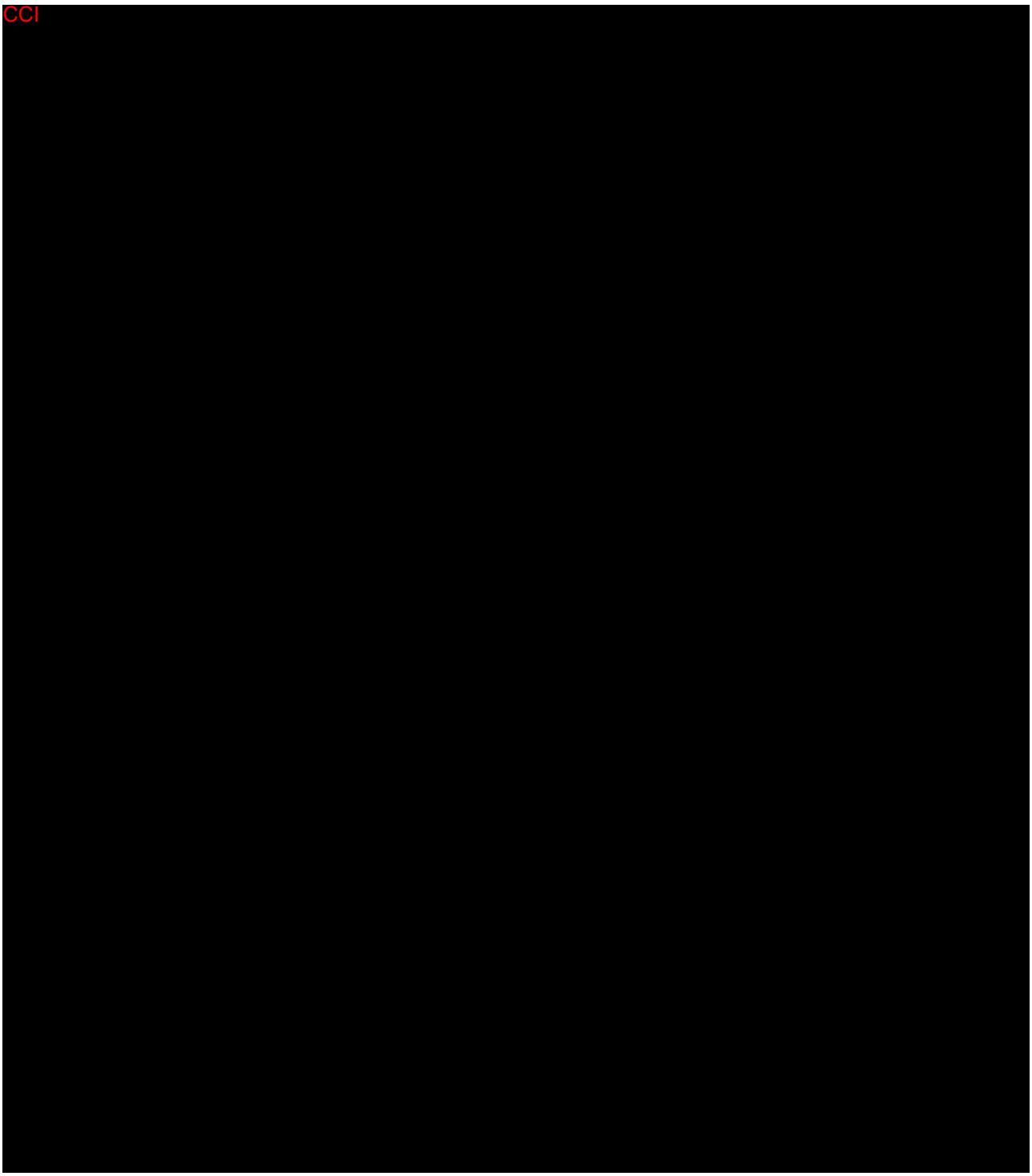

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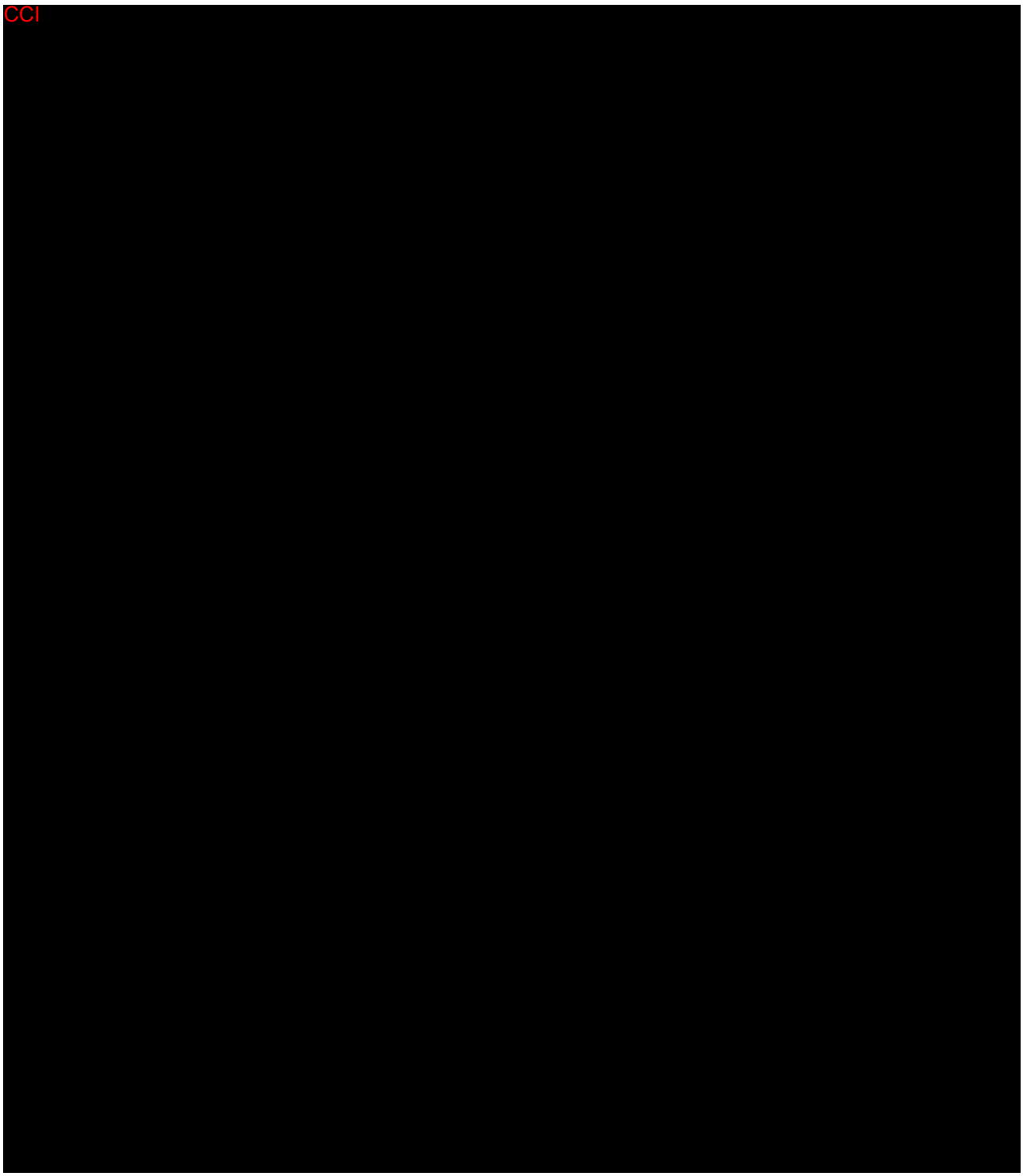

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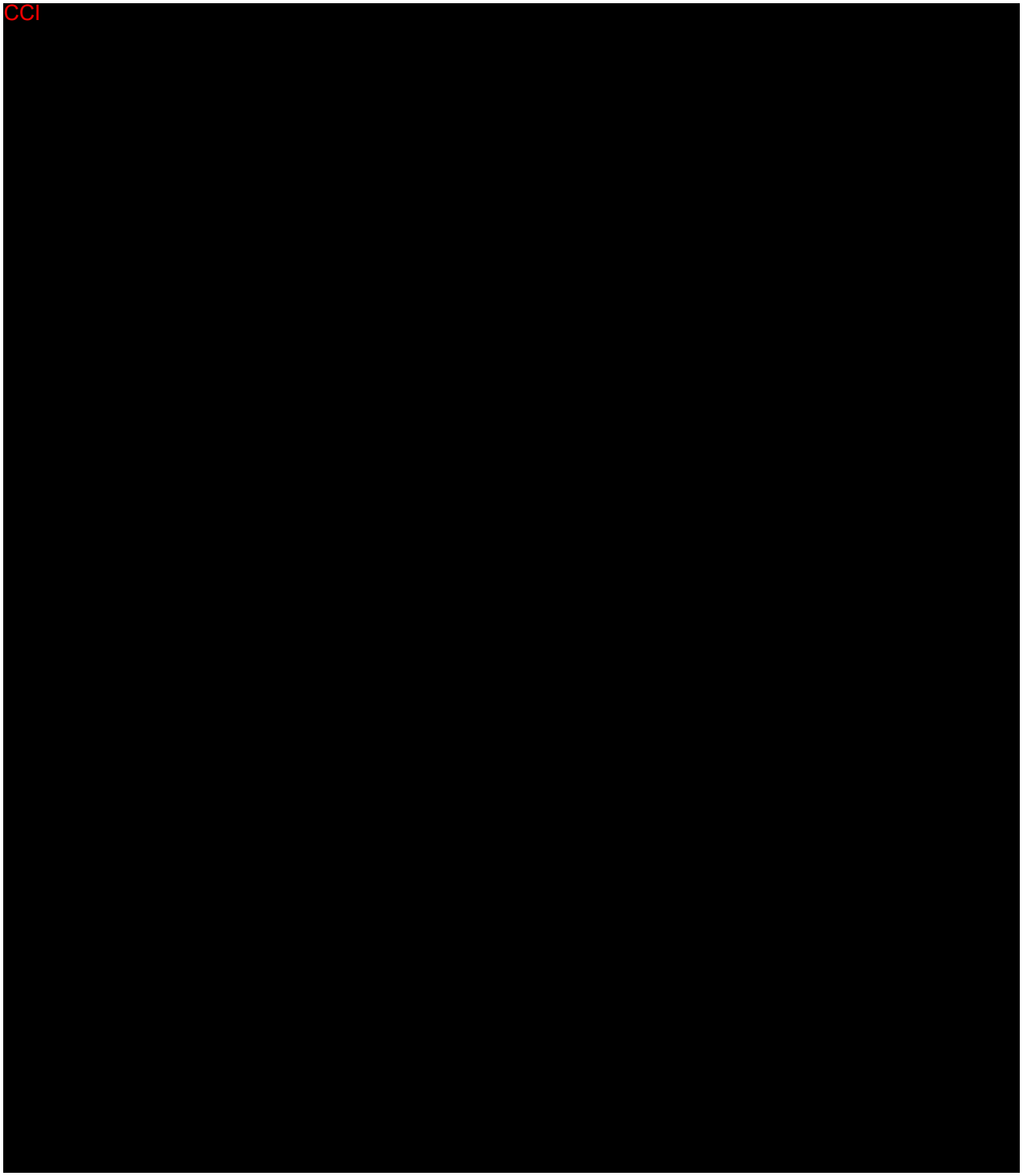

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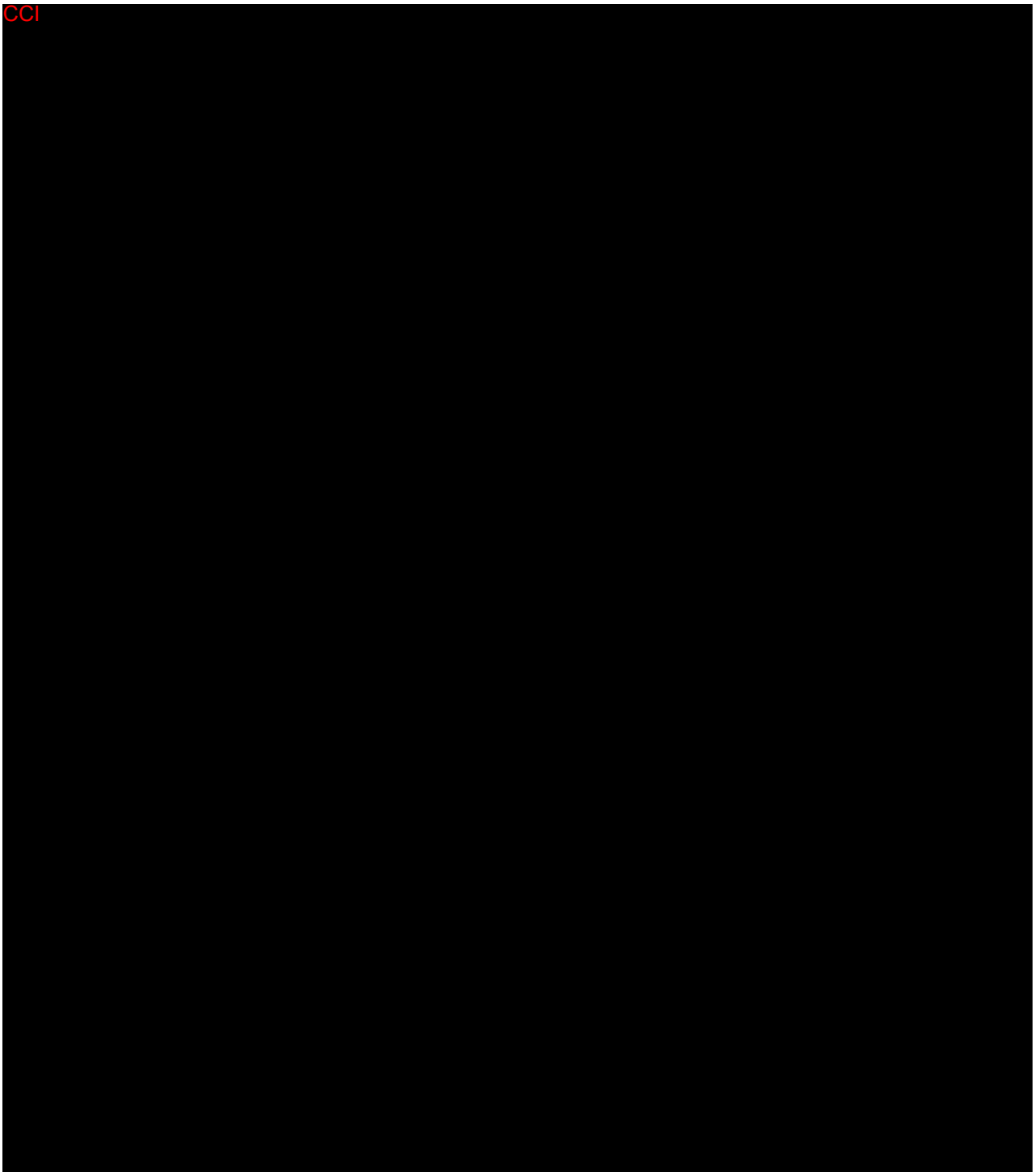


16.3.4. SENSITIVITY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

CCI [redacted]

16.3.5. SUPPLEMENTARY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

CCI [redacted]

16.4. ADDITIONAL EFFICACY

16.4.1. ADDITIONAL EFFICACY ENDPOINT

16.4.1.1. Incidence of All-Cause Mortality through Day 60

An additional efficacy endpoint is the incidence of all-cause mortality through Day 60, defined as the proportion of patients having died due to any cause before or on Day 60. Patients death before or at Day 60 will be based on data captured on the *Death Details* page of the eCRF.

16.4.2. MISSING DATA IMPUTATION METHOD FOR ADDITIONAL EFFICACY ENDPOINT

Patients with an unknown alive/death status at Day 60 will be considered as alive at Day 60.

16.4.3. ANALYSIS OF ADDITIONAL EFFICACY ENDPOINT

The number and percentage of patients alive and dead through Day 60 (refer to Section 16.4.1.1) along with the two-sided 95% CI for the percentage of patients dead through Day 60 will be provided by treatment arm. Primary reason of death will also be summarized by treatment arm. No statistical inference will be performed for this endpoint but treatment effect estimate (i.e., relative risk, odds ratio) and two-sided 95% CI will be provided.

16.4.4. SENSITIVITY ANALYSES FOR ADDITIONAL EFFICACY ENDPOINT

No sensitivity analyses will be performed for the additional efficacy endpoint.

16.4.5. SUPPLEMENTARY ANALYSES FOR ADDITIONAL EFFICACY ENDPOINT

The time to all-cause death through Day 60, in days, will be derived as follows:

- Time to all-cause mortality through Day 60 (days) =
  (Date of death / Date of censoring - Date of Study Day 1 [refer to Section 6.1]) + 1.

The date of death will be taken from data captured on the *Death Details* page of the eCRF.

For patients who were alive or patients with an unknown alive status at the time of the analysis due to missing data, time to all-cause mortality will be censored at the latest date on which the patient was known to be alive before or on Day 60. The last date the patient was known to be alive will be the latest date collected on any page of the eCRF. For patients who discontinued from the study before Day 60, time to all-cause mortality will be censored at the date of study discontinuation, as captured on the *Disposition* page of the eCRF.

Number and percentage of patients with and without the event will be presented by randomized treatment arm. For patients who did not meet the event, the main reason for censoring (refer to Section 16.1.1) will be summarized similarly.

The incidence of all-cause mortality through Day 60 along with its two-sided 95% CI by treatment arm will then be estimated using Kaplan-Meier survival curves of the time to all-cause mortality through Day 60. Kaplan-Meier survival curves by treatment arm will also be provided.

The 25th percentile, 50th percentile (median), and 75th percentile of time to all-cause mortality (days) with the corresponding two-sided 95% CIs based on the Kaplan-Meier survival curves for each treatment arm will be presented. The estimate of the SEs will be computed using Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation.

Finally, a Cox proportional hazard model will be performed, including the baseline clinical severity of 2 on the 8-point ordinal scale for clinical severity (yes or no), remdesivir use at baseline (yes or no) stratification variables, both as captured on the IWRS, country (region), and treatment arm as factors. Ties will be handled using the exact method. The hazard ratio of the candidate agent plus SoC vs. placebo plus SoC and its associated two-sided 95% CI will be provided.

16.5. INTERIM ANALYSIS

16.5.1. INTERIM ANALYSIS FOR FUTILITY

Each candidate agent may be evaluated for futility at up to two IAs.

The IAs will be based on analyses of the primary efficacy endpoint (refer to Section 16.1.1), using the analysis methods described in Section 16.1.3.

The IAs are planned at information fractions of approximately 25% and 55% of expected number of confirmed clinical recoveries (refer to Table 1), i.e., after approximately 123 and 270 patients have met the primary endpoint of confirmed clinical recovery on a particular candidate agent plus SoC and its contemporaneous placebo plus SoC, respectively. However, the timing of these IAs may be adjusted due to operational considerations, e.g., actual enrollment rate.

For the IAs, a Pocock beta spending function will be used for non-binding futility boundary specification. This strategy will allow for ineffective agents to be identified early for discontinuation of further evaluation. Assuming no treatment effect for a candidate agent plus SoC arm compared with placebo plus SoC patients included in the control arm of the candidate agent, there is a 49.7% chance that enrolment to this agent is stopped at the first IA and 34.6% chance at the second IA. Under the scenario that treatment has a negative effect on outcome (refer to Table 2), these probabilities become 72.3% and 24.7%, respectively.

The primary analysis for a candidate agent will occur after 350 patients have been randomized to a particular candidate agent plus SoC and have had the opportunity to complete the Day 29 visit, when approximately 490 confirmed clinical recovery events are expected to have been observed in total across the candidate plus SoC arm and placebo plus SoC patients included in the control arm of the candidate agent, unless a candidate agent is stopped early for futility. The final analysis of a candidate agent will occur after all patients randomized to that candidate agent plus Soc and the concurrent placebo plus SoC controls have had the opportunity to complete the Day 60 visit.

Table 1 and Table 2 present a summary of futility incremental probabilities at the first interim and second interim analyses together with Pocock futility boundaries in the scenario of 88.3% estimated power when the IAs occur at information fraction of 25% and 55% of expected number of recoveries, respectively.

Table 1 Summary of Futility Probabilities and Boundaries with 88.3% Power using Pocock Futility Boundaries

Analysis	Total Number of Events (Information Fraction)	Boundary of Futility, Non-binding (HR)	Boundary of Futility, Non-binding (p-value)	Incremental Probability to Declare Futility under the Null (HR=1)
First Interim	123 (25%)	≤ 0.998	0.503	0.497
Second Interim	270 (55%)	≤ 1.121	0.175	0.346

HR=hazard ratio.
Assume 1-sided α of 0.025.
Interim analyses using Pocock futility boundaries at 25% and 55% information fraction.
HR boundaries are translated from p-values, dependent of relative timing, and will be re-calculated for IDMC.

Table 2 Summary of Futility Probabilities and Boundaries with 88.3% Power using Pocock Futility Boundaries for the Negative Treatment Scenario (HR=0.9)

Analysis	Total Number of Events (Information Fraction)	Boundary of Futility, Non-binding (HR)	Boundary of Futility, Non-binding (p-value)	Incremental Probability to Declare Futility under the Negative Treatment Effect Scenario (HR=0.9)
First Interim	123 (25%)	≤ 0.998	0.503	0.723
Second Interim	270 (55%)	≤ 1.121	0.175	0.247

HR=hazard ratio.
Assume 1-sided α of 0.025.
Interim analyses using Pocock futility boundaries at 25% and 55% information fraction.
HR boundaries are translated from p-values, dependent of relative timing, and will be re-calculated for IDMC.

17. SAFETY ENDPOINTS

All safety summaries will be presented by treatment arm based on the safety analysis set. Further, for each sub-protocol, separate summaries will also be presented for patients randomized to the placebo plus SoC treatment group of the sub-protocol.

There will be no statistical comparisons between the treatment arms for safety data.

17.1. ADVERSE EVENTS

Each AE will be classified as either:

- Prior, defined as any AE that started or worsened in severity on or after the date of signed informed consent but before the first dose of study drug;
- Treatment-emergent, defined as any AE that started or worsened in severity on or after the first dose of study drug.

If time of the first dose of study drug and time of start of AEs are available, then the times will be taken into account for determining TEAEs. Refer to Appendix 1 for handling of partial and completely missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

AEs will be coded using the MedDRA dictionary, version 23.1 or later. Summaries by System Organ Class and PT will be sorted as follows: System Organ Classes will be sorted in alphabetical order and within each System Organ Class, PTs will be sorted by decreasing order to total frequency.

An overall summary of number and percentage of patients within each of the categories described in the sub-sections below will be provided by treatment arm. Should a patient experience multiple events within a category, the patient will be counted only once for that category. Additionally, the risk difference of the overall incidence rates of serious TEAEs and overall incidence rates of AESIs (when applicable for a sub-protocol) between treatment and control arms will be presented along with its 95% two-sided Wald CI.

All AEs (prior and TEAE) will be listed.

17.1.1. ALL TEAEs

Number and percentage of patients with at least one TEAE will be presented by System Organ Class and PT. Should a patient experience multiple events within a System Organ Class or PT, the patient will be counted only once for that System Organ Class or PT.

Number and percentage of patients with at least one TEAE will be broken down further separately by maximum severity (CTCAE Grades 1-5), CTCAE Grade ≥3, relationship to study drug (not related and related), and relationship to non-study drug (not related and related).

17.1.1.1. CTC Grading for AEs

Toxicity will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or fatal (Grade 5) according to the CTCAE, version 5:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Should a patient experience multiple events within a System Organ Class or PT, only the patient's worst CTCAE grade will be counted for that System Organ Class or PT.

17.1.1.2. Relationship to Study Drug, Non-Study Drug, and Study Procedure

Relationship to study drug, relationship to non-study drug, and relationship to study procedure, as indicated by the Investigator, will be classified as unrelated or related.

Should a patient experience multiple events within a System Organ Class or PT, only the patient's worst relationship (i.e., related) will be counted for that System Organ Class or PT.

TEAEs will not be summarized by the relationship to study procedure, but relationship to study procedure will be listed.

17.1.2. FATAL ADVERSE EVENTS

Fatal TEAEs are those events which are recorded as *Fatal* or with a CTCAE grade of 5 on the *Adverse Events* page of the eCRF. A summary of fatal TEAEs by System Organ Class and PT will be prepared.

A listing of all fatal AEs will be provided.

17.1.3. SERIOUS ADVERSE EVENTS

SAEs are those events recorded as *Serious* on the *Adverse Events* page of the eCRF. A summary of serious TEAEs by System Organ Class and PT will be prepared. Should a patient experience multiple events within a System Organ Class or PT, the patient will be counted only once for that System Organ Class or PT.

A listing of all SAEs will be provided

17.1.4. MOST COMMON NON-SERIOUS ADVERSE EVENTS

Number and percentage of patients with at least one most common non-serious TEAE will be presented by PT, where most common is defined as a PT with at least 5% of patients in at least one treatment arm. Should a patient experience multiple events within a PT, the patient will be counted only once for that PT.

17.1.5. TEAES LEADING TO DOSE MODIFICATIONS

TEAEs leading to dose modification are those events recorded with "*Action Taken with study treatment*" on the *Adverse Events* pages of the eCRF of any of the following: *Dose increased*, *Dose reduced*, *Dose rate reduced,* or *Drug interrupted*. A summary of TEAEs leading to dose modification by System Organ Class and PT will be prepared. Should a patient experience multiple events within a System Organ Class or PT, the patient will be counted only once for that System Organ Class or PT.

17.1.6. TEAES LEADING TO DISCONTINUATION OF STUDY TREATMENT

TEAEs leading to permanent discontinuation of study treatment are those events recorded with *Action Taken with study treatment* of *Drug withdrawal* on the *Adverse Events* page of the eCRF. A summary of TEAEs leading to permanent discontinuation of study drug by System Organ Class and PT will be prepared. Should a patient experience multiple events within a System Organ Class or PT, the patient will be counted only once for that System Organ Class or PT.

A listing of all AEs leading to permanent discontinuation of study drug will be provided.

17.1.7. AESIS

For applicable sub-protocols, refer to sub-protocol SAP for more details.

17.2. LABORATORY EVALUATIONS

A serum or urine pregnancy test will be performed at screening. Hematology, coagulation, and chemistry (including cardiac enzymes and liver function tests) laboratory tests will be performed as per the schedule of events (refer to the example schedule of events in Section 1.3 of the master protocol but note that each sub-protocol will have its own schedule of events).

A list of laboratory tests to be included in the outputs is included in Appendix 5. It is to be noted that additional laboratory tests might be collected in a sub-protocol.

Results of quantitative laboratory tests reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. Observed values will then be normalized (refer to Section 17.2.1) before being summarized and changes from baseline will be computed based on the normalized observed values.

The following summaries will be provided by treatment arm for each hematology, coagulation, and chemistry test:

- Observed, change, and percent change from baseline values in Standard International (SI) units by visit (for quantitative tests)
- Box and whisker plots over time in SI units (for selected quantitative tests at IDMC safety data review meetings and IAs only)
- Shift from baseline to the worst post-baseline observed value according to the CTCAE toxicity grades (for quantitative tests with available CTCAE toxicity grades; refer to Section 17.2.2)
- Listing of patients with at least one laboratory observed value meeting a CTCAE toxicity grade ≥ 3 (for quantitative tests with available CTCAE toxicity grades; refer to Section 17.2.2)
- Shifts from baseline to the maximum/minimum post-baseline observed value according to reference range criteria (for quantitative tests without CTCAE toxicity grades; refer to Section 17.2.3)
- Listing of patients with at least one abnormal laboratory observed value outside the reference range criteria (for quantitative tests without CTCAE toxicity grades; refer to Section 17.2.3)
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-baseline total bilirubin observed value categorized

as < 2 x ULN or ≥ 2 x ULN

- Scatter plots of the maximum post-baseline observed value in ALT value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN
- Scatter plots of the maximum post-baseline observed value in AST value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN
- A listing of patients with at least one observed value in ALT value > 3 x ULN, AST value > 3 x ULN or TBL value ≥ 2 x ULN will be provided

17.2.1. LABORATORY NORMALIZATION

If a laboratory test has different reference ranges in the database, observed values of all patients will first be standardized to a common standard unit and then, normalized to a common set of standardized reference range using the location-scale normalization formula (Chuang-Stein, 1992):

- $y = L_y + (x - L_X)\frac{(U_Y - L_Y)}{(U_X - L_X)}$

where:

- y = normalized and standardized observed value;
- x = standardized observed value;
- L_Y = Lower limit of the reference range chosen to be the common standardized reference range;
- U_Y = Upper limit of the reference range chosen to be the common standardized reference range;
- L_X = Lower limit of the reference range associated with the standardized observed value;
- U_X = Upper limit of the reference range associated with the standardized observed value.

It is to be noted that the choice of the common standardized reference range is arbitrary.

17.2.2. CTCAE TOXICITY GRADES

Quantitative laboratory tests with available CTCAE toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to Appendix 6 for each test toxicity grade criteria):

- Grade 1 (i.e., mild);
- Grade 2 (i.e., moderate);
- Grade 3 (i.e., severe);
- Grade 4 (i.e., life-threatening);
- Grade 5 (i.e., death).

Although not defined in the CTCAE toxicity grading system, version 5, non-missing laboratory test results not meeting any of the 5 grades defined in the CTCAE toxicity grading system will be categorized as 'No Event' for the purpose of the shift from baseline summaries.

17.2.3. Laboratory Reference Ranges

Quantitative laboratory tests will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range

17.3. Vital Signs

The following vital sign parameters will be collected as per the schedule of events (refer to the example schedule of events in Section 1.3 of the master protocol, but note that each sub-protocol will have its own schedule of events):

- Systolic blood pressure (SBP) (mmHg);
- Diastolic blood pressure (DBP) (mmHg);
- Pulse rate (beats per minute [bpm]);
- Oxygen saturation (%);
- FiO_2 (%);

- Respiratory rate (breaths/min);
- Body temperature (ºC).

The following summaries will be provided by treatment arm for each vital sign parameter:

- Observed and change from baseline values by visit;
- Number and percentages of patients with at least one markedly abnormal post-baseline observed value/change from baseline (refer to Section 17.3.1);
- Listing of patients with at least one markedly abnormal observed value/change from baseline (refer to Section 17.3.1).

17.3.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal vital sign observed values and/or change from baseline will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from Baseline ≤ -20 mmHg	≥ 180 mmHg AND change from Baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from Baseline ≤ -15 mmHg	≥ 105 mmHg AND change from Baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND change from Baseline ≤ -15 bpm	≥ 120 bpm AND change from Baseline ≥ 15 bpm
Oxygen saturation	%	< 94 %	Not applicable
Body temperature	°C	Not applicable	≥ 38.3 °C AND change from Baseline ≥ 1.1 °C

17.4. ECG EVALUATIONS

12-lead electrocardiograms (ECGs) will be performed at screening only to assess exclusion criteria 3 of the master protocol. As such ECG data will not be assessed as a safety parameter.

17.5. PHYSICAL EXAMINATION

A general physical examination will be performed at screening only. As such, physical examination will not be assessed as a safety parameter.

18. DATA NOT SUMMARIZED OR PRESENTED

Data that will not be summarized or listed are:

- Reason for screen failure;
- Inclusion/exclusion criteria;
- SARS-CoV-2 test results;
- Pharmacogenetics sampling;
- Pregnancy test results;
- Screening ECG parameters;
- Screening physical examination;
- Contact information;
- Comments.

These data will be available in the Study Data Tabulation Model (SDTM) datasets.

19. REFERENCES

Brookmeyer R, Crowley J. A (1982) Confidence Interval for the Median Survival Time. Biometrics 38:29-41.

Chuang-Stein C (1992). Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal 26(1);77-84.

Lipkovich I, Ratitch B, and O'Kelly M (2016). Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. Pharmaceutical Statistics 15;216-229. DOI:10.1002/pst.1738

Moscovici J and Ratitch B (2017). Combining Survival Analysis Results after Multiple Imputation of Censored Event Times. PharmaSUG-Paper SP05.

Royal College of Physicians (2017). National Early Warning Score (NEWS) 2: Standardizing the Assessment of Acute-illness Severity in the NHS – Updated Report of a Working Party. London. https://www.rcplondon.ac.uk/file/8504/download [accessed 08 May 2020].

Rubin DB (1987). Multiple Imputations for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc.

APPENDIX 1 PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	END DATE	ACTION
Known	Known/Partial/ Missing	If AE start date/time < date/time of first dose of study drug, then not a TEAE; Otherwise, TEAE.
Partial, but known components show that AE started before date of first dose of study drug	Known/Partial/ Missing	Not TEAE.
Partial and known components show that AE started on or after date of first dose of study drug	Known/Partial/ Missing	Assume TEAE.
Missing	Known	If AE end date/time < date/time of first dose of study drug, then not TEAE; Otherwise, TEAE.
	Partial	If known components of AE end date/time show that AE stopped before date/time of first dose of study drug, then not TEAE; Otherwise, TEAE.
	Missing	Assume TEAE.

Note: If an AE started prior to first dose of study drug but worsened after the first dose of study drug, it will be reported as a separate adverse event with new AE start date/time.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known, Partial or Missing	Known	If medication stop date < date of first dose of study drug, assign as prior; Otherwise, assign as concomitant
	Partial	If known components of medication stop date show that medication stopped before date of first dose of study drug, assign as prior; Otherwise, assign as concomitant
	Missing, or ongoing	Can never be assigned as prior, therefore assign as concomitant.

APPENDIX 2 PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm.

SPELLING FORMAT

English US.

PAPER SIZE, ORIENTATION, AND MARGINS

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

FONTS

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

PRESENTATION OF TREATMENT ARMS

For outputs, treatment arms will be represented as follows and in the given order:

Treatment arm	Tables and Graphs	Listings
<<Agent>> plus SoC	1	1
Placebo plus SoC	2	2
Total [1]	3	n/a
Screen Failure	n/a	3

[1] Not applicable for efficacy tables, safety tables and graphs.

PRESENTATION OF NOMINAL VISITS

For outputs, nominal visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scrn
Baseline	Base
Day x, where x = 1 to 29	Day x, where x= 1 to 29
Day 60	Day 60

DESCRIPTIVE STATISTICS

If the original data has N decimal places, then the summary statistics will have the following number of decimal places:

- Minimum and maximum: N;
- Mean, Q1, median, Q3, lower and upper bounds of two-sided 95% CI: N + 1;
- SD and SE: N + 2

PERCENTAGES

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

P-VALUES

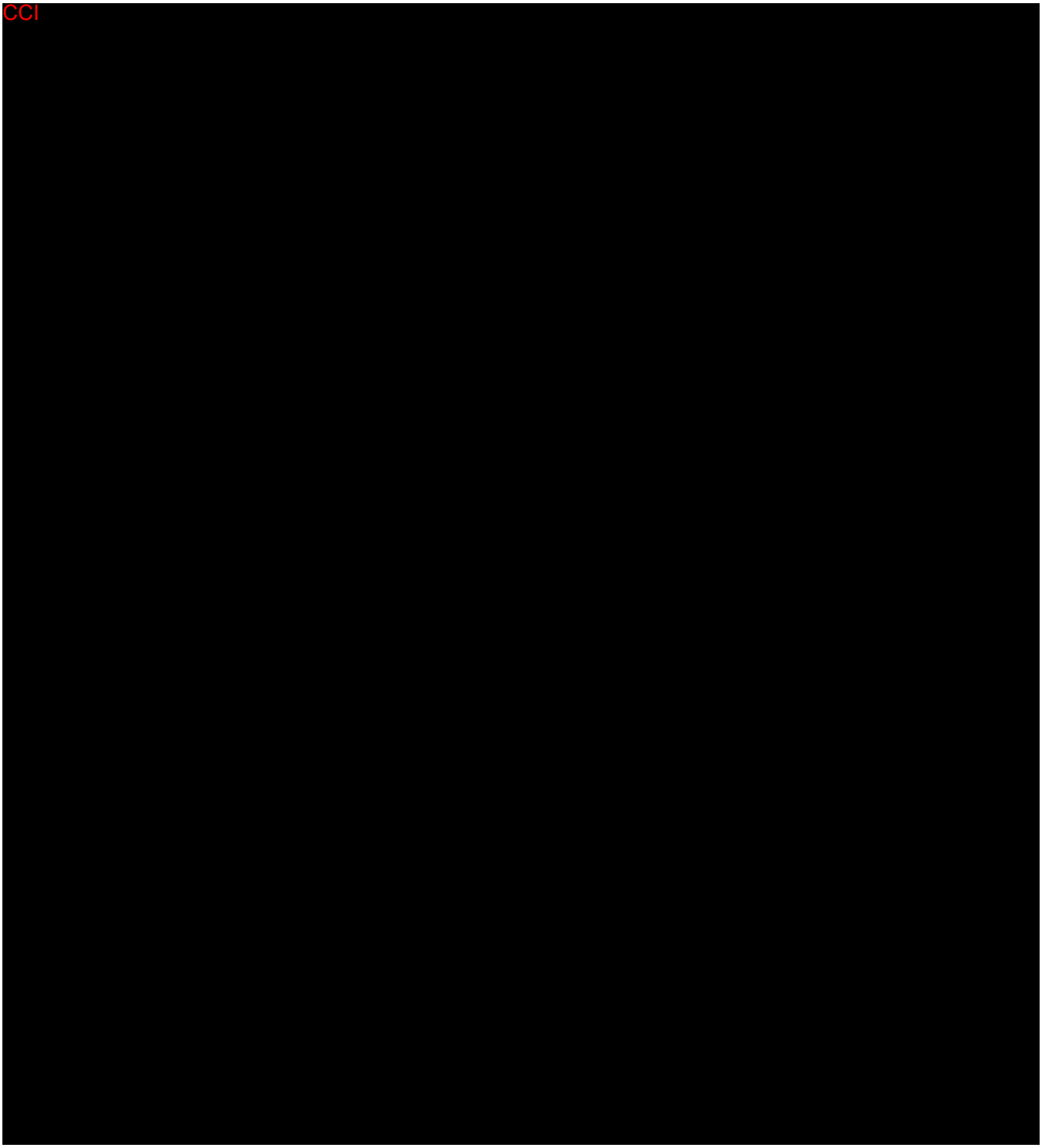
p-values will be reported to three decimal places. Rounding will be applied, except for the p-values < 0.001 which will be presented as '< 0.001' and p-values < 1.000 but > 0.999 which will be presented as '> 0.999'.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Randomized treatment arm (or treatment received if it's a safety output)
- Patient ID
- Parameter, when applicable
- Date/Time, when applicable
- Timepoint, when applicable

CCI



APPENDIX 4 VASOPRESSOR DRUG CODES AS PER THE WHO DRUG GLOBAL DICTIONARY, SEPTEMBER 2020, VERSION B3

Drug code	Product Name	Active Ingredients
00360702173	3-hydroxytyramine HCL	Dopamine hydrochloride
00360702174	3-hydroxytyramine hydrochloride	Dopamine hydrochloride
00493402134	46236	Dobutamine hydrochloride
00360702138	A si ke ding	Dopamine hydrochloride
00360702012	Abbodop	Dopamine hydrochloride
00493402057	Abbott dobutamine hydrochloride	Dobutamine hydrochloride
00360702103	Abbott dopamine hcl	Dopamine hydrochloride
00360702024	Actopamin	Dopamine hydrochloride
00493402099	Adregotec	Dobutamine hydrochloride
00003902019	Adreject	Epinephrine hydrochloride
00003902041	Adren	Epinephrine hydrochloride
00003901075	Adrenaclick	Epinephrine
00003901055	Adrenal	Epinephrine
00003901002	Adrenalin	Epinephrine
00003902015	Adrenalin	Epinephrine hydrochloride
00003903015	Adrenalin	Epinephrine bitartrate
00003903051	Adrenalin aguettant	Epinephrine bitartrate
00003901069	Adrenalin apotek ab	Epinephrine
00003903057	Adrenalin bradex	Epinephrine bitartrate
00003901063	ADRENALIN Carino	Epinephrine
00003901027	Adrenalin chl sankyo	Epinephrine
00003902052	Adrenalin chloride	Epinephrine hydrochloride
00003902031	Adrenalin cl	Epinephrine hydrochloride
00003901103	Adrenalin galen	Epinephrine
00003902026	Adrenalin hcl	Epinephrine hydrochloride
00003902063	Adrenalin hydrochloride	Epinephrine hydrochloride
00003903031	Adrenalin hydrotar	Epinephrine bitartrate
00003902018	Adrenalin IMS	Epinephrine hydrochloride

Drug code	Product Name	Active Ingredients
00003903040	Adrenalin Infectopharm	Epinephrine bitartrate
00003901062	Adrenalin Injeel	Epinephrine
00003903038	Adrenalin Jenapharm	Epinephrine bitartrate
00003901101	Adrenalin labatec	Epinephrine
00003903010	Adrenalin Leiras	Epinephrine bitartrate
00003903048	Adrenalin Martindale Pharma	Epinephrine bitartrate
00003901026	Adrenalin medica	Epinephrine
00003903008	Adrenalin medihal	Epinephrine bitartrate
00003903014	Adrenalin Merck NM	Epinephrine bitartrate
00003903042	Adrenalin mylan	Epinephrine bitartrate
00003901106	Adrenalin osel	Epinephrine
00003901107	Adrenalin solofarm	Epinephrine
00003903052	Adrenalin stragen	Epinephrine bitartrate
00003901022	Adrenalin streuli	Epinephrine
00003903033	Adrenalin Tartrate	Epinephrine bitartrate
00003903024	Adrenalina	Epinephrine bitartrate
00003902037	Adrenalina	Epinephrine hydrochloride
00003901019	Adrenalina	Epinephrine
00003903054	Adrenalina Aguettant	Epinephrine bitartrate
00003902042	Adrenalina apolo	Epinephrine hydrochloride
00003901047	Adrenalina biol	Epinephrine
00003902057	Adrenalina braun	Epinephrine hydrochloride
00003902048	Adrenalina clorhidrato	Epinephrine hydrochloride
00003901048	Adrenalina fada	Epinephrine
00003901066	Adrenalina galenica senese	Epinephrine
00003902013	Adrenalina level	Epinephrine hydrochloride
00003902007	Adrenalina llorente	Epinephrine hydrochloride
00003902014	Adrenalina miro	Epinephrine hydrochloride
00003902065	Adrenalina ogna	Epinephrine hydrochloride
00003902028	Adrenalina pisa	Epinephrine hydrochloride
00003901021	Adrenalina sintetica	Epinephrine
00003903045	Adrenalina wzf	Epinephrine bitartrate
00003903005	Adrenaline	Epinephrine bitartrate

Drug code	Product Name	Active Ingredients
00003902047	Adrenaline	Epinephrine hydrochloride
00003901003	Adrenaline	Epinephrine
00003903055	Adrenaline (Epinephrine) Injection BP 1:1000	Epinephrine bitartrate
00003902060	Adrenaline (HCl) Sterop	Epinephrine hydrochloride
00003901089	Adrenaline (tartrate) Aguettant	Epinephrine
00003903037	Adrenaline (Tartrate) Sterop	Epinephrine bitartrate
00003903026	Adrenaline acid tartrate	Epinephrine bitartrate
00003901040	Adrenaline aguettant	Epinephrine
00003901094	Adrenaline aurum	Epinephrine
00003901041	Adrenaline b.braun	Epinephrine
00003901042	Adrenaline cooper	Epinephrine
00003903036	Adrenaline Demo	Epinephrine bitartrate
00003903056	Adrenaline fresenius	Epinephrine bitartrate
00003902025	Adrenaline hcl	Epinephrine hydrochloride
00003902053	Adrenaline hydrochloride	Epinephrine hydrochloride
00003901098	Adrenaline jr mylan	Epinephrine
00003901072	Adrenaline Lavois	Epinephrine
00003902072	Adrenaline life	Epinephrine hydrochloride
00003903046	Adrenaline link	Epinephrine bitartrate
00003901091	Adrenaline martindale	Epinephrine
00003901099	Adrenaline mylan	Epinephrine
00003902062	Adrenaline Parke-Davis	Epinephrine hydrochloride
00003901058	Adrenaline pch	Epinephrine
00003903049	Adrenaline renaudin	Epinephrine bitartrate
00003901100	Adrenaline solopharm	Epinephrine
00003901093	Adrenaline sophar	Epinephrine
00003903043	Adrenaline tartrate	Epinephrine bitartrate
00003901102	Adrenaline/ariti	Epinephrine
00003902059	Adrenalini	Epinephrine hydrochloride
00003903029	Adrenalini bitartras	Epinephrine bitartrate
00003902068	Adrenalini hcl	Epinephrine hydrochloride
00003902069	Adrenalini hydrochloridum	Epinephrine hydrochloride
00003902056	Adrenalini hydrotartras	Epinephrine hydrochloride

Drug code	Product Name	Active Ingredients
00003903030	Adrenalini hydrotartras	Epinephrine bitartrate
00003903032	Adrenalini tartras	Epinephrine bitartrate
00003904003	Adrenalin-neutrale	Epinephryl borate
00003903016	Adrenalinum	Epinephrine bitartrate
00003901081	Adrenalinum	Epinephrine
00003901087	Adrenol	Epinephrine
00127502065	Adrenor	Norepinephrine bitartrate
00003903027	Adrenotone	Epinephrine bitartrate
00003901051	Adrine	Epinephrine
00003901076	Adrinor	Epinephrine
00127501007	ADS-Noltron	Norepinephrine
00003901097	Adyphren amp kit	Epinephrine
00003901085	Allerject	Epinephrine
00003901061	Altellus	Epinephrine
00493402104	An chang	Dobutamine hydrochloride
00003902051	Anaguard	Epinephrine hydrochloride
00003902012	Ana-guard	Epinephrine hydrochloride
00003901045	Anahelp	Epinephrine
00003901044	Anakit	Epinephrine
00003901031	Anapen	Epinephrine
00003902045	Anapen	Epinephrine hydrochloride
01872201012	Antidiuretic hormone	Vasopressin
00493402085	Ao wan yuan	Dobutamine hydrochloride
00493402067	Ao wang yan	Dobutamine hydrochloride
00360702128	Aprical dopamida	Dopamine hydrochloride
01872201024	Argipresina	Vasopressin
01872201016	Argipressin	Vasopressin
00127503002	Arterenol	Norepinephrine hydrochloride
01872201018	Arterina	Vasopressin
00360702175	Asl-279	Dopamine hydrochloride
00003903035	Aspen Adrenaline	Epinephrine bitartrate
00003903004	Asthmahaler	Epinephrine bitartrate
00003901028	Asthsedan	Epinephrine

Drug code	Product Name	Active Ingredients
00003901073	Auvi q	Epinephrine
00360702159	Bagotropin	Dopamine hydrochloride
00127502064	Biemefrin	Norepinephrine bitartrate
00003902005	Bosmin	Epinephrine hydrochloride
00003901029	Bosmin	Epinephrine
00003901009	Bronkaid	Epinephrine
00003902032	Bronkaid	Epinephrine hydrochloride
00493402010	Bubucin	Dobutamine hydrochloride
00493402112	Butamine	Dobutamine hydrochloride
00493402143	Cardease	Dobutamine hydrochloride
00127502063	Cardenor	Norepinephrine bitartrate
00127502040	Cardiamed	Norepinephrine bitartrate
00493402118	Cardiforce	Dobutamine hydrochloride
00493402050	Cardiject	Dobutamine hydrochloride
00493402056	Cardiomin	Dobutamine hydrochloride
00360702105	Cardiopal	Dopamine hydrochloride
00493402149	Cardiotrex	Dobutamine hydrochloride
00493402160	Cardob	Dobutamine hydrochloride
00493402120	Cardomin	Dobutamine hydrochloride
00360702144	Cardopa	Dopamine hydrochloride
00360702016	Catabon	Dopamine hydrochloride
00360702152	Catherine	Dopamine hydrochloride
00360702038	Catherine amel	Dopamine hydrochloride
00003903058	CCM Adrenaline Injection	Epinephrine bitartrate
00360702109	Cetadop	Dopamine hydrochloride
00003901088	Chenpen	Epinephrine
00360702187	Clorhidrat de dopamina	Dopamine hydrochloride
00360702131	Clorhidrato dopamina	Dopamine hydrochloride
00493402037	Cloridrato de dobutamina	Dobutamine hydrochloride
00360702081	Cloridrato de dopamina	Dopamine hydrochloride
00360702066	Clorpamina	Dopamine hydrochloride
00360702151	Constriction	Dopamine hydrochloride
00493402152	Corbusin	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702167	Cordodopa	Dopamine hydrochloride
00360702170	Cordodopa Forte	Dopamine hydrochloride
00360702052	Corskool	Dopamine hydrochloride
01872201020	Cpressin p	Vasopressin
00360702013	Critpan	Dopamine hydrochloride
00493402025	Cryobutol	Dobutamine hydrochloride
00493402126	Dasomin	Dobutamine hydrochloride
00360702045	Dasomin	Dopamine hydrochloride
00003901049	Davinefrina	Epinephrine
00003901064	Denolin Adrenaline	Epinephrine
00493401002	Dobaden	Dobutamine
00493402093	Dobamin	Dobutamine hydrochloride
00493402044	Dobamine	Dobutamine hydrochloride
00493402088	Dobcard	Dobutamine hydrochloride
00493402052	Dobicard	Dobutamine hydrochloride
00493402147	Dobier s	Dobutamine hydrochloride
00493402109	Dobine	Dobutamine hydrochloride
00493402036	Dobtan	Dobutamine hydrochloride
00493402140	Dobuca	Dobutamine hydrochloride
00493402133	Dobucard	Dobutamine hydrochloride
00493402053	Dobucef	Dobutamine hydrochloride
00493402054	Dobucin	Dobutamine hydrochloride
00493402034	Dobucor	Dobutamine hydrochloride
00493402077	Dobuha	Dobutamine hydrochloride
00493402005	Dobuject	Dobutamine hydrochloride
00493402125	Dobulex	Dobutamine hydrochloride
00493402157	Dobulon	Dobutamine hydrochloride
00493402161	Dobumarc	Dobutamine hydrochloride
00493402151	Dobumean	Dobutamine hydrochloride
00493402045	Dobumin	Dobutamine hydrochloride
00493402137	Dobumine	Dobutamine hydrochloride
00493402116	Dobunex pf	Dobutamine hydrochloride
00493402021	Dobupum	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00493402017	Doburack	Dobutamine hydrochloride
00493402079	Doburak	Dobutamine hydrochloride
00493402043	Doburan	Dobutamine hydrochloride
00493402087	Dobusol	Dobutamine hydrochloride
00493402094	Dobustat	Dobutamine hydrochloride
00493402078	Dobutal	Dobutamine hydrochloride
00493402048	Dobutam	Dobutamine hydrochloride
00493402004	Dobutamin	Dobutamine hydrochloride
00493402012	Dobutamin abbott	Dobutamine hydrochloride
00493402089	Dobutamin Admeda	Dobutamine hydrochloride
00493402159	Dobutamin carinopharm	Dobutamine hydrochloride
00493402102	Dobutamin ebewe	Dobutamine hydrochloride
00493402013	Dobutamin Fresenius	Dobutamine hydrochloride
00493402059	Dobutamin giulini	Dobutamine hydrochloride
00493402130	Dobutamin hameln	Dobutamine hydrochloride
00493402022	Dobutamin hexal	Dobutamine hydrochloride
00493402106	Dobutamin ratiopharm	Dobutamine hydrochloride
00493401004	Dobutamina	Dobutamine
00493402040	Dobutamina	Dobutamine hydrochloride
00493402032	Dobutamina abbott	Dobutamine hydrochloride
00493402086	Dobutamina Aps	Dobutamine hydrochloride
00493402098	Dobutamina bioindustria	Dobutamine hydrochloride
00493402146	Dobutamina Claris	Dobutamine hydrochloride
00493402041	Dobutamina fabra	Dobutamine hydrochloride
00493402115	Dobutamina fu	Dobutamine hydrochloride
00493402138	Dobutamina Generis	Dobutamine hydrochloride
00493402141	Dobutamina genthon	Dobutamine hydrochloride
00493402024	Dobutamina gi pisa	Dobutamine hydrochloride
00493402026	Dobutamina gi tecn	Dobutamine hydrochloride
00493402139	Dobutamina gray	Dobutamine hydrochloride
00493402035	Dobutamina inibsa	Dobutamine hydrochloride
00493402023	Dobutamina kendric	Dobutamine hydrochloride
00493402132	Dobutamina Norgreen	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00493402156	Dobutamina panpharma	Dobutamine hydrochloride
00493402033	Dobutamina rovi	Dobutamine hydrochloride
00493402103	Dobutamina sanderson	Dobutamine hydrochloride
00493401001	Dobutamine	Dobutamine
00493402007	Dobutamine	Dobutamine hydrochloride
00493402062	Dobutamine abbott	Dobutamine hydrochloride
00493402075	Dobutamine Aguettant	Dobutamine hydrochloride
00493402063	Dobutamine antigen	Dobutamine hydrochloride
00493402047	Dobutamine baxter	Dobutamine hydrochloride
00493402068	Dobutamine CF	Dobutamine hydrochloride
00493402122	Dobutamine Claris	Dobutamine hydrochloride
00493402030	Dobutamine dakota	Dobutamine hydrochloride
00493402097	Dobutamine EG	Dobutamine hydrochloride
00493402155	Dobutamine fresenius	Dobutamine hydrochloride
00493402111	Dobutamine hameln	Dobutamine hydrochloride
00493402028	Dobutamine hcl	Dobutamine hydrochloride
00493402073	Dobutamine hcl DBL	Dobutamine hydrochloride
00493402072	Dobutamine hexal	Dobutamine hydrochloride
00493402001	Dobutamine Hydrochloride	Dobutamine hydrochloride
00493403001	Dobutamine lactobionate	Dobutamine lactobionate
00493402046	Dobutamine mayne pharma (ben)	Dobutamine hydrochloride
00493402029	Dobutamine merck	Dobutamine hydrochloride
00493402108	Dobutamine mylan	Dobutamine hydrochloride
00493402076	Dobutamine Panpharma	Dobutamine hydrochloride
00493402113	Dobutamine Qualimed	Dobutamine hydrochloride
00493402136	Dobutamine sdz	Dobutamine hydrochloride
00493402092	Dobutamine winthrop	Dobutamine hydrochloride
00493402049	Dobutamine-abbott	Dobutamine hydrochloride
00493402066	Dobutamine-bc	Dobutamine hydrochloride
00493402091	Dobutamin-hameln	Dobutamine hydrochloride
00493402135	Dobutamini hydrochloridum	Dobutamine hydrochloride
00493401003	Dobutaminum	Dobutamine
00493402039	Dobutamol	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00493402090	Dobutan	Dobutamine hydrochloride
00493402107	Dobutanil	Dobutamine hydrochloride
00493402144	Dobutasel	Dobutamine hydrochloride
00493402061	Dobutel	Dobutamine hydrochloride
00493402150	Dobuthaver	Dobutamine hydrochloride
00493402038	Dobutil	Dobutamine hydrochloride
00493402121	Dobutin	Dobutamine hydrochloride
00493402127	Dobutina	Dobutamine hydrochloride
00493402002	Dobutrex	Dobutamine hydrochloride
00493402080	Dobutrex k	Dobutamine hydrochloride
00493402096	Dobutrim	Dobutamine hydrochloride
00493402158	Dobutrust	Dobutamine hydrochloride
00493402071	Dobux	Dobutamine hydrochloride
00493402019	Dobux nichiiko	Dobutamine hydrochloride
00493402058	Dobuxin	Dobutamine hydrochloride
00493402124	Dobuzef	Dobutamine hydrochloride
00360702101	Docard	Dopamine hydrochloride
00360702064	Dofamin	Dopamine hydrochloride
00360702186	Dofamine	Dopamine hydrochloride
00360702172	Dofamine Ferein	Dopamine hydrochloride
00493402119	Dofuse	Dobutamine hydrochloride
00360702040	Dolpamil	Dopamine hydrochloride
00360702116	Domin	Dopamine hydrochloride
00360702093	Domine	Dopamine hydrochloride
00493402128	Dominic	Dobutamine hydrochloride
00360702014	Dominin	Dopamine hydrochloride
00360702162	Domins	Dopamine hydrochloride
00360702050	Donapan	Dopamine hydrochloride
00360702044	Doncal	Dopamine hydrochloride
00360702058	Dopa kit	Dopamine hydrochloride
00360702082	Dopabane	Dopamine hydrochloride
00360702185	Dopabas	Dopamine hydrochloride
00360702113	Dopac	Dopamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702161	Dopacef	Dopamine hydrochloride
00360702147	Dopacin	Dopamine hydrochloride
00360702083	Dopacris	Dopamine hydrochloride
00360702140	Dopadren	Dopamine hydrochloride
00360702178	Dopaglan	Dopamine hydrochloride
00360702143	Dopamax	Dopamine hydrochloride
00360702117	Dopamex	Dopamine hydrochloride
00360702003	Dopamin	Dopamine hydrochloride
00360702136	Dopamin Admeda	Dopamine hydrochloride
00360702030	Dopamin braun	Dopamine hydrochloride
00360702065	Dopamin ebewe	Dopamine hydrochloride
00360702029	Dopamin fresenius	Dopamine hydrochloride
00360702025	Dopamin giulini	Dopamine hydrochloride
00360702114	Dopamin hausmann	Dopamine hydrochloride
00360702070	Dopamin natter	Dopamine hydrochloride
00360702150	Dopamin Sintetica	Dopamine hydrochloride
00360702126	Dopamin solvay	Dopamine hydrochloride
00360701004	Dopamina	Dopamine
00360702080	Dopamina	Dopamine hydrochloride
00360702165	Dopamina 3m	Dopamine hydrochloride
00360702076	Dopamina abbott	Dopamine hydrochloride
00360702182	Dopamina basi	Dopamine hydrochloride
00360702168	Dopamina clorhidrato	Dopamine hydrochloride
00360702194	Dopamina cloridrato	Dopamine hydrochloride
00360702087	Dopamina duncan	Dopamine hydrochloride
00360702164	Dopamina exakta	Dopamine hydrochloride
00360702130	Dopamina fides	Dopamine hydrochloride
00360702160	Dopamina fu	Dopamine hydrochloride
00360702069	Dopamina gi zafiro	Dopamine hydrochloride
00360702181	Dopamina grifols	Dopamine hydrochloride
00360702068	Dopamina kendrick	Dopamine hydrochloride
00360702163	Dopamina northia	Dopamine hydrochloride
00360702078	Dopamina pht	Dopamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702077	Dopamina salf	Dopamine hydrochloride
00360702183	Dopamina surar pharma	Dopamine hydrochloride
00360701001	Dopamine	Dopamine
00360702007	Dopamine	Dopamine hydrochloride
00360702119	Dopamine abbott	Dopamine hydrochloride
00360702074	Dopamine aguettant	Dopamine hydrochloride
00360702095	Dopamine fresenius	Dopamine hydrochloride
00360702071	Dopamine hcl	Dopamine hydrochloride
00360702111	Dopamine hcl abbott	Dopamine hydrochloride
00360702102	Dopamine hcl-fresenius	Dopamine hydrochloride
00360702096	Dopamine hycrochloride	Dopamine hydrochloride
00360702001	Dopamine hydrochloride	Dopamine hydrochloride
00360702115	Dopamine hydrochloride dbl	Dopamine hydrochloride
00360702124	Dopamine hydrochloride kobayashi	Dopamine hydrochloride
00360702134	Dopamine Hydrochloride Mochida	Dopamine hydrochloride
00360702133	Dopamine Hydrochloride Shionogi	Dopamine hydrochloride
00360702073	Dopamine lucien	Dopamine hydrochloride
00360702075	Dopamine merck	Dopamine hydrochloride
00360702193	Dopamine mylan	Dopamine hydrochloride
00360702127	Dopamine nativelle	Dopamine hydrochloride
00360702146	Dopamine PCH	Dopamine hydrochloride
00360702072	Dopamine pierre fabre	Dopamine hydrochloride
00360702062	Dopamine premix	Dopamine hydrochloride
00360702135	Dopamine Renaudin	Dopamine hydrochloride
00360702057	Dopamine towa	Dopamine hydrochloride
00360702190	Dopamine/anfarm	Dopamine hydrochloride
00360702099	Dopamine-p	Dopamine hydrochloride
00360702100	Dopaminex	Dopamine hydrochloride
00360702176	Dopamini hydrochloridum	Dopamine hydrochloride
00360701003	Dopaminum	Dopamine
00360702129	Dopaminum hydrochloricum	Dopamine hydrochloride
00360702085	Dopamol	Dopamine hydrochloride
00360702094	Dopan	Dopamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702098	Dopaplus	Dopamine hydrochloride
00360702166	Dopaqard	Dopamine hydrochloride
00360702041	Doparalmin	Dopamine hydrochloride
00360702192	Dopasel	Dopamine hydrochloride
00360702092	Dopasin	Dopamine hydrochloride
00360702191	Dopasunny	Dopamine hydrochloride
00360702180	Dopatropin	Dopamine hydrochloride
00360702123	Dopavate	Dopamine hydrochloride
00360702195	Dopazef	Dopamine hydrochloride
00360702110	Doperba	Dopamine hydrochloride
00360702063	Dophamin	Dopamine hydrochloride
00360702120	Dopin	Dopamine hydrochloride
00360702106	Dopina	Dopamine hydrochloride
00360702097	Dopinga	Dopamine hydrochloride
00360702033	Dopmin	Dopamine hydrochloride
00360701002	Dopmin	Dopamine
00493402016	Dopmin	Dobutamine hydrochloride
00493402081	Dopmin-k	Dobutamine hydrochloride
00360702179	Dopnax	Dopamine hydrochloride
00360702088	Dopramine	Dopamine hydrochloride
00360702139	Dopress	Dopamine hydrochloride
00360702196	Doprina	Dopamine hydrochloride
00493402082	Doputamin	Dobutamine hydrochloride
00493402100	Doputamin Fuji	Dobutamine hydrochloride
00493402020	Doputamin h hexal	Dobutamine hydrochloride
00493402083	Doputamin k	Dobutamine hydrochloride
00493402101	Dotamin	Dobutamine hydrochloride
00493402055	Dotrex	Dobutamine hydrochloride
00493402145	Dotropina	Dobutamine hydrochloride
00003901079	Drenalin	Epinephrine
00127502068	Drenorep	Norepinephrine bitartrate
00493402148	Dubuject	Dobutamine hydrochloride
00493402114	Duvig	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702079	Dynatra	Dopamine hydrochloride
00360702021	Dynatra dopamine	Dopamine hydrochloride
00360702020	Dynos	Dopamine hydrochloride
00003902039	Dyspne inhalante	Epinephrine hydrochloride
00003901039	Dyspne-inhal	Epinephrine
00493402142	E.m.c. dobutamina	Dobutamine hydrochloride
00493402123	Easydobu	Dobutamine hydrochloride
00360702149	Easydopa	Dopamine hydrochloride
00003901065	Efrinalin	Epinephrine
00360702047	Elebumin	Dopamine hydrochloride
00003903047	Emerade	Epinephrine bitartrate
00003903044	Enatrate	Epinephrine bitartrate
01872201008	Encrise	Vasopressin
00003901096	Ephedrix	Epinephrine
00003902033	Epi e-z	Epinephrine hydrochloride
00003902034	Epi e-z pen jr.	Epinephrine hydrochloride
00003902071	Epibbas	Epinephrine hydrochloride
00003903034	Epifrin	Epinephrine bitartrate
00003902022	Epifrin	Epinephrine hydrochloride
00003904004	Epinal	Epinephryl borate
00003902049	Epinefrina	Epinephrine hydrochloride
00003901050	Epinefrina	Epinephrine
00003901001	Epinephrine	Epinephrine
00003902030	Epinephrine	Epinephrine hydrochloride
00003903006	Epinephrine	Epinephrine bitartrate
00003903001	Epinephrine bitartrate	Epinephrine bitartrate
00003902070	Epinephrine HCL	Epinephrine hydrochloride
00003902001	Epinephrine hydrochloride	Epinephrine hydrochloride
00003901070	Epinephrine minijet	Epinephrine
00003901108	Epinephrine professional	Epinephrine
00003901105	Epinephrinesnap v	Epinephrine
00003901077	Epinephrinum	Epinephrine
00003904001	Epinephryl borate	Epinephryl borate

Drug code	Product Name	Active Ingredients
00127504004	Epinor	Norepinephrine bitartrate monohydrate
00003901014	Epipen	Epinephrine
00003901082	Epipen 2-pak	Epinephrine
00003901084	Epipen jr	Epinephrine
00003901037	Epipen jr 2-pak	Epinephrine
00003901104	Epipen junior	Epinephrine
00003901020	Epiquick	Epinephrine
00003902043	Epiren	Epinephrine hydrochloride
00003902054	Epirenamin	Epinephrine hydrochloride
00003902064	Epirenin	Epinephrine hydrochloride
00003901086	Episnap	Epinephrine
00003901071	Epista	Epinephrine
00003903003	Epitrate	Epinephrine bitartrate
00003902073	Epix	Epinephrine hydrochloride
00003901024	Eppy	Epinephrine
00003904002	Eppy n	Epinephryl borate
00003901013	Eppy plus	Epinephrine
00360702022	Evetant	Dopamine hydrochloride
00360702059	Evetant hexal	Dopamine hydrochloride
00360702056	Evetant towa	Dopamine hydrochloride
00003902011	Fastjekt	Epinephrine hydrochloride
00003902038	Fastjekt junior	Epinephrine hydrochloride
00127502036	Fioritina	Norepinephrine bitartrate
00127502073	Forefrin	Norepinephrine bitartrate
00360702042	Gabans	Dopamine hydrochloride
00493402065	Gendobu	Dobutamine hydrochloride
00360702004	Giludop	Dopamine hydrochloride
00003902066	Gingi pak z twist	Epinephrine hydrochloride
00003901012	Gingipak	Epinephrine
00360702156	Gipamine	Dopamine hydrochloride
00003902027	Glaucon	Epinephrine hydrochloride
00003903011	Glaucon	Epinephrine bitartrate
00003902010	Glaufrin	Epinephrine hydrochloride

Drug code	Product Name	Active Ingredients
00003901015	Glauposine	Epinephrine
00127502028	Hemitartarato de Norepinefrina	Norepinephrine bitartrate
00493402015	Hercarenone d	Dobutamine hydrochloride
00360702086	Hettytropin	Dopamine hydrochloride
00003901046	Hydren	Epinephrine
00127502014	Hyponor	Norepinephrine bitartrate
00493402153	Imatim	Dobutamine hydrochloride
00003902023	Ims adrenaline	Epinephrine hydrochloride
00360702061	Ims dopamine	Dopamine hydrochloride
00360702112	Indop	Dopamine hydrochloride
00003902055	Infectokrupp	Epinephrine hydrochloride
00003903053	Infectokrupp	Epinephrine bitartrate
00127502034	Infunor	Norepinephrine bitartrate
00493402095	Inocard	Dobutamine hydrochloride
00493402131	Inodex	Dobutamine hydrochloride
00493402117	Inoject	Dobutamine hydrochloride
00360702090	Inophan	Dopamine hydrochloride
00360702118	Inopin	Dopamine hydrochloride
00493402027	Inotop	Dobutamine hydrochloride
00493402003	Inotrex	Dobutamine hydrochloride
00493402060	Inotrop	Dobutamine hydrochloride
00360702067	Inotropin	Dopamine hydrochloride
00360702084	Inotropisa	Dopamine hydrochloride
00360702005	Inovan	Dopamine hydrochloride
00360702002	Intropin	Dopamine hydrochloride
00360702060	Intropin ahs	Dopamine hydrochloride
00003901032	Isopto ephinal	Epinephrine
00003901025	Isopto epinal	Epinephrine
00003901007	Isoptoepinal	Epinephrine
00003903039	Jext	Epinephrine bitartrate
00360702031	Kakodin	Dopamine hydrochloride
00360702137	Kakodin D	Dopamine hydrochloride
00493402051	Kardia	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00127502049	L noradrenalina braun	Norepinephrine bitartrate
00003901035	L-adrenalin	Epinephrine
00003901078	L-epinephrine	Epinephrine
00127501003	Levarterenol	Norepinephrine
00127502038	Levarterenol bitartrate	Norepinephrine bitartrate
00127503007	Levarterenol HCL	Norepinephrine hydrochloride
00127503008	Levarterenol hydrochloride	Norepinephrine hydrochloride
00003902008	Levocon	Epinephrine hydrochloride
00127502005	Levonor	Norepinephrine bitartrate
00127502002	Levophed	Norepinephrine bitartrate
00127502023	Levophed bitartrat	Norepinephrine bitartrate
00127502003	Levophed bitartrate	Norepinephrine bitartrate
00127501009	Levophrine	Norepinephrine
00003903019	Liadren	Epinephrine bitartrate
00360702177	Loxin	Dopamine hydrochloride
00003903009	Lyophrin	Epinephrine bitartrate
00360702043	Martburn	Dopamine hydrochloride
00003902024	Mediastman	Epinephrine hydrochloride
00003903020	Medihaler	Epinephrine bitartrate
00003903002	Medihaler-epi	Epinephrine bitartrate
00360702169	Medopa	Dopamine hydrochloride
00360702158	Megadose	Dopamine hydrochloride
00493402162	Mekard	Dobutamine hydrochloride
00127502081	Mephrin	Norepinephrine bitartrate
00003901030	Mf adrenalin	Epinephrine
00360702148	Micro Dopamine	Dopamine hydrochloride
00003903028	Micro-adrenaline	Epinephrine bitartrate
00003902004	Micronefrin	Epinephrine hydrochloride
00003901059	Min-I-Jet Adrenalin	Epinephrine
00360702141	Miocina	Dopamine hydrochloride
00493402031	Miozac	Dobutamine hydrochloride
00360702051	Mitasmin	Dopamine hydrochloride
00493402129	Mobitil	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702104	Myocard	Dopamine hydrochloride
00360702184	Myofast	Dopamine hydrochloride
00360702171	Myomine	Dopamine hydrochloride
00360702189	Myotil	Dopamine hydrochloride
00127502058	N Epi	Norepinephrine bitartrate
00003901004	Nebulogenum hectalini	Epinephrine
00127502086	Nefrinor	Norepinephrine bitartrate
00003902058	Neosynephrine Badrial	Epinephrine hydrochloride
00127502090	Nevoleen	Norepinephrine bitartrate
00127502083	Nobify	Norepinephrine bitartrate
00127502008	Nor adrenalin	Norepinephrine bitartrate
00127501010	Nor adrenalin	Norepinephrine
00127502020	Norad	Norepinephrine bitartrate
00127502087	Norad 4	Norepinephrine bitartrate
00127502041	Noradrec	Norepinephrine bitartrate
00127502013	Noradren	Norepinephrine bitartrate
00127501005	Noradrenalin	Norepinephrine
00127502006	Noradrenalin	Norepinephrine bitartrate
00127503005	Noradrenalin	Norepinephrine hydrochloride
00127503006	Nor-Adrenalin	Norepinephrine hydrochloride
00127502017	Nor-adrenalin	Norepinephrine bitartrate
00127502051	Noradrenalin Abcur	Norepinephrine bitartrate
00127502084	Noradrenalin aguettant	Norepinephrine bitartrate
00127502010	Noradrenalin Bichsel	Norepinephrine bitartrate
00127502045	Noradrenalin Hospira	Norepinephrine bitartrate
00127502094	Noradrenalin ligula pharma	Norepinephrine bitartrate
00127502011	Noradrenalin mayrhofer	Norepinephrine bitartrate
00127502042	Noradrenalin naf sykehusapoteket	Norepinephrine bitartrate
00127502061	Noradrenalin orpha	Norepinephrine bitartrate
00127502007	Noradrenalin sad	Norepinephrine bitartrate
00127502098	Noradrenalin sintetica	Norepinephrine bitartrate
00127503004	Noradrenalina	Norepinephrine hydrochloride
00127502043	Noradrenalina	Norepinephrine bitartrate

Drug code	Product Name	Active Ingredients
00127501006	Noradrenalina	Norepinephrine
00127502071	Noradrenalina basi	Norepinephrine bitartrate
00127502015	Noradrenalina biol	Norepinephrine bitartrate
00127502025	Noradrenalina braun	Norepinephrine bitartrate
00127502050	Noradrenalina Combino pharm	Norepinephrine bitartrate
00127502067	Noradrenalina Generis	Norepinephrine bitartrate
00127501008	Noradrenalina Max vision	Norepinephrine
00127502029	Noradrenalina Normon	Norepinephrine bitartrate
00127502089	Noradrenalina novophar	Norepinephrine bitartrate
00127502016	Noradrenalina richet	Norepinephrine bitartrate
00127502033	Noradrenalina tartrato	Norepinephrine bitartrate
00127502092	Noradrenalina tartrato aguettant	Norepinephrine bitartrate
00127501002	Noradrenaline	Norepinephrine
00127502021	Noradrenaline	Norepinephrine bitartrate
00127504003	Noradrenaline	Norepinephrine bitartrate monohydrate
00127502097	Noradrenaline (Norpinephrine)	Norepinephrine bitartrate
00127502055	Noradrenaline acid tartrate anhydrous	Norepinephrine bitartrate
00127502012	Noradrenaline aguettant	Norepinephrine bitartrate
00127502079	Noradrenaline bnm	Norepinephrine bitartrate
00127503009	Noradrenaline dl-form hydrochloride	Norepinephrine hydrochloride
00127502046	Noradrenaline Hospira	Norepinephrine bitartrate
00127503010	Noradrenaline hydrochloride	Norepinephrine hydrochloride
00127503011	Noradrenaline hydrochloride, dl-form	Norepinephrine hydrochloride
00127502088	Noradrenaline kabi	Norepinephrine bitartrate
00127502078	Noradrenaline medis	Norepinephrine bitartrate
00127502026	Noradrenaline Merck	Norepinephrine bitartrate
00127502085	Noradrenaline mylan	Norepinephrine bitartrate
00127502072	Noradrenaline myx	Norepinephrine bitartrate
00127502037	Noradrenaline PCH	Norepinephrine bitartrate
00127502027	Noradrenaline Renaudin	Norepinephrine bitartrate
00127502059	Noradrenaline saiph	Norepinephrine bitartrate
00127502091	Noradrenaline Sintetica	Norepinephrine bitartrate
00127502074	Noradrenaline tartrate renaudin	Norepinephrine bitartrate

Drug code	Product Name	Active Ingredients
00127502056	Noradrenalini tartras	Norepinephrine bitartrate
00127501012	Noradrenalinum	Norepinephrine
00127502053	Noradria	Norepinephrine bitartrate
00127502047	Norages	Norepinephrine bitartrate
00127502060	Noraline	Norepinephrine bitartrate
00127502069	Norbit	Norepinephrine bitartrate
00127502077	Norene	Norepinephrine bitartrate
00127502044	Norepin	Norepinephrine bitartrate
00127502039	Norepine	Norepinephrine bitartrate
00127502035	Norepinefrina	Norepinephrine bitartrate
00127501014	Norepinefrina	Norepinephrine
00127502048	Norepinefrina northia	Norepinephrine bitartrate
00127502075	Norepinefrina vitalis	Norepinephrine bitartrate
00127502024	Norepinefrine	Norepinephrine bitartrate
00127503003	Norepinephrine	Norepinephrine hydrochloride
00127502004	Norepinephrine	Norepinephrine bitartrate
00127501001	Norepinephrine	Norepinephrine
00127502001	Norepinephrine Bitartrate	Norepinephrine bitartrate
00127504001	Norepinephrine bitartrate monohydrate	Norepinephrine bitartrate monohydrate
00127503012	Norepinephrine HCL	Norepinephrine hydrochloride
00127503001	Norepinephrine hydrochloride	Norepinephrine hydrochloride
00127502093	Norepinephrine sopharma	Norepinephrine bitartrate
00127502057	Norepinephrine tartrate	Norepinephrine bitartrate
00127501013	Norepinephrinum	Norepinephrine
00127502019	Norepirin	Norepinephrine bitartrate
00127502082	Noreprin	Norepinephrine bitartrate
00127502052	Norphed	Norepinephrine bitartrate
00127501011	Norpin	Norepinephrine
00127502018	Norpine	Norepinephrine bitartrate
00127502096	Northix	Norepinephrine bitartrate
01872201009	Novopressina-V	Vasopressin
00003902061	Oboi Epinephrine	Epinephrine hydrochloride
00003901034	Oftan adrenalin	Epinephrine

Drug code	Product Name	Active Ingredients
00003901011	Oftan-adrenalin	Epinephrine
00360702107	Oridop	Dopamine hydrochloride
00003902009	Orostat	Epinephrine hydrochloride
00003901095	Penepin	Epinephrine
00003903041	Pharma Q Adrenaline	Epinephrine bitartrate
00360702188	Pharma q dopamine	Dopamine hydrochloride
00003903050	Pharma-q adrenaline	Epinephrine bitartrate
00003902050	Phenylephrin	Epinephrine hydrochloride
00003901080	Phinev	Epinephrine
00127502032	Pidram	Norepinephrine bitartrate
00003901036	Pinadrina	Epinephrine
01872202006	Pitressin	Vasopressin tannate
01872201002	Pitressin	Vasopressin
01872201006	Pitressin aqueous	Vasopressin
01872201013	Pitressin tanato	Vasopressin
01872202004	Pitressin Tannat in Oil	Vasopressin tannate
01872202002	Pitressin tannate	Vasopressin tannate
01872201011	Pitressin tannate	Vasopressin
01872202007	Pitressin tannate in oil	Vasopressin tannate
01872201015	Pitressin tannate in oil	Vasopressin
01872202003	Pitressin tannate oil	Vasopressin tannate
00493402008	Posiject	Dobutamine hydrochloride
00003901056	Posumin	Epinephrine
00360702032	Predopa	Dopamine hydrochloride
00360702132	Predopa Kyowa	Dopamine hydrochloride
00360702125	Predopa merck hoei	Dopamine hydrochloride
01872201003	Pressyn	Vasopressin
01872201007	Pressyn ar	Vasopressin
00127502009	Pridam	Norepinephrine bitartrate
00003901067	Primatene	Epinephrine
00003901060	Primatene mist	Epinephrine
00360702108	Proinfark	Dopamine hydrochloride
00493402154	Pusogard	Dobutamine hydrochloride

Drug code	Product Name	Active Ingredients
00127502066	Q phrine	Norepinephrine bitartrate
00003903021	Racepinephrine	Epinephrine bitartrate
00003902006	Racord	Epinephrine hydrochloride
00127502062	Radline	Norepinephrine bitartrate
00127504002	Raivas	Norepinephrine bitartrate monohydrate
00493402110	Retamex	Dobutamine hydrochloride
00360702006	Revimine	Dopamine hydrochloride
00360702015	Revivan	Dopamine hydrochloride
00003903017	S2	Epinephrine bitartrate
00003902036	S-2	Epinephrine hydrochloride
00360702018	Sabax dopamine	Dopamine hydrochloride
00127502080	Sandine	Norepinephrine bitartrate
00003903012	Sanepi	Epinephrine bitartrate
00127502070	Seladrenalin	Norepinephrine bitartrate
00360702153	Seminiet	Dopamine hydrochloride
00003901008	Simplene	Epinephrine
00127502076	Sinora	Norepinephrine bitartrate
00127502095	Softamicid	Norepinephrine bitartrate
00003902067	Spinefe	Epinephrine hydrochloride
00493402084	Starzen	Dobutamine hydrochloride
00127502054	Stenor	Norepinephrine bitartrate
00127502031	Steradin	Norepinephrine bitartrate
00360702157	Sterile dopamine concentrate	Dopamine hydrochloride
01872201014	Stimate	Vasopressin
00003901090	Supradin	Epinephrine
00003901005	Suprarenin	Epinephrine
00003902029	Suprarenin	Epinephrine hydrochloride
00003901074	Surgident	Epinephrine
00003902002	Sus-phrine	Epinephrine hydrochloride
00003901038	Sus-phrine	Epinephrine
00003901092	Symjepi	Epinephrine
00360702055	Taiadopa	Dopamine hydrochloride
00360702017	Tensamin	Dopamine hydrochloride

Drug code	Product Name	Active Ingredients
00493402042	Toburex	Dobutamine hydrochloride
00003901023	Tonogen	Epinephrine
00360702154	Tronjin	Dopamine hydrochloride
00360702089	Tropin	Dopamine hydrochloride
00360702046	Tsurudopami	Dopamine hydrochloride
00127502099	Turktipsan noradrenalin	Norepinephrine bitartrate
00003901057	Twinject	Epinephrine
00360702091	Udopa	Dopamine hydrochloride
00360702145	Upamine	Dopamine hydrochloride
00360702121	Uramin	Dopamine hydrochloride
00493402064	Utamine	Dobutamine hydrochloride
00003902003	Vaponefrin	Epinephrine hydrochloride
00003902020	Vaponefrin hisamitsu	Epinephrine hydrochloride
00003902021	Vaponefrin tokyo mi shokai	Epinephrine hydrochloride
01872201023	Vascel	Vasopressin
00127502022	Vascon	Norepinephrine bitartrate
00003903025	Vasocon	Epinephrine bitartrate
01872201025	Vasopar	Vasopressin
01872201017	Vasopin	Vasopressin
01872201001	Vasopressin	Vasopressin
01872201010	Vasopressin injection	Vasopressin
01872201022	Vasopressin sandoz	Vasopressin
01872201005	Vasopressin tannat	Vasopressin
01872202005	Vasopressin tannat	Vasopressin tannate
01872202001	Vasopressin tannate	Vasopressin tannate
01872201019	Vasopressina	Vasopressin
01872201004	Vasopressine	Vasopressin
01872202008	Vasopressini tannas	Vasopressin tannate
01872201021	Vasostrict	Vasopressin
00360702122	Vidopa	Dopamine hydrochloride
00003901053	Weradren	Epinephrine
00360702155	Yaelista	Dopamine hydrochloride
00360702049	Yaelista mita	Dopamine hydrochloride

Drug code	Product Name	Active Ingredients
00360702142	Zetarina	Dopamine hydrochloride

APPENDIX 5 LABORATORY ASSESSMENTS

Hematology (SI unit)

- Platelets count (x10E9/L)
- Hemoglobin (g/L)
- White blood cell (WBC) count total (x10E9/L)
- Absolute neutrophils count (x10E9/L)
- Relative neutrophils count (%)
- Absolute lymphocyte count (x10E9/L)
- Relative lymphocyte count (%)
- Absolute monocyte count (x10E9/L)
- Relative monocyte count (%)
- Absolute eosinophils count (x10E9/L)
- Relative eosinophils count (%)
- Absolute basophils count (x10E9/L)
- Relative basophils count (%)

Coagulation (SI unit)

- D-dimer (mg/Lmg/L)
- C-reactive protein (CRP) (mg/L)
- Fibrinogen (g/L)
- Ferritin (µg/L)
- Activated partial thromboplastin time (s)
- Lactate dehydrogenase (LDH) (IU/L)
- Prothrombin time (PT) (s)
- Procalcitonin (µg/L)
- International normalized ratio (INR)

Chemistry (SI unit)

- General
  - Potassium (mmol/L)
  - Sodium (mmol/L)
  - Calcium (mmol/L)
  - Magnesium (mmol/L)
  - Phosphate (mmol/L)
  - Bicarbonate (mmol/L)
  - Creatinine (µmol/L)
  - Glucose (mmol/L)
- Liver Function Tests
  - Alkaline phosphatase (ALP) (IU/L)
  - Total bilirubin (µmol/L)
  - Aspartate transaminase (AST) (IU/L)
  - Alanine transaminase (ALT) (IU/L)
  - Gamma glutamyl transferase (GGT) (IU/L)
- Cardiac Panel
  - Creatine kinase (CK) (IU/L)
  - CK MB isoenzyme fraction of CK (IU/L)
  - Triglycerides (mmol/L)
  - Troponin I (µg/L)
  - Troponin T (µg/L)

APPENDIX 6 CTCAE TOXICITY GRADE, VERSION 5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed on 22-Apr-2020)

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	Platelet count (x10E9/L)	≥ LLN	≥ 75 x 10E9/L – < LLN	≥ 50 - < 75 x 10E9/L	≥ 25 - < 50 x 10E9/L	< 25 x 10E9/L	n/a
Anemia	Hemoglobin (g/L)	≥ LLN	≥ 100 g/L - < LLN	≥ 80 - < 100 g/L	< 80 g/L	n/a	n/a
Hemoglobin increased	Hemoglobin (g/L)	No increase from baseline	Increase from baseline > 0 - ≤ 20 g/L	Increase from baseline > 20 - ≤ 40 g/L	Increase from baseline > 40 g/L	n/a	n/a
White blood cell (WBC) decreased	WBC (x 10E9/L)	≥ LLN	≥ 3.0 x 10E9/L – < LLN	≥ 2.0 - < 3.0 x 10E9/L	≥ 1.0 - < 2.0 x 10E9/L	< 1.0 x 10E9/L	n/a
Leukocytosis	WBC (x 10E9/L)	≤ 100 x 10E9/L	n/a	n/a	> 100 x 10E9/L	n/a	n/a
Absolute neutrophils count decreased	Absolute neutrophils count (x 10E9/L)	≥ LLN	≥ 1.5 x 10E9/L – < LLN	≥ 1.0 - < 1.5 x 10E9/L	≥ 0.5 - < 1.0 x 10E9/L	< 0.5 x 10E9/L	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Absolute lymphocytes count decreased	Absolute lymphocytes count (x 10E9/L)	≥ LLN	≥ 0.8 x 10E9/L – < LLN	≥ 0.5 - < 0.8 x 10E9/L	≥ 0.2 - < 0.5 x 10E9/L	< 0.2 x 10E9/L	n/a
Absolute lymphocytes count increased	Absolute lymphocytes count (x 10E9/L)	≤ 4 x 10E9/L	n/a	> 4 – ≤ 20 x 10E9/L	> 20 x 10E9/L	n/a	n/a
Eosinophilia	Absolute eosinophils count (x 10E9/L)	≤ ULN or ≤ Baseline	> ULN and > Baseline	n/a	n/a	n/a	n/a
Fibrinogen decreased	Fibrinogen (g/L)	≥ LLN if baseline normal; no decrease from baseline if baseline abnormal	≥ 0.75 - < 1 x LLN if baseline normal; > 0 - < 25% decrease from baseline if baseline abnormal	≥ 0.5 - < 0.75 x LLN if baseline normal; ≥ 25 - < 50% decrease from baseline if baseline abnormal	≥ 0.25 - < 0.5 x LLN if baseline normal; ≥ 50 - < 75% decrease from baseline if baseline abnormal	< 0.25 x LLN if baseline normal; ≥ 75% decrease from baseline if baseline abnormal	
Activated partial thromboplastin time (aPTT) prolonged	aPTT (s)	≤ ULN	> ULN – ≤ 1.5 x ULN	> 1.5 – ≤ 2.5 x ULN	> 2.5 ULN	n/a	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
International normalized ratio (INR) increased	INR	≤ 1.2 if not on anticoagulant; ≤ baseline if on anticoagulant	> 1.2 – ≤1.5 if not on anticoagulant; > baseline - ≤ 1.5 x baseline if on anticoagulant	> 1.5 – ≤2.5 if not on anticoagulant; > 1.5 - ≤ 2.5 x baseline if on anticoagulant	> 2.5 if not on anticoagulant; > 2.5 x baseline if on anticoagulant	n/a	n/a
Blood lactate dehydrogenase (LDH) increased	LDH (IU/L)	≤ ULN	> ULN	n/a	n/a	n/a	n/a
Hyperkalemia	Potassium (mmol/L)	≤ ULN	> ULN – ≤ 5.5 mmol/L	> 5.5 – ≤ 6.0 mmol/L	> 6.0 – ≤ 7.0 mmol/L	> 7.0 mmol/L	n/a
Hypokalemia	Potassium (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN; asymptomatic; no intervention indicated	≥ 3.0 mmol/L – < LLN; symptomatic; intervention indicated	≥ 2.5 - < 3.0 mmol/L	< 2.5 mmol/L	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypernatremia	Sodium (mmol/L)	≤ ULN	> ULN – ≤ 150 mmol/L	> 150 – ≤ 155 mmol/L	> 155 – ≤ 160 mmol/L	> 160 mmol/L	n/a
Hyponatremia	Sodium (mmol/L)	≥ LLN	≥ 130 mmol/L – < LLN	≥ 125 - < 130 mmol/L and asymptomatic	≥ 120 - < 125 mmol/L **or** ≥ 125 - < 130 mmol/L and symptomatic	< 120 mmol/L	n/a
Hypermagnesemia	Magnesium (mmol/L)	≤ ULN	> ULN – ≤ 1.23 mmol/L	n/a	> 1.23 – ≤ 3.30 mmol/L	> 3.30 mmol/L	n/a
Hypomagnesemia	Magnesium (mmol/L)	≥ LLN	≥ 0.5 mmol/L – < LLN	≥ 0.4 - < 0.5 mmol/L	≥ 0.3 - < 0.4 mmol/L	< 0.3 mmol/L	n/a
Blood bicarbonate decreased	Bicarbonate (mmol/L)	≥ LLN	< LLN	n/a	n/a	n/a	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	Creatinine (µmol/L)	≤ ULN	> ULN – ≤ 1.5 x ULN	> 1.5 – ≤ 3.0 x ULN **or** > 1.5 – ≤3.0 x baseline	> 3.0 – ≤ 6.0 x ULN **or** > 3.0 x baseline	> 6.0 x ULN	n/a
Hypoglycemia	Glucose (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	≥ 2.2 - < 3.0 mmol/L	≥ 1.7 - < 2.2 mmol/L	< 1.7 mmol/L	n/a
Alkaline phosphatase (ALP) increased	ALP (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5 x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	Total bilirubin (µmol/L)	≤ ULN if baseline normal; ≤ baseline if baseline abnormal	> ULN – ≤ 1.5 x ULN if baseline normal; > baseline - ≤ 1.5 x baseline if baseline abnormal	> 1.5 – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 10.0 x ULN if baseline normal; > 3.0 - ≤ 10.0 x baseline if baseline abnormal	> 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal	n/a
Aspartate transaminase (AST) increased	AST (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine transaminase (ALT) increased	ALT (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Gamma glutamyl transferase (GGT) increased	GGT (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 - ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 - ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
CPK increased	Creatine kinase (U/L)	≤ ULN	> ULN – ≤ 2.5 x ULN	> 2.5 – ≤ 5 x ULN	> 5 – ≤ 10 x ULN	> 10 x ULN	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertriglyceridemia	Triglycerides (mmol/L)	≤ 1.71 mmol/L	> 1.71 – ≤ 3.42 mmol/L	> 3.42 - ≤ 5.70 mmol/L	> 5.70 - ≤ 11.40 mmol/L	> 11.40 mmol/L	n/a

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/23/2021 4:15:59 PM
Certified Delivered	Security Checked	4/23/2021 9:22:08 PM
Signing Complete	Security Checked	4/23/2021 9:23:12 PM
Completed	Security Checked	4/23/2021 9:23:12 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 3/3/2020 2:03:57 PM
Parties agreed to: PPD

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If you withhold consent to electronic delivery or execution, or withdraw your consent at a later date, all Documents will be sent to your mailing address following our receipt of notice of such action. The following sections explain the consequences of withholding or withdrawing your consent to electronic delivery and execution of Documents, and also the procedures you must follow in order to effectuate delivery to your mailing address.

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By electing to only receive and execute Documents sent to your mailing address, we will not be able to carry out transactions or services as efficiently. For instance, some transactions or services require your express consent. We can perform these transaction or services only if we first receive an acknowledgement that indicates you received and consent to the Document related to the proposed transaction or service.

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.
Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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COV-01-001 STATISTICAL ANALYSIS PLAN

INDUSTRY ALLIANCE PLATFORM TRIAL TO ASSESS THE EFFICACY AND SAFETY OF MULTIPLE CANDIDATE AGENTS FOR THE TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

SUB-PROTOCOL NUMBER: COV-01-001

SUB-PROTOCOL FOR CANDIDATE AGENT: LANADELUMAB-IV

AUTHOR: PPD

VERSION NUMBER AND DATE: AMENDMENT 3 V1.0, 23-JUL-2021

TAKEDA SUB-PROTOCOL STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Takeda sub-protocol COV-01-001 Statistical Analysis Plan (SAP) Amendment 3 v1.0 (dated 23-Jul-2021).

	Name	Signature	Date (DD-Mmm-YYYY)
Author:	PPD	PPD	
Position:	PPD		
Company:	CCI		

Upon review of this document, the undersigned approves this version of the sub-protocol COV-01-001 SAP, authorizing that the content is acceptable for the reporting specific to this sub-protocol.

	Name	Signature	Date (DD-Mmm-YYYY)
Approved by:	PPD	PPD	
Position:	PPD		
Company:	CCI		
On behalf of:	PPD		
Position:	PPD		
Company:	CCI		
Approved by:	PPD	PPD	
Position:	PPD		
Company:	Takeda		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
Final, v1.0	14-Dec-2020	PPD	Not Applicable – First Version
Amendment 1, v1.0	27-Apr-2021	PPD	Updated COV-01-001 sub-protocol version on which this subprotocol SAP is based from version 1.2, dated 26Oct2020, to version 2.0, dated 14Apr2021 Update title of Sections 11and 13 to be in line with Master SAP; Added a subgroup that will be used to perform supportive analysis for selected safety data and related additional supportive analysis; Added the risk difference of the overall incidence rates of having any treatment-emergent AESI between the treatment groups will be presented along with its 95% two-sided Wald CI; Added Appendices 1 and 2.

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
Amendment 2, v1.0	24-Jun-2021	PPD	Specified that the two Interim Analyses (IAs) and Primary Analysis at Day 29 will not be performed for this sub-protocol since enrollment into COV-01-001 sub-protocol was early terminated by the Sponsor on 03-May-2021 i.e., before the trigger of each of these analyses was met. Exception of summary statistics for the primary efficacy, key secondary, and other secondary efficacy endpoints, removed all planned efficacy analyses given that 1) enrollment into COV-01-001 sub-protocol was early terminated by the Sponsor on 03-May-2021, 2) number of patients to be included in COV-01-001 sub-protocol final analysis, and 3) an abbreviated Clinical Study Report will be created for this sub-protocol. Added two-sided 95% exact binomial Confidence Interval within each treatment arm, when applicable. Removed the additional subgroup analyses that were to be performed as supportive analysis for selected safety data.
Amendment 3, v1.0	23-Jul-2021	PPD	Updated the definition of the Shared Placebo Arm

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of data specific to sub-protocol COV-01-001 of master protocol COV-01. It describes the specific data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This sub-protocol SAP is based on version 2.0 of the sub-protocol COV-01-001, dated 14-Apr 2021.

For the rules and conventions to be used in the presentation and analysis of data common across all sub-protocols, refer to the Master COV-01 SAP.

2. STUDY OBJECTIVES

The study objectives are described in the Master COV-01 SAP.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

The general description is available in the Master COV-01 SAP.

3.2. SCHEDULE OF ACTIVITIES

The schedule of activities can be found in Section 1.2 of the sub-protocol COV-01-001.

3.3. CHANGES TO PLANNED ANALYSES FROM MASTER PROTOCOL AND SUB-PROTOCOL COV-01-001

Enrollment into sub-protocol COV-01-001 was prematurely terminated by the Sponsor on 03-May-2021 due issues with the administration of the study drug. In conformance with the Food and Drug Administration (FDA) Guidance for Submission of Abbreviated Report and Synopsis in Support of Marking Application, an abbreviated Clinical Study Report (CSR) will be written for this sub-protocol. As such, not all analyses planned in the master protocol

will be performed for sub-protocol COV-01-001 (refer to Section 4 for more details concerning the analyses to be performed for this sub-protocol).

Definition of the control arm (i.e., the shared placebo + standard of care [SoC] arm) was updated for this sub-protocol to minimize the randomization imbalance issue noted by the CCI Unblinded Biostatistician and IDMC members at the time of CCI [redacted] (refer to Section 4.5).

4. PLANNED ANALYSES

The analyses initially planned to be performed are listed and described in the Master COV-01 SAP. However, the two Interim Analyses (IAs) for futility and Primary Analysis will not be performed for this sub-protocol since enrollment into sub-protocol COV-01-001 was early terminated by the Sponsor on 03-May-2021 (refer to Section 3.3 for additional details) i.e., before the trigger for each of these analyses was met. That is, the only analysis that will be performed, in addition to the monthly IDMC Safety analyses, is the final analysis after all patients who were ongoing at the time Sponsor early terminated this sub-protocol completed the study (Day 60 visit) or discontinued early from the study, whichever occurs first.

All outputs described in this sub-protocol SAP will be produced at the time of sub-protocol COV-01-001 final analysis.

4.1. IDMC SAFETY ANALYSES

Details are provided in the Master COV-01 SAP.

4.2. INTERIM ANALYSES

No IAs will be performed for this sub-protocol (refer to Section 4).

4.3. PRIMARY ANALYSIS

No primary analysis will be performed for this sub-protocol (refer to Section 4).

4.4. FINAL ANALYSIS

The final analysis for this sub-protocol will take place after:

- Sponsor Authorization of this SAP.
- Final database lock of the database including data from screen failed patients.
- Final database lock of the database of each sub-protocol contributing to the control arm of this sub-protocol (refer to Section 4.5).
- Final database lock of the database of this sub-protocol.

All planned analyses identified in this sub-protocol SAP will be performed by CCI [redacted] Biostatistics at the time of the final analysis of this sub-protocol.

4.5. SELECTION OF THE CONTROL ARM FOR AN ANALYSIS

4.5.1. IDMC SAFETY ANALYSES

Details are provided in Master SAP Section 4.5.

4.5.2. FINAL ANALYSIS

For final analysis of this sub-protocol, the control arm (also referred to as shared placebo + SoC arm) will include all patients randomized to the placebo arm of any sub-protocol before this sub-protocol was early terminated (refer to section 3.3) at a site at which:

- This sub-protocol was opened for enrollment.
- At least one patient was randomized to either this sub-protocol active (Lanadelumab- intra-venous [IV] + SoC) or placebo (placebo to Lanadelumab-IV + SoC) arms.

That is, patients that satisfy these criteria will be included in the control arm of this sub-protocol regardless of 1) whether patients was randomized before this sub-protocol was opened for enrollment at the site (that is, patients randomized after enrollment into COV-01-001 sub-protocol was early terminated will be excluded from the control

arm of this sub-protocol) and 2) patient's eligibility to this sub-protocol specific inclusion/ exclusion criteria.

The purpose of this change from the Master SAP control arm definition (Master SAP Section 4.5) is to minimize the randomization imbalance issue noted by the CCI Unblinded Biostatistician and IDMC members at the time of CCI [redacted]. At the time this sub-protocol SAP was finalized, the randomization imbalance was estimated to be approximately 7:1 between this sub-protocol active and control arms, should the original control arm definition would have been retained for the final analysis of this sub-protocol.

5. ANALYSIS SETS

Analysis sets are described in the COV-01 Master SAP.

Additional analysis sets that are specific to sub-protocol COV-01-001 are described below:

5.1. PRIMARY ANALYSIS SET

The primary analysis set will include all randomized patients with a baseline clinical severity status of Grade 3 to 5 on the 8-point ordinal scale for clinical severity.

For displays and analyses based on the primary analysis set, patients will be classified according to the randomized treatment.

The main analyses of all efficacy endpoints will be performed on the primary analysis set.

5.2. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic (PK) analysis set will include patients from the safety analysis set (refer to Master COV-01 SAP Section 5.2) randomized to the Lanadelumab-(IV + SoC arm who have at least one measured concentration post dose of Lanadelumab-IV.

5.3. PHARMACODYNAMIC ANALYSIS SET

The pharmacodynamic (PD) analysis set will include patients from the safety analysis set (refer to Master COV-01

SAP Section 5.2) randomized to COV-01-001 sub-protocol (i.e., Lanadelumab- IV + Standard of Care (SoC) arm or Placebo to Lanadelumab-IV + SoC) who have at least one measured biomarker level post dose of Lanadelumab-IV (e.g., cHMWk, pKAL, etc.).

5.4. PLASMA ANTI-DRUG ANTIBODY ANALYSIS SET

The plasma anti-drug antibody (ADA) analysis set will include patients from the safety analysis set (refer to Master COV-01 SAP Section 5.2) randomized to COV-01-001 sub-protocol (i.e., Lanadelumab- IV + Standard of Care (SoC) arm or Placebo to Lanadelumab-IV + SoC) who have at least one evaluated ADA response.

5.5. PROCESS FOR ANALYSIS SET ASSIGNMENT

As the primary, PK, PD and ADA analysis sets are defined based on objective criteria only, the authorization of this sub-protocol SAP will stand for the agreement and authorization of the inclusion/exclusion of each patient in the primary, PK, PD and ADA analysis sets.

6. GENERAL CONSIDERATIONS

Details are provided in the Master COV-01 SAP.

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE CALCULATION

Details are provided in the Master COV-01 SAP.

7.2. MISSING DATA

Details are provided in the Master COV-01 SAP.

7.3. STATISTICAL TESTS

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.5. MULTICENTER STUDIES

Details are provided in the Master COV-01 SAP.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.7. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for the final analysis of this sub-protocol.

7.8. SOFTWARE VERSION

Details are provided in Master COV-01 SAP.

8. OUTPUT PRESENTATIONS

Output presentations are described in the Master COV-01 SAP.

9. DISPOSITION AND WITHDRAWALS

Analysis of disposition and withdrawals will be presented as described in the Master COV-01 SAP.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics and other baseline characteristics data will be presented as described in the Master COV-01 SAP.

11. DISEASE HISTORY

Analysis of disease history will be performed as described in the Master COV-01 SAP.

12. MEDICAL HISTORY

Analysis of medical history will be performed as described in the Master COV-01 SAP.

13. PRIOR AND CONCOMITANT MEDICATIONS

Analysis of prior and concomitant medications will be performed as described in the Master COV-01 SAP.

14. EXPOSURE TO STUDY DRUG

Patients randomized to sub-protocol COV-01-001

Patients randomized to the Lanadelumab-IV + SoC or Placebo + SoC treatment groups of COV-01-001 sub-protocol will receive an IV injection of either Lanadelumab-IV 300 mg diluted in normal saline or placebo (normal saline), as applicable, in a double-blind manner, one dose on Day 1 and a second dose on Day 4, along with SoC.

Reason for dose modification of study drug (i.e., dose increased, dose reduced, drug interrupted and drug withdrawal) will be captured on the *Exposure* page of the eCRF.

Patients included in the control arm of COV-01-001 sub-protocol who were randomized to the Placebo + SoC group of a sub-protocol other than COV-01-001

It is to be noted that the planned duration of exposure to a study drug, planned frequency of administration of the study drug, and planned route of administration of the study drug will vary from one sub-protocol to the other, but similar information as for COV-01-001 sub-protocol will be captured on the *Exposure* page of the eCRF of these other sub-protocol.

Exposure to study drug

The exposure to study drug will be summarized by treatment arm (breaking down the Placebo + SoC arm by sub-protocol) based on the safety analysis set as follows:

- Duration of exposure:
    - Duration of exposure (days) as a continuous variable
    - Duration of exposure (days) as a categorical variable: 1 to 3, > 3 to 7, > 7 to 14, > 14 to 29, and > 29
    - Total number of doses received as a continuous variable, where the total number of dosed received is defined as the total number of doses received by each patient, not the total number of doses received across all patients
    - For patients randomized to COV-01-001 sub-protocol only, number and percentages of patients who received only one dose and number and percentages of patients who received two doses.
- Dose modifications:
    - For patients randomized to COV-01-001 sub-protocol only, number and percentage of patients with at least one dose partially administered overall and for each dose
    - Number and percentage of patients with at least one interrupted dose
    - Number and percentage of patients with at least one dose interruption by reason for dose interruption:
        - Adverse events
        - Other.
    - Total number of dose interruptions as a continuous variable, where the total number of dose

interruptions is defined similarly to the total number of doses received

- Among patients with a dose interruption, number and percentage of patients with dose subsequently restarted at planned dose level.

All dosing and exposure data will also be listed. A listing including patients with at least one dose modification only will also be provided.

14.1. DERIVATIONS

For patients randomized to a study drug planned to be administered on a daily basis, duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = (Date of last dose of study drug – Date of first dose of study drug) + 1

For all other patients (i.e. randomized to a study drug planned to be administered not on a daily basis), duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = {[Earliest date of (end of planned study treatment period, hospital discharge or discontinuation from study drug)] – Date of first dose of study drug} + 1

15. COMPLIANCE WITH STUDY DRUG

Compliance with study drug will be summarized by treatment arm (breaking down the Placebo + SoC arm by sub-protocol) based on the safety analysis set. In addition to the descriptive summary, number and percentage of patients in each of the following compliance categories will be presented:

- < 50%
- ≥ 50 to < 80%
- ≥ 80% to ≤ 100%
- > 100%.

Compliance data will also be listed.

15.1. DERIVATIONS

For each patient, the compliance will be computed as follows:

- Compliance (%) = (Actual total number of doses / Expected total number of doses) x 100

where:

- Actual total number of doses is defined as the sum of all doses taken through the course of the study
- Expected total number of doses is defined as the sum of protocol-defined doses to be taken through the course of the study and is computed as follows:
    - For patients randomized to a study drug administered on a daily basis:
        - Expected total number of doses = expected number of doses per day * expected number of days under treatment, where the expected number of days under treatment is defined as: {[Earliest date of (end of planned study treatment period, hospital discharged or discontinuation from study drug)] – Date of first dose of study drug} + 1.
    - For patients randomized to a study drug planned to be administered not on a daily basis:
        - Expected total number of doses = Expected number of doses (injections) per day * expected number of administration days between randomization and the earliest of (end of planned study treatment period, hospital discharged or discontinuation from study drug).

          For example, if a study drug is planned to be administered once on Day 1 and once on Day 4, the expected total number of doses is 2; unless patient discontinued from study drug or was discharged from the hospital on or after Day 1 but before Day 4, in which case the expected total number of doses is 1. As another example, if the study drug is planned to be administered twice daily on every other day from Day 1 to Day 14, the expected total number of doses is 14; unless patient discontinued from study drug or was discharged from the hospital let say, on Day 10, in which case the expected total number of doses is 10 (i.e., 2 doses [injection] per days * 5 administration days).

16. EFFICACY ENDPOINTS

Given that only 29 patients were randomized into COV-01-001 sub-protocol and that is expected ~34 patients will be included in final analysis of this sub-protocol when taking the shared placebo arm into account instead of ~700 as required by the sample size (refer to Master SAP Section 7.1), no statistical inferences will be performed for any efficacy endpoint, but two-sided 95% exact binomial Confidence Interval (CI) within each treatment arm will be provided, when possible.

In conformance with the FDA's Guidance for Submission of Abbreviated Report and Synopsis in Support of Marking and publication requirements of *ClinicalTrials.gov*, summary tables will be presented for the primary and key secondary efficacy endpoints (refer to Master SAP Sections 16.1.1, 16.2.1.1, 16.2.1.2, and 16.2.1.3). Although not required by the previously mentioned FDA's Guidance, summary tables will also be provided for the other secondary efficacy endpoints (refer to Master SAP Sections 16.2.1.4 to 16.2.1.9) in order to be compliant with the publication requirements of *ClinicalTrials.gov*.

Efficacy summaries will be performed as described in the Master COV-01 SAP, except that all endpoints will be analyzed on the primary analysis set (refer to Section 5.1) instead of the FAS.

16.1. PRIMARY EFFICACY

16.1.1. TIME TO CONFIRMED CLINICAL RECOVERY THROUGH DAY 29, WITHOUT RE-HOSPITALIZATION THROUGH DAY 29

Details are provided in the Master COV-01 SAP.

16.1.2. MISSING DATA IMPUTATION METHOD FOR PRIMARY EFFICACY ENDPOINT

Details are provided in the Master COV-01 SAP.

16.1.3. MAIN ANALYSIS OF PRIMARY EFFICACY ENDPOINT

For the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, as defined in the Master SAP Section 16.1.1, the number and percentage of patients with and without the event will be presented by randomized treatment arm. Two-sided 95% exact binomial CI for the percentage of patients with the event within

each treatment group will be provided. For patients who did not meet the event, the main reason for censoring will be summarized similarly.

Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the time to confirmed clinical recovery though Day 29, without re-hospitalization through Day 29. Kaplan-Meier estimate of the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, in days, will be provided at the 25th, 50th (median), and 75th percentiles time along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation. Kaplan-Meier estimates of the probability of having the event will also be provided at Day 29 along with the number of patients with the event and the number of patients at risk at that time.

16.1.4. Sensitivity Analyses for Primary Efficacy Endpoint

No sensitivity analyses will be performed for this sub-protocol.

16.1.5. Supplementary Analyses for Primary Efficacy Endpoint

No supplementary analyses will be performed for this sub-protocol.

16.2. Secondary Efficacy

16.2.1. Secondary Efficacy Endpoints

16.2.1.1. Incidence of Patients with Oxygen-Free Recovery at Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.2. Incidence of Patients with ≥ 2-point Improvement from Baseline or Fit for Discharge on the Ordinal Scale at Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.3. Incidence of All-Cause Mortality through Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.4. Distribution of Patients across the Categories of the 8-point Ordinal Scale for Clinical Severity at Days 8, 15, and 29

Details are provided in the Master COV-01 SAP.

16.2.1.5. Worst Post-Baseline Score on 8-point Ordinal Scale from Baseline to Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.6. Number of ICU Days from Day 1 through Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.7. Number of Invasive Mechanical Ventilator Days from Day 1 through Day 29

Details are provided in the Master COV-01 SAP.

16.2.1.8. Incidence of Patients with Clinical Recovery by Days 8, 15, and 29

Details are provided in the Master COV-01 SAP.

16.2.1.9. Incidence of Patients with Sustained Clinical Recovery as Confirmed by Day 60 Follow-up

Details are provided in the Master COV-01 SAP.

16.2.2. Missing Data Imputation Method for Secondary Efficacy Endpoints

16.2.2.1. Binary Endpoints

Details are provided in the Master COV-01 SAP.

16.2.2.2. Ordinal Endpoints

Details are provided in the Master COV-01 SAP.

16.2.3. MAIN ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

16.2.3.1. Binary Endpoints

For the incidence of patients with oxygen-free recovery at Day 29 (refer to Section 16.2.1.1), incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29 (refer to Section 16.2.1.2), incidence of all-cause mortality through Day 29 (refer to Section 16.2.1.3) , incidence of patients with clinical recovery at Days 8, 15 and 29 (refer to Section 16.2.1.8), and incidence of patients with sustained clinical recovery as confirmed by Day 60 follow-up (refer to Section 16.2.1.9), the number and percentage of patients with and without the event will be provided by treatment arm. Two-sided 95% exact binomial CI for the percentage of patients with the event within each treatment group will be provided.

For the incidence of all-cause mortality, primary reason of death will also be summarized by treatment arm.

16.2.3.2. Ordinal Endpoints

For the incidence of patients in each category of the 8-point ordinal scale for clinical severity at Days 8, 15, and 29 endpoints (refer to Section 16.2.1.4), the number and percentage of patients in each ordinal scale category will be provided at each specified Day for each treatment arm. The worst post-baseline score on the 8-point ordinal scale for clinical severity from randomization to Day 29 (refer to Section 16.2.1.5) and each "number of days" endpoint (refer to Sections 16.2.1.6 and 16.2.1.7) will be summarized similarly.

Shift tables from baseline to each post-baseline day up to Day 29 as well as to the worst post-baseline score will also be provided for the 8-point ordinal scale for clinical severity.

16.2.4. SENSITIVITY ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

No sensitivity analyses will be performed for this sub-protocol.

16.2.5. SUPPLEMENTARY ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

The only supplementary analyses that will be performed for this sub-protocol is that Kaplan-Meier product-limit estimates of the time to all-cause mortality through Day 29 as described in the Master SAP Section 16.2.5, but the hazard ratio of the Lanadelumab-IV + SoC vs. shared placebo + SoC, its associated two-sided 95% CI, and p-value based on the Cox proportional hazard model described in the Master SAP will not be provided.

16.3. EXPLORATORY EFFICACY

CCI [redacted]

16.4. ADDITIONAL EFFICACY

CCI [redacted]

16.5. INTERIM ANALYSIS

No IAs will be performed for this sub-protocol since enrollment into this sub-protocol was early terminated by the Sponsor before the trigger for the first IA was reached (refer to Master SAP Section 16.5).

17. SAFETY ENDPOINTS

The safety analyses will be performed as described in the Master COV-01 SAP based on the safety analysis set.

In addition, the following analyses will also be performed for the sub-protocol COV-01-001 based on the safety analysis set.

17.1. ADVERSE EVENTS

17.1.1. ADVERSE EVENTS OF SPECIAL INTEREST

The following are defined as adverse events of special interest (AESIs) for Lanadelumab-IV and will be identified based on investigator-reported AESIs on the AE page of the CRF:

- Hypersensitivity reactions (refer to Appendix 1);
- Events of disordered coagulation (i.e., bleeding AESIs or hypercoagulable AESIs; refer to Appendix 2)

A summary of AESIs, overall and by AESI category and PT will be prepared by treatment arm for patients randomized to COV-01-001 only. Should a patient experience multiple events within an AESI category or PT, the patient will be counted only once for that AESI category or PT. Additionally, the risk difference of the overall incidence rates of having any treatment-emergent AESI between the treatment arms will be presented along with its 95% two-sided Wald CI.

A listing of all AESIs will be provided.

17.2. LABORATORY EVALUATIONS

In addition to the laboratory tests listed in Appendix 5 of the Master COV-01 SAP, the fibrin degradation products (FDPs) will be included in the outputs.

The analysis for laboratory parameters is described in the Master COV-01 SAP.

17.3. VITAL SIGNS

Analysis of vital signs data will be performed as described in the Master COV-01 SAP.

17.4. ECG EVALUATION

Electrocardiogram (ECG) evaluation will be performed at screening and on the day of discharge from the hospital. The following ECG parameters will be collected:

- Heart rate (beats per minutes [bpm]);
- PR interval (milliseconds [msec]);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTc interval (msec);
- QTcB interval (msec);
- QTcF inerval (msec);
- Overall ECG interpretation as assessed by Investigator (normal; abnormal, not clinically significant; and abnormal, clinically significant).

The observed and change from baseline values of each continuous ECG parameter will be summarized using descriptive statistics by treatment arm and visit based on the safety analysis set.

Number and percentage of patients in each category of the overall ECG interpretation as assessed by the Investigator will also be provided by treatment arm and visit based on the safety analysis set.

17.5. PHYSICAL EXAMINATION

Analysis of physical examination data will be performed as described in the Master COV-01 SAP.

18. PHARMACOKINETICS

PK concentrations of Lanadelumab-IV will be summarized by visit and timepoint (refer to Section 3.2) based on the PK analysis set (refer to Section 5.2) overall and broken down further by the ordinal scale for clinical severity score at baseline (2 or 3 to 5). Concentrations that are below the limit of quantification (BLQ) will be treated as a numeric value of zero and will be excluded from the geometric statistics. All PK concentrations will be reported and analyzed with 3 significant figures. For the reporting of descriptive statistics, the mean, standard deviation, standard error (if reported), and confidence interval (if reported) will be presented to one digit more precision than the source

data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 2 decimal places.

For Day 1, PK concentrations of Lanadelumab-IV will be summarized for the pre- and post-infusion separately.

Post-dose timepoints will be presented for Days 4, 7, 15, 29, and day of discharge as PK blood samples can be collected at any time during each of these days.

PK concentrations will be listed according to nominal time points scheduled.

19. PHARMACODYNAMICS

CCI [redacted]

20. PLASMA ANTI-DRUG ANTIBODY TESTING

Absence (negative) or presence (positive) of ADA will be summarized and listed by treatment arm across all visits (refer to Section 3.2) based on the ADA analysis set. Positive ADA will be broken down further by neutralizing and non-neutralizing ADA.

21. DATA NOT SUMMARIZED OR PRESENTED

The list of data not summarized or presented is available in the Master COV-01 SAP.

APPENDIX 1 HYPERSENSITIVITY REACTIONS

Preferred Term
• Administration site hypersensitivity
• Documented hypersensitivity to administered product
• Drug hypersensitivity
• Hypersensitivity
• Infusion related hypersensitivity reaction
• Infusion site hypersensitivity
• Injection site hypersensitivity
• Type I hypersensitivity
• Type II hypersensitivity
• Type IV hypersensitivity

APPENDIX 2 EVENTS OF DISORDERED COAGULATION

Preferred Term

- Abnormal clotting factor
- Acquired antithrombin III deficiency
- Acquired dysfibrinogenaemia
- Acquired factor IX deficiency
- Acquired factor VIII deficiency
- Acquired factor XI deficiency
- Acquired haemophilia
- Acquired protein S deficiency
- Acquired Von Willebrand's disease
- Activated protein C resistance
- Acute haemorrhagic oedema of infancy
- Anaphylactoid syndrome of pregnancy
- Antiphospholipid syndrome
- Antithrombin III deficiency
- Chronic pigmented purpura
- Coagulation disorder neonatal
- Coagulation factor deficiency
- Coagulation factor mutation
- Coagulopathy

Preferred Term

- Congenital coagulopathy
- Congenital dysfibrinogenaemia
- Congenital hypercoagulation
- Dilutional coagulopathy
- Disseminated intravascular coagulation
- Disseminated intravascular coagulation in newborn
- Ecchymosis
- Endothelial protein C receptor polymorphism
- Factor I deficiency
- Factor II deficiency
- Factor II inhibition
- Factor II mutation
- Factor III deficiency
- Factor IX deficiency
- Factor IX inhibition
- Factor V deficiency
- Factor V inhibition
- Factor V Leiden mutation
- Factor VII deficiency
- Factor VII inhibition

Preferred Term

- Factor VIII deficiency
- Factor VIII inhibition
- Factor X deficiency
- Factor X inhibition
- Factor XI deficiency
- Factor XII deficiency
- Factor XIII deficiency
- Factor XIII Inhibition
- Haemophilia
- Haemophilia A with anti factor VIII
- Haemophilia A without inhibitors
- Haemophilia B with anti factor IX
- Haemophilia B without inhibitors
- Haemophilic pseudotumour
- Haemorrhage
- Haemorrhagic diathesis
- Haemorrhagic disease of newborn
- Haemorrhagic disorder
- Haemorrhagic vasculitis
- Henoch-Schonlein purpura

Preferred Term

- Henoch-Schonlein purpura nephritis
- Heparin resistance
- Heparin-induced thrombocytopenia
- Hermansky-Pudlak syndrome
- Hypercoagulation
- Hyperfibrinogenaemia
- Hyperfibrinolysis
- Hyperhomocysteinaemia
- Hyperprothrombinaemia
- Hypersensitivity vasculitis
- Hyperthrombinaemia
- Hypocoagulable state
- Hypofibrinogenaemia
- Hypoprothrombinaemia
- Hypothrombinaemia
- Hypothromboplastinaemia
- Increased tendency to bruise
- Infantile scurvy
- Methylenetetrahydrofolate reductase deficiency
- Methylenetetrahydrofolate reductase polymorphism

Preferred Term

- Mouth haemorrhage
- Oral purpura
- Petechiae
- Plasminogen activator inhibitor polymorphism
- Protein C deficiency
- Protein S deficiency
- Pulmonary embolism
- Purpura
- Purpura fulminans
- Purpura neonatal
- Purpura non-thrombocytopenic
- Purpura senile
- Secondary thrombocytosis
- Septic coagulopathy
- Spontaneous haematoma
- Spontaneous haemorrhage
- Thrombocytosis
- Thrombotic microangiopathy
- Vascular purpura
- Vitamin C deficiency

Preferred Term
• Von Willebrand's disease
• Von Willebrand's factor inhibition

DocuSign

Certificate Of Completion

PPD

Status: Completed

PPD

Record Tracking

Status: Original
7/26/2021 10:50:49 AM

Holder: PPD

Location: DocuSign

Signer Events	Signature	Timestamp
PPD		

Signer Events	Signature	Timestamp
PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/26/2021 10:52:45 AM
Certified Delivered	Security Checked	7/26/2021 10:58:59 AM
Signing Complete	Security Checked	7/26/2021 11:00:43 AM
Completed	Security Checked	7/26/2021 11:16:49 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 3/3/2020 2:03:57 PM
Parties agreed to: PPD

CONSENT TO ELECTRONIC DELIVERY AND EXECUTION OF DOCUMENTS

From time to time, CCI ("we" or "us") may provide you certain written contracts, notices, disclosures, authorizations, acknowledgements or other documents (collectively, the "Documents") electronically. Please read this consent form carefully. It explains the terms and conditions under which such Documents are provided by us and executed by you electronically through your DocuSign, Inc. ("DocuSign") user account. If you consent to the delivery and execution of such Documents electronically, please click the "I Agree" button.

Documents will be sent to you electronically

If you consent to electronic delivery, Documents will be sent to your DocuSign user account. You may request a paper copy of documents previously made available through your DocuSign user account, but an additional charge may be incurred. Alternatively, you can download and print documents sent to your DocuSign user account. Unless otherwise noted, you can access a Document up to 30 days from the date we first sent the Document to you.

Withhold Consent or Withdrawing Consent to Electronic Delivery

If you withhold consent to electronic delivery or execution, or withdraw your consent at a later date, all Documents will be sent to your mailing address following our receipt of notice of such action. The following sections explain the consequences of withholding or withdrawing your consent to electronic delivery and execution of Documents, and also the procedures you must follow in order to effectuate delivery to your mailing address.

Consequences of Withdrawing Consent

By electing to only receive and execute Documents sent to your mailing address, we will not be able to carry out transactions or services as efficiently. For instance, some transactions or services require your express consent. We can perform these transaction or services only if we first receive an acknowledgement that indicates you received and consent to the Document related to the proposed transaction or service.

To withhold consent now or withdraw consent at a later date, please sign DocuSign's "Withdraw Consent" form on the signing page of your DocuSign user account. This will indicate that you have withdrawn your consent to receive Documents electronically. Once you sign the "Withdraw Consent" form, you will no longer be able to use your DocuSign user account to execute Documents electronically and we will send Documents to your mailing address. Withdrawal of consent does not affect the validity of any Documents previously executed electronically prior to such withdrawal of Consent. In addition, should you execute any Documents electronically, your execution of such Documents shall indicate your continued consent to execute such Documents electronically.

How to contact CCI :

If you would like us to send the Documents to a different e-mail address, request paper copies of Documents you have previously received electronically, or withdraw your consent to receive electronic documents, please follow the instructions below. If you have any other questions, please contact: CCI

1. To advise CCI of your new e-mail address

If you would like your Documents sent to a different e-mail address, you must send an e-mail message to CCI . In the body of the e-mail please state the following: (i) your previous e-mail address, and (ii) your new e-mail address. No other information is required.

In addition, you must notify DocuSign of your new e-mail address. Please log into your DocuSign user account, and follow the instructions to update your e-mail address.

2. To request paper copies from CCI
To request paper copies of Documents you have received previously through your DocuSign user account, send an e-mail to CCI
In the body of the e-mail please state the following: (i) your e-mail address, (ii) full name, (iii) U.S. Postal address, and (iv) telephone number. Additional charges may apply for such paper copies.

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i. decline to sign a document from within your DocuSign user account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent; or
ii. send us an e-mail to CCI and in the body of such request you must state your e-mail, full name, US Postal Address, telephone number, and account number. No additional information is necessary.

Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.
Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically
To confirm you can access this information electronically and that you consent to receiving and executing Documents electronically on the terms and conditions described above, please let us know by clicking the "I Agree" button.
By clicking the "I Agree" button, you confirm that

- You can access and read this Consent To Electronic Delivery and Execution of Documents; and
- You can print on paper the disclosure or save or send the disclosure to a place where you can print it, for future reference and access; and
- Until or unless you notify CCI as described above, you consent to the delivery and execution of Documents electronically.

COV-01-004 STATISTICAL ANALYSIS PLAN

INDUSTRY ALLIANCE PLATFORM TRIAL TO ASSESS THE EFFICACY AND SAFETY OF MULTIPLE CANDIDATE AGENTS FOR THE TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

SUB-PROTOCOL NUMBER: COV-01-004

SUB-PROTOCOL FOR CANDIDATE AGENT: APREMILAST

AUTHOR: PPD

VERSION NUMBER AND DATE: AMENDMENT 1 V1.0, 23APR2021

SUB-PROTOCOL STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Sub-protocol Statistical Analysis Plan (SAP) Amendment 1 v1.0 (dated 23Apr2021) for sub-protocol COV-01-004.

	Name	Signature	Date (DDMmmYYYY)
Author:	PPD	PPD	
Position:	PPD		
Company:	CCI		

Upon review of this document, the undersigned approves this version of the sub-protocol COV-01-004 SAP, authorizing that the content is acceptable for the reporting specific to this sub-protocol.

	Name	Signature	Date (DDMmmYYYY)
Approved by:	PPD	PPD	
Position:	PPD		
Company:	CCI		
On behalf of:	PPD		
Position:	PPD		
Company:	CCI		
Approved by:	PPD	PPD	
Position:	PPD		
Company:	Amgen, Inc.		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
Final, v1.0	24Nov2020	PPD	Not Applicable – First Version
Amendment 1, v1.0	23Apr2021	PPD	Updated COV-01-004 sub-protocol version on which this subprotocol SAP is based from version 3.1, dated 26Oct2020, to version 4.0. dated 14Apr2021 Removed Section 11 (COVID-19 Co-Morbidities) since this section is now combined with Section 12 (Medical History) in Master SAP Updated title of former Sections 12 (now Section 11) and 14 (now 13) to be in line with Master SAP. Added pharmacodynamic (PD) analysis set CCI [redacted]

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of data specific to sub-protocol COV-01-004 of master protocol COV-01. It describes the specific data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This sub-protocol SAP is based on version 4.0 of the sub-protocol COV-01-004, dated 14Apr2021.

For the rules and conventions to be used in the presentation and analysis of data common across all sub-protocols, refer to the Master COV-01 SAP.

2. STUDY OBJECTIVES

The study objectives are described in the Master COV-01 SAP.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

The general description is available in the Master COV-01 SAP.

3.2. SCHEDULE OF ACTIVITIES

The schedule of activities can be found in Section 1.2 of the sub-protocol COV-01-004.

3.3. CHANGES TO PLANNED ANALYSES FROM MASTER PROTOCOL COV-01 AND SUB-PROTOCOL COV-01-004

There are no changes to the analyses planned for master protocol COV-01 and sub-protocol COV-01-004.

4. PLANNED ANALYSES

The planned analyses are listed and described in the Master COV-01 SAP.

All outputs described in this sub-protocol SAP will be produced at the time of sub-protocol COV-01-004 primary analysis (refer to COV-01 Master SAP).

In addition to the outputs planned to be produced at the time of COV-01-004 sub-protocol final analysis (refer to COV-01 Master SAP), safety outputs described in this sub-protocol SAP will also be produced at the time of COV-01-004 sub-protocol final analysis (refer to Section 17.1).

5. ANALYSIS SETS

Analysis sets are described in the Master COV-01 SAP.

An additional analysis set that is specific to sub-protocol COV-01-004 is described below:

5.1. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic (PK) analysis set will include all patients included in the safety analysis set (refer to Master COV-01 SAP Section 5.2) who were randomized to the apremilast plus Standard of Care (SoC) treatment group and have at least one measured PK concentration.

5.2. PHARMACODYNAMIC ANALYSIS SET

The pharmacodynamic (PD) analysis set will include all patients included in the safety analysis set (refer to Master COV-01 SAP Section 5.2) who were randomized to the COV-01-004 sub-protocol (i.e., apremilast plus SoC or placebo to apremilast + SoC treatment groups) and have at least one measured post-baseline biomarker level.

5.3. PROCESS FOR ANALYSIS SET ASSIGNMENT

As the PK analysis set is defined based on objective criteria only, the authorization of this sub-protocol SAP will stand for the agreement and authorization of the inclusion/exclusion of each patient in this PK analysis set.

6. GENERAL CONSIDERATIONS

Details are provided in the Master COV-01 SAP.

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE CALCULATION

Details are defined in the Master COV-01 SAP.

7.2. MISSING DATA

Details are defined in the Master COV-01 SAP.

7.3. STATISTICAL TESTS

Details are defined in the Master COV-01 SAP.

7.4. MULTIPLE COMPARISONS/MULTIPLICITY

Details are defined in the Master COV-01 SAP.

7.5. MULTICENTER STUDY

Details are defined in the Master COV-01 SAP.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Details are defined in the Master COV-01 SAP.

7.7. EXAMINATION OF SUBGROUPS

For sub-protocol COV-01-004, additional subgroup analyses will be performed for selected safety data (refer to Section 17.1). The additional subgroup is:

- Patients randomized to sub-protocol COV-01-004 (apremilast plus SoC and placebo plus SoC treatment groups) plus patients included in COV-01-004 control arm (refer to Master COV-01 SAP Section 4.5) that have been randomized to the placebo plus SoC treatment group of a sub-protocol other than COV-01-004 and who did not receive any concomitant dose of apremilast during the course of the study (refer to Master COV-01 SAP Section 14 for concomitant use definition). That is, placebo plus SoC patients included in the control arm of COV-01-004 who were randomized to a sub-protocol other than COV-01-004 and who concomitantly took apremilast during the course of the study will be excluded from this subgroup.

It is to be noted that these subgroup analyses will be performed only if more than 10% of patients included in COV-01-004 control arm, that have been randomized to a sub-protocol other than COV-01-004, concomitantly took apremilast during the course of the study.

7.8. SOFTWARE VERSION

Details are defined in the Master COV-01 SAP.

8. OUTPUT PRESENTATIONS

Output presentations are described in the Master COV-01 SAP.

9. DISPOSITION AND WITHDRAWALS

Analysis of disposition and withdrawals is described in the Master COV-01 SAP.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Analysis of demographic and other baseline characteristics is described in the Master COV-01 SAP.

11. DISEASE HISTORY

Analysis of disease history at screening is described in the Master COV-01 SAP.

12. MEDICAL HISTORY

Analysis of medical history is described in the Master COV-01 SAP.

13. PRIOR AND CONCOMITANT MEDICATIONS

Analysis of prior and concomitant medications is described in the Master COV-01 SAP.

14. EXPOSURE TO STUDY DRUG

Patients randomized to sub-protocol COV-01-004

Patients randomized to the apremilast plus SoC or placebo plus SoC treatment groups of COV-01-004 sub-protocol will receive either an apremilast 30 mg or matching placebo tablet, as applicable, twice daily (BID) in a double-blind manner for 14 days or until hospital discharge, death, or discontinuation of study drug, whichever occurs first, in addition to SoC.

Reason for dose modification of study drug (i.e., dose increased, dose reduced, drug interrupted, drug withdrawal, and unknown) will be captured on the *Exposure* page of the electronic Case Report Form (eCRF).

Patients included in the control arm of COV-01-004 sub-protocol who were randomized to the placebo plus SoC group of a sub-protocol other than COV-01-004

It is to be noted that the planned duration of exposure to a study drug, planned frequency of administration of the study drug, and planned route of administration of the study drug will vary from one sub-protocol to the other, but similar information as for COV-01-004 sub-protocol will be captured on the *Exposure* page of the eCRF of these other sub-protocols.

Exposure to study drug

The exposure to study drug will be summarized by treatment arm (breaking down the placebo plus SoC arm by sub-protocol) based on the safety analysis set as follows:

- Duration of exposure:
    - Duration of exposure (days) as a continuous variable;
    - Duration of exposure (days) as a categorical variable: 1 to 3, > 3 to 7, > 7 to 14, and > 14;
    - Total number of doses received as a continuous variable, where the total number of doses received is defined as the total number of doses received by each patient, not the total number of doses received across all patients.
- Average dose (mg/day) only for patients randomized to sub-protocol COV-01-004;
- Dose modifications:
    - Number and percentage of patients with at least one dose reduction;
    - Number and percentage of patients with a dose reduction by reason for dose reductions:
        - Adverse events;
        - Due to creatinine clearance < 30 mL/min*;
        - Due to renal replacement therapy*;
        - Other.
    - Total number of dose reductions as a continuous variable, where the total number of dose reductions defined similarly to the total number of doses received;
    - Among patients with a dose reduction, number and percentage of patients with dose subsequently increased back to the planned dose level;
    - Number and percentage of patients with at least one interrupted dose;

- Number and percentage of patients with at least one dose interruption by reason for dose interruption:
  - Adverse events;
  - Due to creatinine clearance < 30 mL/min*;
  - Due to renal replacement therapy*;
  - Other.
- Total number of dose interruptions as a continuous variable, where the total number of dose interruptions is defined similarly to the total number of doses received;
- Among patients with a dose interruption, number and percentage of patients with dose subsequently restarted at planned dose level;
- Number and percentage of patients with at least one overdose.

* Applicable only for patients randomized to sub-protocol COV-01-004.

All dosing and exposure data will also be listed.

14.1. DERIVATIONS

For patients randomized to a study drug planned to be administered on a daily basis, duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = (Date of last dose of study drug – Date of first dose of study drug) + 1

For all other patients (i.e. randomized to a study drug planned to be administered not on a daily basis), duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = {[Earliest date of (end of planned study treatment period, hospital discharge or discontinuation from study drug)] – Date of first dose of study drug} + 1

For patients randomized to sub-protocol COV-01-004 only, the average dose per day will be computed as follows:

- Average dose (mg/day) = Total cumulative dose (mg) / duration of exposure (days)

where the total cumulative dose is the computed total cumulative dose (mg) taken by a patient during the course of the study.

15. COMPLIANCE WITH STUDY DRUG

Compliance with study drug will be summarized by treatment arm (breaking down the placebo plus SoC arm by sub-protocol) based on the safety analysis set. In addition to the descriptive summary, the following compliance categories will be presented:

- < 80%;
- ≥ 80% to < 100%
- 100%;
- > 100%.

Compliance data will also be listed.

15.1. DERIVATIONS

For each patient, the compliance will be computed as follows:

- Compliance (%) = (Actual total number of doses / Expected total number of doses) x 100

where:

- Actual total number of doses is defined as the sum of all doses taken through the course of the study
- Expected total number of doses is defined as the sum of protocol-defined doses to be taken through the course of the study and is computed as follows:
    - For patients randomized to a study drug administered on a daily basis:
        - Expected total number of doses = expected number of doses (injections) per day * expected number of days under treatment, where the expected number of days under treatment is defined as: {[Earliest date of (end of planned study treatment period, hospital discharged or discontinuation

from study drug)] – Date of first dose of study drug} + 1

- For patients randomized to a study drug planned to be administered not on a daily basis:
  - Expected total number of doses = Expected number of doses (injections) per day * number of expected administration days between randomization and the earliest of (end of planned study treatment period, hospital discharged or discontinuation from study drug).

    For example, if a study drug is planned to be administered once on Day 1 and once on Day 4, the expected total number of doses is 2; unless patient discontinued from study drug or was discharged from the hospital on or after Day 1 but before Day 4, in which case the expected total number of doses is 1. As another example, if the study drug is planned to be administered twice daily on every other day from Day 1 to Day 14, the expected total number of doses is 14; unless patient discontinued from study drug or was discharged from the hospital let say, on Day 10, in which case the expected total number of doses is 10 (i.e., 2 doses [injection] per days * 5 administration days).

16. EFFICACY ENDPOINTS

Efficacy analyses are described in the Master COV-01 SAP.

17. SAFETY ENDPOINTS

17.1. ADVERSE EVENTS

In addition to the safety analyses described in the Master COV-01 SAP, the following analyses will be repeated for the subgroup of patients defined in Section 7.7 based on the safety analysis set:

- Overview of treatment-emergent adverse events (TEAEs);
- TEAEs by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade, System Organ Class and Preferred Term (PT);

- TEAEs with a CTCAE grade ≥ 3 by System Organ Class and PT:
- Fatal TEAEs by System Organ Class and PT;
- Serious TEAEs by System Organ Class and PT;
- Most common serious TEAEs by PT, where a most common is defined as at least 1% in at least one treatment arm;
- TEAEs leading to dose modification by System Organ Class and PT;
- TEAEs leading to discontinuation of study drug by System Organ Class and PT;

Patients excluded from the subgroup defined in Section 7.7 will be flagged in the listings of all fatal AEs, all SAEs, and all AEs leading to permanent discontinuation of study drug.

Refer the Master COV-01 SAP Section 18.1 for additional details about these summaries and listings.

17.2. Laboratory Evaluations

Analysis of laboratory evaluations is described in the Master COV-01 SAP.

17.3. Vital Signs

Analysis of vital signs is described in the Master COV-01 SAP.

17.4. ECG Evaluations

Analysis of electrocardiogram (ECG) evaluations is described in the Master COV-01 SAP.

17.5. Physical Examination

Analysis of physical examination is described in the Master COV-01 SAP.

18. PHARMACOKINETICS

PK concentrations of apremilast will be summarized and listed by visit and timepoints based on the PK analysis set. In addition to the descriptive statistics mentioned in Master COV-01 SAP Appendix 2, the coefficient of variation (CV%), geometric mean, geometric standard deviation (SD), and geometric CV% will also be provided for the PK concentrations. Concentrations that are below the limit of quantification (BLQ) will be treated as a numeric value of zero.

PK concentrations of apremilast will be summarized for the following time categories:

- 0 - < 3 hours post morning administration of study drug;
- 3 - <6 hours post morning administration of study drug;
- 6 - < 9 hours post morning administration of study drug;
- 9 - <12 hours post morning administration of study drug
- 0 - < 3 hours post evening administration of study drug;
- 3 - <6 hours post evening administration of study drug;
- 6 - < 9 hours post evening administration of study drug;
- 9 - <12 hours post evening administration of study drug.

Scatter plots of plasma concentrations against the time since last dose, in hours, will be provided for each day and each dose of study drug (i.e., Day 8 post morning administration of study drug, Day 8 post evening administration of study drug, Day 15 post morning administration of study drug, and Day 15 post evening administration of study drug).

18.1. DERIVATIONS

For each day where a blood sample for PK concentration is planned to collected, the time of the two administrations of study drug taken on a day will be compared with the time of the blood sample for PK concentration collected on that day as follows in order to derive the timepoint categories specified in Section 18:

- Time post morning administration of study drug (hours) = {[Time (hours & minutes) of collection of the blood sample for PK concentration – Time (hours & minutes) of the morning administration of the study drug] + 1} / 60 minute if time of collection of the blood sample for PK concentration is before the time of the evening administration of the study drug;
- Time post evening administration of study drug (hours) = {[Time (hours & minutes) of collection of the blood sample for PK concentration – Time (hours & minutes) of the evening the administration of study drug] + 1} / 60 minute if time of collection of the blood sample for PK concentration is on or after the time of the evening administration of the study drug but before the time of the morning administration of study drug of the next day.

19. PHARMACODYNAMICS

CCI [redacted]

20. DATA NOT SUMMARIZED OR PRESENTED

The list of data not summarized or presented is available in the Master COV-01 SAP.

Certificate Of Completion

PPD

Status: Completed

PPD

Record Tracking

Status: Original
4/23/2021 4:17:13 PM

Holder: PPD

Location: DocuSign

Signer Events	Signature	Timestamp
PPD		

Signer Events	Signature	Timestamp
PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/23/2021 4:19:03 PM
Certified Delivered	Security Checked	4/23/2021 4:20:35 PM
Signing Complete	Security Checked	4/23/2021 4:21:02 PM
Completed	Security Checked	4/23/2021 6:03:23 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 3/3/2020 2:03:57 PM
Parties agreed to: PPD

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In addition, you must notify DocuSign of your new e-mail address. Please log into your DocuSign user account, and follow the instructions to update your e-mail address.

2. To request paper copies from CCI

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ii. send us an e-mail to CCI and in the body of such request you must state your e-mail, full name, US Postal Address, telephone number, and account number. No additional information is necessary.

Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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COV-01-005 STATISTICAL ANALYSIS PLAN

INDUSTRY ALLIANCE PLATFORM TRIAL TO ASSESS THE EFFICACY AND SAFETY OF MULTIPLE CANDIDATE AGENTS FOR THE TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

SUB-PROTOCOL NUMBER: COV-01-005

SUB-PROTOCOL FOR CANDIDATE AGENT: ZILUCOPLAN

AUTHOR: PPD

VERSION NUMBER AND DATE: Amendment 2 v1.0, 28-Jul-2021

SUB-PROTOCOL COV-01-005 STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Sub-protocol COV-01-005 Statistical Analysis Plan (SAP) Amendment 2 v1.0 (dated 28-Jul-2021).

	Name	Signature	Date (DD-Mmm-YYYY)
Author:	PPD	PPD	
Position:	PPD		
Company:	CCI		

Upon review of this document, the undersigned approves this version of the sub-protocol COV-01-005 SAP, authorizing that the content is acceptable for the reporting specific to this sub-protocol.

	Name	Signature	Date (DD-Mmm-YYYY)
On behalf of:	PPD	PPD	
Position:	PPD		
Company:	CCI		
Approved By:	PPD	PPD	
Position:	PPD		
Company:	UCB Biopharma SRL		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Final, v1.0	11-Jan-2021	PPD	Not Applicable – First Version
Amendment 1, v1.0	27-Apr-2021	PPD	Update title of Sections 11and 13 to be in line with Master SAP; Removed the Ukrainian and Non-Ukrainian subgroups and related supplementary analyses; Removed supplementary analyses adjusted for Ukrainians vs. Non-Ukrainians patients' status; Added subgroup of patients randomized to this subprotocol and related supplementary analyses; Added that the risk difference of the overall incidence rates of having any treatment-emergent AESI between the treatment groups will be presented along with its 95% two-sided Wald CI.

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Amendment 2, v1.0	28-Jul-2021	PPD	Specified that the two Interim Analyses (IAs) and Primary Analysis at Day 29 will not be performed for this sub-protocol since enrollment into this sub-protocol was terminated early by the Sponsor on 07-Jun-2021 before the trigger of each of these analyses was met. Exception of summary statistics for the primary efficacy endpoint, secondary efficacy endpoints (key and other), and the additional efficacy endpoint of all-cause mortality through Day 60, removed all planned efficacy analyses given that 1) enrollment into this sub-protocol was terminated early by the Sponsor on 07-Jun-2021, 2) number of patients to be included in COV-01-005 sub-protocol final analysis, and 3) an abbreviated Clinical Study Report will be created for this sub-protocol. Added two-sided 95% exact binomial Confidence Interval within each treatment arm, when applicable. Removed additional subgroup analyses that were to be performed for sub-protocol primary and key secondary efficacy endpoints.

TABLE OF CONTENTS

1. INTRODUCTION

This sub-protocol statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of data specific to COV-01-005 sub-protocol of Master Protocol COV-01. It describes the specific data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This sub-protocol SAP is based on sub-protocol version 1.2, dated 03-Nov-2020.

For the rules and conventions to be used in the presentation and analysis of data common across all sub-protocols, refer to the Master COV-01 SAP.

CCI [redacted]

2. STUDY OBJECTIVES

The study objectives are described in the Master COV-01 SAP.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

The general description is available in the Master COV-01 SAP.

3.2. SCHEDULE OF ACTIVITIES

Schedule of activities can be found in Section 1.2 of COV-01-005 sub-protocol.

3.3. CHANGES TO ANALYSIS FROM MASTER PROTOCOL COV-01 AND SUB-PROTOCOL COV-01-005

Enrollment into sub-protocol COV-01-005 was prematurely terminated by the Sponsor on 07-Jun-2021. In conformance with the Food and Drug Administration (FDA) Guidance for Submission of Abbreviated Report and Synopsis in Support of Marking Application, an abbreviated Clinical Study Report (CSR) will be written for this

sub-protocol. As such, not all analyses initially planned in the Master Protocol COV-01 and Sub-protocol COV-01-005 will be performed for this sub-protocol (refer to Section CCI [redacted]. for more details concerning the analyses to be performed for this sub-protocol).

4. PLANNED ANALYSES

The analyses initially planned to be performed are listed and described in the Master COV-01 SAP. It is to be noted that enrollment into sub-protocol COV-01-005 was terminated early by the Sponsor on 07-Jun-2021 before the trigger for the two Interim Analyses (IAs) for futility and Primary Analysis have been reached (refer to Master SAP Sections 4.2 and 4.3, respectively). Hence, these analyses will not be performed for this sub-protocol and the only analysis that will be performed, in addition to the monthly IDMC Safety analyses, is the final analysis (refer to Section 4.4).

4.1. IDMC SAFETY ANALYSES

Details are provided in the Master COV-01 SAP.

4.2. INTERIM ANALYSES

No IAs will be performed for this sub-protocol (refer to Section 4).

4.3. PRIMARY ANALYSIS

No primary analysis will be performed for this sub-protocol (refer to Section 4).

4.4. FINAL ANALYSIS

The final analysis for this sub-protocol will take place after:

- All patients to be included in this sub-protocol final analysis who were ongoing at the time Sponsor terminated early this sub-protocol completed the study (Day 60 visit) or discontinued early from the study, whichever occurs first.

- Sponsor Authorization of this SAP.
- Final database lock of the database including data from screen failed patients.
- Final database lock of the database of each sub-protocol contributing to the control arm of this sub-protocol (refer to Section 4.5).
- Final database lock of the database of this sub-protocol.

All planned analyses identified in this sub-protocol SAP will be performed by CCI Biostatistics at the time of the final analysis of this sub-protocol.

4.5. SELECTION OF THE CONTROL ARM FOR AN ANALYSIS

4.5.1. IDMC SAFETY ANALYSES

Details are provided in Master SAP Section 4.5.

4.5.2. FINAL ANALYSIS

For final analysis of this sub-protocol, the control arm (also referred to as shared placebo plus standard of care (SoC) arm) will include all patients randomized to the placebo arm of any sub-protocol at a site at which:

- This sub-protocol was opened for enrollment.
- At least one patient was randomized to either this sub-protocol active (zilucoplan plus SoC) or placebo (placebo to zilucoplan plus SoC) arms.

That is, patients that satisfy these criteria will be included in the control arm of this sub-protocol regardless of 1) the timing of patient's randomization into a sub-protocol (i.e., regardless of if patient was randomized before or after this sub-protocol was opened for enrollment at the site) and 2) patient's eligibility to this sub-protocol specific inclusion/ exclusion criteria.

The purpose of this change from the Master SAP control arm definition (Master SAP Section 4.5) is to minimize the randomization imbalance issue noted by the CCI Unblinded Biostatistician and IDMC members at the time of CCI At the time this sub-protocol SAP was finalized, the randomization imbalance was estimated to be approximately 7:1

between this sub-protocol active and control arms, should the original control arm definition would have been retained for the final analysis of this sub-protocol.

5. ANALYSIS SETS

Analysis sets are described in the Master COV-01 SAP.

Additional analysis sets that are specific to sub-protocol COV-01-005 are described below.

5.1. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic (PK) analysis set will include patients from the safety analysis set (refer to Master COV-01 SAP Section 5.2) who were randomized to the zilucoplan plus SoC treatment arm and had at least one measured post-baseline concentration (refer to Master COV-01 SAP Section 6.2 for baseline definition).

5.2. PHARMACODYNAMIC ANALYSIS SET

The pharmacodynamic (PD) analysis set will include patients from the safety analysis set (refer to Master COV-01 SAP Section 5.2) who were randomized to COV-01-005 sub-protocol and had at least one measured biomarker (e.g., C5, etc.).

5.3. ANTI-DRUG ANTIBODY ANALYSIS SET

The anti-drug antibody (ADA) analysis set will include patients from the safety analysis set (refer to Master COV-01 SAP Section 5.2) who were randomized to COV-01-005 sub-protocol and had at least one evaluated ADA sample (negative or positive).

5.4. PROCESS FOR ANALYSIS SET ASSIGNMENT

As the PK, PD, and ADA analysis sets are defined based on objective criteria only, the authorization of this sub-protocol SAP will stand for the agreement and authorization of the inclusion/exclusion of each patient in these PK, PD, and ADA analysis sets.

6. GENERAL CONSIDERATIONS

Details are provided in the Master COV-01 SAP.

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE CALCULATION

Details are defined in the Master COV-01 SAP.

7.2. MISSING DATA

Details are defined in the Master COV-01 SAP.

7.3. STATISTICAL TESTS

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.4. MULTIPLE COMPARISONS/MULTIPLICITY

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.5. MULTICENTER STUDY

Details are defined in the Master COV-01 SAP.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable since no statistical inferences will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.7. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for the final analysis of this sub-protocol (refer to Section 16).

7.8. SOFTWARE VERSION

Details are defined in the Master COV-01 SAP.

8. OUTPUT PRESENTATIONS

Output presentations are described in the Master COV-01 SAP.

9. DISPOSITION AND WITHDRAWALS

Analysis of disposition and withdrawals will be presented as described in the Master COV-01 SAP.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics and other baseline characteristics data will be presented as described in the Master COV-01 SAP.

11. DISEASE HISTORY

Analysis of disease history at screening will be performed as described in the Master COV-01 SAP.

12. MEDICAL HISTORY

Analysis of medical history will be performed as described in the Master COV-01 SAP.

13. PRIOR AND CONCOMITANT MEDICATIONS

In addition to the analysis of prior and concomitant medications described in the Master COV-01 SAP, antibiotic prophylaxis, collected on the *Antibiotic Prophylaxis* page of the electronic Case Report Form (eCRF), will also be coded to the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020 (or later).

Concomitant use (refer to Master COV-01 SAP Section 13 for definition of concomitant use) of antibiotic for any indication as well as of antibiotic prophylaxis for Neisseria infection will be summarized separately by Anatomical Therapeutic Class (ATC) level 2, preferred drug name, and treatment arm based on the FAS (refer to Master COV-01 SAP Section 5.1). Separate summary of patients randomized to COV-01-005 placebo plus SoC treatment group will be provided. A patient having more than one medication within the same ATC level 2 or preferred drug name will be counted only once for that ATC level 2 or preferred drug name.

Furthermore, duration of concomitant use of antibiotic for any indication (days) and number and percentage of patients who received antibiotic prophylaxis for Neisseria infections concurrently while receiving the study drug and up to 14 days after the last dose of the study drug will be presented by treatment arm based on the FAS. Separate summary of patients randomized to COV-01-005 placebo plus SoC treatment group will be provided.

All antibiotic prophylaxis will be listed.

13.1. DERIVATION

Duration of concomitant use of antibiotic for any indication, in days, will be derived as follows:

- Duration of concomitant use of antibiotic for any indication (days) = {[Date of latest stop date of any antibiotic received on or after the first dose of study drug – Latest of (date of earliest start date of antibiotic received on or after the first dose of study drug, date of first dose of study drug)] + 1} – [sum of any gap (days) in concomitant use of antibiotics for any indication on or after the first dose of study drug]

14. EXPOSURE TO STUDY DRUG

Patients randomized to sub-protocol COV-01-005

Patients randomized to zilucoplan plus standard of care (SoC) and placebo plus SoC treatment arms of COV-01-005 sub-protocol will receive a single daily dose of 32.4 mg of the study drug (prefilled syringes containing 0.81 mL of zilucoplan or placebo, as appropriate) administered by subcutaneous (SC) injection in the abdomen (preferred site), thigh or upper arm.

The daily administration of study treatment will start on Day 1 (baseline) and continue to Day 14 or until hospital discharge, whichever occurs first. If the patient is discharged before 14 days of treatment, zilucoplan or placebo should be stopped at time of discharge or 24 hours before discharge.

Reason for dose modification of study drug (i.e. dose interrupted or drug withdrawal) will be captured in the *Exposure* page of the eCRF.

Patients included in the control arm of COV-01-005 sub-protocol who were randomized to the placebo plus SoC group of a sub-protocol other than COV-01-005

It is to be noted that the planned duration of exposure to a study drug, planned frequency of administration of the study drug, and planned route of administration of the study drug will vary from one sub-protocol to the other, but similar information as for COV-01-005 sub-protocol will be captured on the *Exposure* page of the eCRF of these other sub-protocols.

Exposure to study drug

The exposure to study drug will be summarized by treatment arm (breaking down the placebo plus SoC arm by sub-protocol) based on the safety analysis set as follows:

- Duration of exposure:
    - Duration of exposure (days) as a continuous variable;
    - Duration of exposure (days) as a categorical variable: 1 to 3, > 3 to 7, > 7 to 14, and > 14;
    - Total number of doses received as a continuous variable, where the total number of doses received is defined as the total number of doses received by each patient, not the total number of doses received across all patients.

- Dose modifications:
    - Number and percentage of patients with at least one interrupted dose;
    - Number and percentage of patients with at least one dose interruption by reason for dose interruptions:
        - Adverse events;
        - Other.
    - Total number of dose interruptions as a continuous variable, where the total number of dose interruptions is defined similarly to the total number of doses received;
- Number and percentage of patients with at least one overdose.

All dosing and exposure data will also be listed.

14.1. DERIVATIONS

For patients randomized to a study drug planned to be administered on a daily basis, duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = (Date of last dose of study drug – Date of first dose of study drug) + 1

For all other patients (i.e. randomized to a study drug planned to be administered not on a daily basis), duration of exposure to study drug, in days, will be computed as follows:

- Duration of exposure (days) = {[Earliest date of (end of planned study treatment period, hospital discharge or discontinuation from study drug)] – Date of first dose of study drug} + 1

15. COMPLIANCE WITH STUDY DRUG

Compliance with study medication will be summarized by treatment arm (breaking down the placebo plus SoC control arm by sub-protocol) based on the safety analysis set. In addition to the descriptive summary, the following compliance categories will be presented:

- < 80%;
- ≥ 80% to < 100%;
- 100%;
- > 100%.

Compliance data will also be listed.

15.1. DERIVATIONS

For each patient, the compliance will be computed as follows:

- Compliance (%) = (Actual total number of doses / Expected total number of doses) x 100

where:

- Actual total number of doses is defined as the total number of doses (injections) taken (received) through the course of the study;
- Expected total number of doses is defined as the total number of protocol-defined doses (injections) to be taken (received) through the course of the study and is computed as follows:
    - For patients randomized to a study drug administered on a daily basis:
        - Expected total number of doses = Expected number of doses (injections) per day * expected number of days under treatment, where the expected number of days under treatment is defined as: {[Earliest date of (end of planned study treatment period, hospital discharged or discontinuation from study drug)] – Date of first dose of study drug} + 1

- For patients randomized to a study drug planned to be administered not on a daily basis:
  - Expected total number of doses = Expected number of doses (injections) per day * expected number of administration days between randomization and the earliest of (end of planned study treatment period, hospital discharged or discontinuation from study drug)
- For example, if a study drug is planned to be administered once on Day 1 and once on Day 4, the expected total number of doses is 2; unless patient discontinued from study drug or was discharged from the hospital on or after Day 1 but before Day 4, in which case the expected total number of doses is 1. As another example, if the study drug is planned to be administered twice daily on every other day from Day 1 to Day 14, the expected total number of doses is 14; unless patient discontinued from study drug or was discharged from the hospital let say, on Day 10, in which case the expected total number of doses is 10 (i.e., 2 doses [injection] per day * 5 administration days).

16. EFFICACY ENDPOINTS

Given that only 108 patients were randomized into COV-01-005 sub-protocol by the time enrollment into this sub-protocol was terminated early by the Sponsor and that is expected that less than the third of the total number of patients required by the sample size (i.e., ~700; refer to Master SAP Section 7.1) will be included in the final analysis of this sub-protocol, no statistical inferences will be performed for any efficacy endpoint, but two-sided 95% confidence interval (CI) within each treatment arm will be provided, when possible.

In conformance with the FDA's Guidance for Submission of Abbreviated Report and Synopsis in Support of Marking, summary tables will be presented for the primary and key secondary efficacy endpoints (refer to Master SAP Sections 16.1.1, 16.2.1.1, 16.2.1.2, and 16.2.1.3). Although not required by the previously mentioned FDA's Guidance, summary tables will also be provided for the other secondary efficacy endpoints (refer to Master SAP Sections 16.2.1.4 to 16.2.1.9) in order to be compliant with the publication requirements of *ClinicalTrials.gov*. In addition, summary tables will also be provided for the additional efficacy endpoint of incidence of all-cause mortality through Day 60 (refer to Master SAP Section 16.4.1.1).

Efficacy summaries will be performed as described in the Master COV-01 SAP.

16.1. PRIMARY EFFICACY

16.1.1. TIME TO CONFIRMED CLINICAL RECOVERY THROUGH DAY 29, WITHOUT RE-HOSPITALIZATION THROUGH DAY 29

Details are provided in the Master COV-01 SAP.

16.1.2. MISSING DATA IMPUTATION METHOD FOR PRIMARY EFFICACY ENDPOINT

Details are provided in the Master COV-01 SAP.

16.1.3. MAIN ANALYSIS OF PRIMARY EFFICACY ENDPOINT

For the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, as defined in the Master SAP Section 16.1.1, the number and percentage of patients with and without the event will be presented by randomized treatment arm. Two-sided 95% exact binomial Confidence Interval (CI) will also be provided by treatment arm for the percentage of patients with the event. For patients who did not meet the event, the main reason for censoring will be summarized similarly.

Kaplan-Meier curves (product-limit estimate) will be provided by treatment arm for the time to confirmed clinical recovery though Day 29, without re-hospitalization through Day 29. Kaplan-Meier estimate of the time to confirmed clinical recovery through Day 29, without re-hospitalization through Day 29, in days, will be provided at the 25th, 50th (median), and 75th percentiles time along with their corresponding two-sided 95% CIs. The estimates of the SEs will be computed using the Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation. Kaplan-Meier estimates of the probability of having the event will also be provided at Day 29 along with the number of patients with the event and the number of patients at risk at that time.

16.1.4. SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

No sensitivity analyses will be performed for this sub-protocol.

16.1.5. SUPPLEMENTARY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

No supplementary analyses will be performed for this sub-protocol.

16.2. SECONDARY EFFICACY

16.2.1. SECONDARY EFFICACY ENDPOINTS

Details are provided in the Master COV-01 SAP.

16.2.2. MISSING DATA IMPUTATION METHOD FOR SECONDARY EFFICACY ENDPOINTS

Details are provided in the Master COV-01 SAP.

16.2.3. MAIN ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

Details are provided in the Master COV-01 SAP.

16.2.3.1. Binary Endpoints

For the incidence of patients with oxygen-free recovery at Day 29 (refer to Master SAP Section 16.2.1.1), incidence of patients with ≥ 2-point improvement from baseline or fit for discharge on the ordinal scale at Day 29 (refer to Master SAP Section 16.2.1.2), incidence of all-cause mortality through Day 29 (refer to Master SAP Section 16.2.1.3) , incidence of patients with clinical recovery at Days 8, 15 and 29 (refer to Master SAP Section 16.2.1.8), and incidence of patients with sustained clinical recovery as confirmed by Day 60 follow-up (refer to Master SAP Section 16.2.1.9), the number and percentage of patients with and without the event will be provided by treatment arm. Two-sided 95% exact binomial CI will also be provided by treatment arm for the percentage of patients with the event.

For the incidence of all-cause mortality, primary reason of death will also be summarized by treatment arm.

16.2.3.2. Ordinal Endpoints

For the incidence of patients in each category of the 8-point ordinal scale for clinical severity at Days 8, 15, and 29 endpoints (refer to Master SAP Section 16.2.1.4), the number and percentage of patients in each ordinal scale

category will be provided at each specified Day for each treatment arm. The worst post-baseline score on the 8-point ordinal scale for clinical severity from randomization to Day 29 (refer to Master SAP Section 16.2.1.5) and each "number of days" endpoint (refer to Master SAP Sections 16.2.1.6 and 16.2.1.7) will be summarized similarly.

Shift tables from baseline to each post-baseline day up to Day 29 as well as to the worst post-baseline score will also be provided for the 8-point ordinal scale for clinical severity.

16.2.4. SENSITIVITY ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

No sensitivity analyses will be performed for this sub-protocol.

16.2.5. SUPPLEMENTARY ANALYSES FOR SECONDARY EFFICACY ENDPOINTS

For the incidence of all-cause mortality through Day 29 key secondary efficacy endpoint, the time to all-cause mortality through Day 29, in days, associated will be derived as follows:

- Time to all-cause mortality through Day 29 (days) =
  (Date of death / Date of censoring - Date of Study Day 1 [refer to Maser SAP Section 6.1]) + 1.

The date of death will be taken from data captured on the *Death Details* page of the eCRF.

For patients who were alive on Day 29, time to all cause-mortality will be censored at Day 29. For patients with an unknown alive status at the time of the analysis due to missing data, time to all-cause mortality will be censored at the latest date on which the patient was known to be alive before or on the data cut-off date of the analysis. The last date the patient was known to be alive will be the latest date collected on any page of the eCRF. For patients who discontinued from the study before the time of the analysis, time to all-cause mortality will be censored at the date of study discontinuation, as captured on the *Disposition* page of the eCRF.

Number and percentage of patients with and without the event will be presented by randomized treatment arm. For patients who did not meet the event, the main reason for censoring will be summarized similarly.

Kaplan-Meier survival curves by treatment arm will be provided. The 25th percentile, 50th percentile (median), and 75th percentile of time to all-cause mortality through Day 29 (days) with the corresponding two-sided 95% CIs based on the Kaplan-Meier survival curves (refer to Master SAP Section 16.2.4) for each treatment arm will also be presented. The estimate of the SEs will be computed using Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982) and the other CIs will be derived from the Kaplan-Meier

estimates using the log-log transformation. Kaplan-Meier estimates of the probability of having the event will also be provided at Day 29 along with the number of patients with the event and the number of patients at risk at that time.

No supplementary analyses will be performed for the any other secondary efficacy endpoints.

16.3. EXPLORATORY EFFICACY

CCI [redacted]

16.4. ADDITIONAL EFFICACY

16.4.1. ADDITIONAL EFFICACY ENDPOINT

16.4.1.1. Incidence of All-Cause Mortality through Day 60

Details are provided in the Master COV-01 SAP.

16.4.2. MISSING DATA IMPUTATION METHOD FOR ADDITIONAL EFFICACY ENDPOINT

Details are provided in the Master COV-01 SAP.

16.4.3. ANALYSIS OF ADDITIONAL EFFICACY ENDPOINT

The number and percentage of patients alive and dead through Day 60 (refer to Section 16.4.1.1) will be provided by treatment arm along with the two-sided 95% exact binomial CI for the percentage of patients dead through Day 60. Primary reason of death will also be summarized by treatment arm.

16.4.4. SENSITIVITY ANALYSES FOR ADDITIONAL EFFICACY ENDPOINT

No sensitivity analyses will be performed for the additional efficacy endpoint.

16.4.5. SUPPLEMENTARY ANALYSES FOR ADDITIONAL EFFICACY ENDPOINT

The time to all-cause death through Day 60, in days, will be derived as follows:

- Time to all-cause mortality through Day 60 (days) =
  (Date of death / Date of censoring - Date of Study Day 1 [refer to Maser SAP Section 6.1]) + 1.

The date of death will be taken from data captured on the *Death Details* page of the eCRF.

For patients who were alive or patients with an unknown alive status at the time of the analysis due to missing data, time to all-cause mortality will be censored at the latest date on which the patient was known to be alive before or on Day 60. The last date the patient was known to be alive will be the latest date collected on any page of the eCRF. For patients who discontinued from the study before Day 60, time to all-cause mortality will be censored at the date of study discontinuation, as captured on the *Disposition* page of the eCRF.

Number and percentage of patients with and without the event will be presented by treatment arm. For patients who did not meet the event, the main reason for censoring will be summarized similarly.

Kaplan-Meier survival curves by treatment arm will be provided. The 25th percentile, 50th percentile (median), and 75th percentile of time to all-cause mortality (days) through Day 60 with the corresponding two-sided 95% CIs based on the Kaplan-Meier survival curves for each treatment arm will be presented. The estimate of the SEs will be computed using Greenwood's formula, the CI for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at above mentioned time points will be derived from the Kaplan-Meier estimates using the log-log transformation. Kaplan-Meier estimates of the probability of having the event will also be provided at Day 60 along with the number of patients with the event and the number of patients at risk at that time.

16.5. INTERIM ANALYSIS

No IAs will be performed for this sub-protocol since the trigger for the first IA was not reached by the time enrollment into this sub-protocol was terminated early by Sponsor (refer to Master SAP Section 16.5).

17. SAFETY ENDPOINTS

In addition to the safety analyses are described in Master COV-01 SAP, the following safety analysis will also be provided based on the safety analysis set (refer to Master SAP Section 5.2).

17.1. ADVERSE EVENTS

17.1.1. ADVERSE EVENTS OF SPECIAL INTEREST

The following are defined as adverse events of special interest (AESIs) for this sub-protocol and will be identified based on pre-defined coded preferred terms (PTs), high-level terms (HLTs, and/or system organ class:

- Anaphylactic reactions (Medical Dictionary for Regulatory Activities [MedDRA] algorithmic approached; refer to Appendix 1);
- Serious anaphylactic reactions (MedDRA algorithmic approached; refer to Appendix 1);
- Hypersensitivity reactions (standardized MedDRA query [SMQ] – narrow scope; refer to Appendix 2);
- Serious hypersensitivity reactions (SMQ – narrow scope: refer to Appendix 2);
- Infections (MedDRA system organ class of 'Infections and infestations');
- Serious infections (MedDRA system organ class of 'Infections and infestations');
- Neisseria infections (MedDRA high level term [HLT] of 'Neisseria infections');
- Serious Neisseria infections (HLT of 'Neisseria infections');
- Drug related hepatic disorders (SMQ – comprehensive search; refer to Appendix 3), excluding the 'Liver neoplasms, benign (incl. cysts and polyps)' and 'Liver neoplasms, malignant and unspecified' sub-SMQs.

A summary of treatment-emergent (refer to Master COV-01 SAP Section 17.1) AESIs overall and by AESI category and preferred term (PT) will be prepared by treatment arm for patients randomized to COV-01-005 only. Should a patient experience multiple events within an AESI category or PT, the patient will be counted only once for that AESI category or PT. The risk difference of the overall incidence rates of having any treatment-emergent AESI between the treatment arms will be presented along with its two-sided 95% Wald CI. A listing of all AESIs will be provided for patients randomized to COV-01-005 only.

17.2. LABORATORY EVALUATIONS

17.2.1. POTENTIAL HY'S LAW EVENTS

In addition to the laboratory analyses described in the Master COV-01 SAP for the identification of the potential Hy' law events, the following summary will also be provided:

- Number and percentages of patients with (ALT > 3 x ULN or AST > 3 x ULN) AND (total bilirubin > 2 x ULN) AND (alkaline phosphatase [ALP] < 2 x ULN) at any time after the first dose of study drug and by visit for each treatment arm as well as for the subset of patients randomized to the placebo to zilucoplan + SoC treatment arm.

17.3. VITAL SIGNS

Analysis of vital signs is described in the Master COV-01 SAP.

17.4. ELECTROCARDIOGRAM EVALUATIONS

Analysis of electrocardiogram (ECG) evaluations is described in the Master COV-01 SAP.

17.5. PHYSICAL EXAMINATION

Analysis of physical examination is described in the Master COV-01 SAP.

18. PHARMACOKINETIC ASSESSMENTS

Concentrations of zilucoplan will be summarized descriptively at each scheduled assessment based on the PK analysis set (refer to Section 5.1). Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of zilucoplan concentration data. Geometric coefficient of variation will be reported as a percentage to 1 decimal place and the 95% CI for the geoMean will use the same number of decimal places as the geoMean. It will be left blank if the geoCV is 0.

When reporting individual zilucoplan concentration data in listings and presenting summary statistics in tables, the following rules will apply:

- Missing data should be reported as 'NV' (no value) in the listings;
- Concentrations below the lower limit of quantification (LLOQ) should be reported as BLQ (below the limit of quantification) in the listings;
- To calculate summary statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded;
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this scheduled assessment. Other summary statistics should be reported as missing ("-"). The minimum should be reported as BLQ;
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ values replaced by half the LLOQ value";
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ").

Zilucoplan concentrations will be listed.

18.1. DERIVATION

The geoCV, in percentage, will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

- GeoCV (%) = sqrt[exp(SD^2) – 1] x 100

19. PHARMACODYNAMIC AND OTHER BIOMARKER ASSESSMENTS

CCI [redacted]

20. ANTI-DRUG ANTIBODY TESTING

Number and percentage of patients with a negative ADA response (i.e., either [negative screen] or [positive screen and negative immunodepletion]) and a positive ADA response (i.e., positive screen and positive immunodepletion) will be summarized by scheduled visit and treatment arm based on the ADA analysis set (refer to Section 5.3).

Number and percentage of patients in each of the following categories will also be summarized by treatment arm:

1. Treatment-induced ADA negative, defined as patients who were ADA negative at baseline as well as at all post-baseline scheduled visit;
2. Treatment-induced ADA positive, defined as patients who were ADA negative at baseline and ADA positive at at least one post-baseline scheduled visit. This category also includes patients with a missing ADA response status at baseline who had at least one ADA positive response at any post-baseline scheduled visit;
3. Treatment-reduced ADA, defined as patients who were ADA positive at baseline and ADA negative at all post-baseline scheduled visit;
4. Treatment-unaffected ADA, defined as patients who were ADA positive at baseline and ADA positive at at least one post-baseline scheduled visit with titer values of the same magnitude as baseline (i.e., equal or less than a pre-defined fold difference increase from the baseline value, where the pre-defined fold difference increase from the baseline value is defined as the minimum significant ratio [MSR] determined during assay validation);
5. Treatment-boosted ADA positive, defined as patients who were ADA positive at baseline and ADA positive at at least one post-baseline scheduled visit with increased in titer values as compare to baseline (i.e., greater than the pre-defined fold difference increase from baseline value);
6. Inconclusive, defined as patients who were ADA negative or positive at baseline for whom some post-baseline ADA response assessments are missing, while all other post-baseline ADA response assessments are ADA negative;
7. Total prevalence of pre-Ab i.e., patients in categories 3, 4, and 5 combined;
8. Total incidence of treatment-emergent ADA positive i.e., patients in categories 2 and 5 combined.

The fold difference increase from baseline (i.e., the MSR determined during the assay validation) needed to consider a titer value reported post-baseline to be above the assay validation will be noted in the relevant tables and listings.

All ADA data will be listed.

21. DATA NOT SUMMARIZED OR PRESENTED

The list of data not summarized or presented is available in the Master COV-01 SAP.

APPENDIX 1 MEDDRA ALGORITHMIC APPROACH TO ANAPHYLAXIS

The SMQ anaphylactic reactions consists of three parts:

- A narrow search containing PTs that represent core anaphylactic reaction terms:

Category A
o Anaphylactic reaction
o Anaphylactic shock
o Anaphylactic transfusion reaction
o Anaphylactoid reaction
o Anaphylactoid shock
o Circulatory collapse
o Dialysis membrane reaction
o Kronis syndrome
o Shock
o Shock symptom
o Type I hypersensitivity

- A broad search that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C or D.

Category B (Upper Airway/ Respiratory)

o Acute respiratory failure	o Irregular breathing	o Respiratory failure
o Asthma	o Laryngeal dyspnea	o Reversible airways obstruction
o Bronchial oedema	o Laryngeal oedema	o Sensation of foreign body
o Brochospasm	o Laryngospasm	o Sneezing
o Cardio-respiratory distress	o Laryngotracheal oedema	o Stridor
o Chest discomfort	o Mouth swelling	o Swollen tongue
o Chocking	o Nasal obstruction	o Tachypnoea
o Chocking sensation	o Oedema mouth	o Throat tightness
o Circumoral oedema	o Oropharyngeal spasm	o Tongue oedema
o Cough	o Oropharyngeal swelling	o Tracheal obstruction
o Cyanosis	o Respiratory arrest	o Tracheal oedema
o Dyspnoea	o Respiratory distress	o Upper airway obstruction
o Hyperventilation	o Respiratory dyskinesia	o Wheezing

Category C (Angioedema/ Urticaria/ Pruritus/ Flush)

o Allergic oedema	o Injection site urticaria	o Rash
o Angioedema	o Lip oedema	o Rash erythematous
o Erythema	o Lip swelling	o Rash generalized

Category C (Angioedema/ Urticaria/ Pruritus/ Flush)		
○ Eye oedema	○ Nodular rash	○ Rash pruritic
○ Eye pruritus	○ Ocular hyperaemia	○ Skin swelling
○ Eye swelling	○ Oedema	○ Swelling
○ Eyelid oedema	○ Periorbital oedema	○ Swelling face
○ Face oedema	○ Pruritus	○ Urticaria
○ Flushing	○ Pruritus allergic	○ Urticaria papular
○ Generalised erythema	○ Pruritus generalised	

Category D (Cardiovascular / Hypotension)		
○ Blood pressure decreased	○ Cardiac arrest	○ Diastolic hypotension
○ Blood pressure diastolic decreased	○ Cardio-respiratory arrest	○ Hypotension
○ Blood pressure systolic decreased	○ Cardiovascular insufficiency	

- An algorithm approach which combines a number of anaphylactic reaction symptoms in order to increase specificity will be used for this sub-protocol. A potential anaphylactic reaction is defined meeting at least one of the following criteria where the different terms occur on either the same day as when an injection was administered or one day after:
    - A narrow PT from Category A;
    - A PT from Category B AND a PT from Category C;
    - A PT from Category D AND (a PT from Category B OR a term from Category C).

APPENDIX 2 SMQ OF HYPERSENSITIVITY REACTIONS (NARROW SCOPE)

Preferred Term
• Administration site hypersensitivity
• Documented hypersensitivity to administered product
• Drug hypersensitivity
• Hypersensitivity
• Infusion related hypersensitivity reaction
• Infusion site hypersensitivity
• Injection site hypersensitivity
• Type I hypersensitivity
• Type II hypersensitivity
• Type IV hypersensitivity

APPENDIX 3 SMQ OF DRUG RELATED HEPATIC DISORDERS (COMPREHENSIVE SEARCH)

Preferred Term	
• 5'nucleotidase increased	• Acute graft versus host disease in liver
• Abnormal LFTs	• Acute hepatic congestion
• Abnormal liver function tests	• Acute hepatic failure
• Acholia	• Acute liver damage
• Acquired afibrinogenaemia	• Acute liver failure
• Acquired afibrinogenemia	• Acute liver injury
• Acquired antithrombin III deficiency	• Acute on chronic hepatic failure
• Acquired factor IX deficiency	• Acute on chronic liver failure
• Acquired factor VIII deficiency	• Acute yellow liver atrophy
• Acquired factor XI deficiency	• Advanced chronic liver disease
• Acquired fibrinogen deficiency	• Aggravated bilirubinemia
• Acquired hepatocerebral degeneration	• Alanine aminotransferase abnormal
• Acquired protein S deficiency	• Alanine aminotransferase abnormal NOS
• Acute cholestatic hepatitis	• Alanine aminotransferase increase
• Acute cytolytic hepatitis	• Alanine aminotransferase increased
• Acute derangement of liver function	• Alkaline phosphatase raised
• Acute fatty liver	• Alkaline phosphatase increased
• Acute fulminant hepatitis	• Alkaline phosphatase NOS increased

Preferred Term	
• Alkaline phosphatase serum increased	• Antithrombin III decreased
• Allergic hepatitis	• Artificial extracorporeal liver support
• Alloimmune hepatitis	• Ascites
• ALP increased	• Ascites chylous
• Al-P increased	• Aspartate aminotransferase abnormal
• ALPPS	• Aspartate aminotransferase abnormal NOS
• ALT flare up	• Aspartate aminotransferase increase
• ALT high	• Aspartate aminotransferase increased
• ALT increased	• Associating liver partition and portal vein ligation for staged hepatectomy
• Ammonia abnormal	• AST flare up
• Ammonia abnormal NOS	• AST high
• Ammonia increased	• AST increased
• Angioma spider	• AST/ALT ratio abnormal
• Anicteric cholestasis	• Asterixis
• Anorectal varices	• AT-3 decreased
• Anorectal varices bleeding	• Atrophy liver
• Anorectal varices hemorrhage	• Atrophy of hepatocytes
• Anti factor X activity abnormal	• Autoimmune hepatitis
• Anti factor X activity decreased	• Anti factor X activity increased

Preferred Term	
• Bacterascites	• Bilirubin total abnormal
• Bile output abnormal	• Bilirubin total high
• Bile output decreased	• Bilirubin total increased
• Biliary ascites	• Bilirubin unconjugated increased
• Biliary cirrhosis	• Bilirubin urine present
• Biliary cirrhosis NOS	• Bilirubin value increased
• Biliary cirrhosis primary	• Bilirubinaemia
• Biliary cirrhosis secondary	• Bilirubinaemia aggravated
• Biliary enzyme increased	• Bilirubinemia
• Biliary fibrosis	• Bilirubinemia aggravated
• Biliary stasis	• Biliverdin increased
• Bilirubin abnormal	• Biopsy liver abnormal
• Bilirubin conjugated abnormal	• Bleeding esophageal varices
• Bilirubin conjugated increased	• Bleeding oesophageal varices
• Bilirubin elevated	• Blood alkaline phosphatase abnormal
• Bilirubin excretion disorder	• Blood alkaline phosphatase bone increased
• Bilirubin excretion disorder NOS	• Blood alkaline phosphatase high
• Bilirubin increased	• Blood alkaline phosphatase increased
• Bilirubin indirect increased	• Blood alkaline phosphatase intestine increased
• Bilirubin non-glucuronides high	• Blood alkaline phosphatase liver increased

Preferred Term	
• Blood alkaline phosphatase NOS increased	• Blood alkaline phosphatase NOS abnormal
• Blood alkaline phosphatase placental increased	• Blood thromboplastin decreased
• Blood alkaline phosphatase renal abnormal	• Bone alkaline phosphatase increased
• Blood alkaline phosphatase renal increased	• Bromosulphthalein retention
• Blood antithrombin III low	• Bromosulphthalein test abnormal
• Blood bilirubin abnormal	• Bromsulphalein retention
• Blood bilirubin increased	• Bromsulphthalein retention
• Blood bilirubin indirect increased	• Bruised liver
• Blood bilirubin unconjugated increased	• BSP abnormal
• Blood cholinesterase abnormal	• BSP excretion delayed
• Blood cholinesterase decreased	• Caput medusae
• Blood fibrinogen abnormal	• Cardia variceal ligation
• Blood fibrinogen abnormal NOS	• Cardiohepatic syndrome
• Blood fibrinogen decreased	• Charcot's cirrhosis
• Blood galactose tolerance abnormal	• Child-Pugh-Turcotte score abnormal
• Blood thrombin abnormal	• Child-Pugh-Turcotte score increased
• Blood thrombin abnormal NOS	• Child-Turcotte-Pugh class A
• Blood thrombin decreased	• Child-Turcotte-Pugh class B
• Blood thromboplastin abnormal	• Child-Turcotte-Pugh class C
• Blood thromboplastin abnormal NOS	• Cholemia

Preferred Term	
• Cholestasis extrahepatic	• Cholestasis
• Cholestasis intrahepatic	• Chronic non-suppurative destructive cholangitis
• Cholestatic hepatic disorder	• Chronic passive congestion of liver
• Cholestatic hepatitis	• Chronic persistent hepatitis
• Cholestatic icterus	• Chylous ascites
• Cholestatic jaundice	• Cirrhosis biliary
• Cholestatic liver disease	• Cirrhosis liver
• Cholestatic liver injury	• Cirrhosis liver post necrotic
• Cholestatic pruritus	• Cirrhosis liver postnecrotic
• Cholinesterase blood decreased	• Cirrhosis of liver
• Cholinesterase decreased	• Cirrhosis of liver without mention of alcohol
• Cholinesterase low	• Coagulation factor decreased
• Chronic active hepatitis	• Coagulation factor II level abnormal NOS
• Chronic graft versus host disease in liver	• Coagulation factor II level decreased
• Chronic hepatic failure	• Coagulation factor IX level abnormal
• Chronic hepatitis	• Coagulation factor IX level abnormal NOS
• Chronic hepatitis, unspecified	• Coagulation factor IX level decreased
• Chronic hepatopathy due to metabolic defect	• Coagulation factor IX level low
• Chronic liver disease	• Coagulation factor V level abnormal
• Chronic liver injury	• Coagulation factor V level abnormal NOS

Preferred Term	
• Coagulation factor V level low	• Coagulation factor V level decreased
• Coagulation factor VII level abnormal	• Conjugated bilirubinemia
• Coagulation factor VII level abnormal NOS	• Conjunctiva bulbi coloring yellow
• Coagulation factor VII level decreased	• Conjunctiva bulbi colouring yellow
• Coagulation factor VII level low	• Conjunctiva coloring yellow
• Coagulation factor X level abnormal	• Conjunctiva colouring yellow
• Coagulation factor X level abnormal NOS	• Cruveilhier-Baumgarten syndrome
• Coagulation factor X level decreased	• Cryptogenic cirrhosis
• Coagulation factors decreased	• CT scan liver
• Coloring yellow	• Cytolytic hepatitis
• Colouring yellow	• Damage liver
• Coma hepatic	• De Ritis ratio abnormal
• Compensated cirrhosis	• Decompensated cirrhosis
• Complications of transplanted liver	• Decreased INR
• Computerized tomogram liver	• Decreased plasma fibrinogen
• Computerized tomogram liver abnormal	• Deficiency of bile secretion
• Congestive gastropathy	• Degeneration fatty liver
• Conjugated bilirubin level increased	• Deranged liver function tests
• Conjugated bilirubin level raised	• Derangement of liver function tests
• Conjugated bilirubinaemia	• Diabetic hepatopathy

Preferred Term	
• DILI	• Encephalopathy hepatic
• Direct bilirubin abnormal	• End stage liver disease
• Direct bilirubin increased	• Esophageal varices
• Direct hyperbilirubinaemia	• Esophageal varices hemorrhage
• Direct hyperbilirubinemia	• Esophageal varices in cirrhosis of liver
• Disease hepatocellular	• Esophageal varices ruptured
• Disorder hepatic	• Esophageal varices with bleeding
• Disorder liver	• Esophageal varices without mention of bleeding
• Disturbance of liver function tests	• Esophagogastric devascularization
• Drug-induced hepatitis	• Exaggerated hypoprothrombinemia
• Drug-induced hepatotoxicity	• Failure hepatorenal
• Drug-induced liver disease	• Failure liver
• Drug-induced liver injury	• Fatty liver
• Duodenal varices	• Fatty liver infiltration
• Dyscholia	• Fatty liver metamorphosis
• Dyscholia	• Fetor hepaticus
• Dysfunction hepatic non-icteric	• Fibrinogen decreased
• Edema due to hepatic disease	• Fibrinogen plasma decreased
• Elevated liver enzyme levels	• Fibrinogenopenia
• Elevated liver enzymes	• Fibrinopenia

Preferred Term	
• Fibrosis biliary	• Gamma-glutamyltransferase high
• Fibrosis liver	• Gamma-glutamyltransferase increased
• Flapping tremor	• Gammaglutamyltranspeptidase abnormal
• Focal hepatic steatosis	• Gamma-GT increased
• Foetor hepaticus	• Gastric variceal injection
• Fulminant hepatic failure	• Gastric variceal ligation
• Function liver abnormal	• Gastric varices
• Function liver decreased	• Gastric varices bleeding
• Function tests multiple liver abnormal	• Gastric varices hemorrhage
• Galactose elimination capacity test abnormal	• Gastric varices ruptured
• Galactose elimination capacity test decreased	• Gastroesophageal variceal hemorrhage prophylaxis
• Gallbladder ejection fraction decreased	• Gastroesophageal varices
• Gallbladder varices	• Gastroesophageal varices hemorrhage
• Gamma glutamyl transpeptidase increased	• Gastrooesophageal variceal hemorrhage prophylaxis
• Gamma GT abnormal	• Gastrooesophageal varices
• Gamma GT increased	• Gastrooesophageal varices haemorrhage
• Gamma GT raised	• GGT increased
• Gamma-glutamyltransferase abnormal	• GGTP abnormal
• Gamma-glutamyltransferase abnormal NOS	• GGTP increase

Preferred Term	
• Glutamate dehydrogenase increased	• Hepaplastin value decreased
• Glutamic-oxaloacetic transaminase increased	• Hepaplastin low
• Glutamic-pyruvate transaminase increased	• Hepatectomy
• Glutamic-pyruvic transaminase increased	• Hepatectomy NOS
• Glycocholic acid increased	• Hepatic artery flow decreased
• Glycogenic hepatopathy	• Hepatic atrophy
• GOT abnormal	• Hepatic calcification
• GOT increased	• Hepatic cirrhosis
• GOT increased transient	• Hepatic cirrhosis NOS
• GPT abnormal	• Hepatic cirrhosis post necrotic
• GPT increased	• Hepatic coma
• GPT increased transient	• Hepatic congestion
• Graft versus host disease in liver	• Hepatic cyst excision
• Granulomatous liver disease	• Hepatic cytolysis
• Guanase increased	• Hepatic damage
• Hanot's cirrhosis	• Hepatic damage (NOS)
• Hemihepatectomy	• Hepatic decompensation
• Hemorrhagic ascites	• Hepatic disease
• Hepaplastin abnormal	• Hepatic disease NOS
• Hepaplastin decreased	• Hepatic disorder aggravated

Preferred Term	
• Hepatic disorder NOS	• Hepatic hydrothorax
• Hepatic dysfunction allergic	• Hepatic hypertrophy
• Hepatic dysfunction non-icteric	• Hepatic impairment
• Hepatic dysfunction NOS	• Hepatic induced edema
• Hepatic dysfunction transient	• Hepatic induced oedema
• Hepatic encephalopathy	• Hepatic infiltration eosinophilic
• Hepatic encephalopathy prophylaxis	• Hepatic insufficiency
• Hepatic enzyme abnormal	• Hepatic intracellular deposit of bilirubin
• Hepatic enzyme decreased	• Hepatic intracellular pigmentation
• Hepatic enzyme increased	• Hepatic lesion
• Hepatic enzymes increased	• Hepatic lesion NOS
• Hepatic failure	• Hepatic lipogranuloma
• Hepatic fibrosis	• Hepatic lobule necrosis
• Hepatic fibrosis marker abnormal	• Hepatic lymphocytic infiltration
• Hepatic fibrosis marker increased	• Hepatic macrosteatosis
• Hepatic function abnormal	• Hepatic mass
• Hepatic function abnormal NOS	• Hepatic microsteatosis
• Hepatic function decreased	• Hepatic necrosis
• Hepatic function disorder	• Hepatic necrosis extensive
• Hepatic granuloma	• Hepatic pain

Preferred Term	
• Hepatic sequestration	• Hepatitis chronic persistent
• Hepatic shock	• Hepatitis drug-induced
• Hepatic size reduced	• Hepatitis flare
• Hepatic steato-fibrosis	• Hepatitis fulminant
• Hepatic steatosis	• Hepatitis granulomatous
• Hepatic trauma	• Hepatitis granulomatous NOS
• Hepatic vascular resistance increased	• Hepatitis necrotising
• Hepatic venous pressure gradient abnormal	• Hepatitis necrotizing
• Hepatic venous pressure gradient increased	• Hepatitis non-icteric
• Hepatitis	• Hepatitis nonspecific
• Hepatitis acute	• Hepatitis NOS
• Hepatitis acute toxic	• Hepatitis reactive non-specific
• Hepatitis aggravated	• Hepatitis symptom
• Hepatitis allergic drug-induced	• Hepatitis toxic
• Hepatitis autoimmune	• Hepatitis toxic drug-induced
• Hepatitis cholestatic	• Hepatitis toxic obstructive
• Hepatitis chronic active	• Hepatitis, unspecified
• Hepatitis chronic active (immune)	• Hepatobiliary disease
• Hepatitis chronic active aggravated	• Hepatobiliary disease NOS
• Hepatitis chronic NOS	• Hepatobiliary insufficiency

Preferred Term	
• Hepatobiliary pain	• Hepatotoxicity aggravated
• Hepatobiliary scan abnormal	• Hepatotoxicity NOS
• Hepatocellular abnormality	• Hyperammonemia
• Hepatocellular damage	• Hyperbilirubinaemia aggravated
• Hepatocellular damage aggravated	• Hyperbilirubinemia
• Hepatocellular damage NOS	• Hyperbilirubinemia aggravated
• Hepatocellular disturbances	• Hypercholia
• Hepatocellular foamy cell syndrome	• Hyperfibrinolysis
• Hepatocellular injury	• Hypertension portal
• Hepatomegaly	• Hypertransaminasaemia
• Hepatopathy	• Hypertransaminasemia
• Hepatopulmonary syndrome	• Hypertrophic cirrhosis
• Hepatorenal failure	• Hypoalbuminemia
• Hepatorenal syndrome	• Hypocholia
• Hepatosis	• Hypocoagulable state
• Hepatosis aggravated	• Hypofibrinogenemia
• Hepatosplenomegaly	• Hypohepatia
• Hepatosplenomegaly NOS	• Hypoprothrombinemia
• Hepatotoxic effect	• Hypothrombinemia
• Hepatotoxicity	• Hypothromboplastinaemia

Preferred Term	
• Hypothromboplastinemia	• INR abnormal
• Hy's law case	• INR decreased
• Icteric conjunctivae	• INR increased
• Icteric sclera	• International normalised ratio abnormal NOS
• Icterus	• International normalized ratio abnormal
• Icterus index increased	• International normalized ratio decreased
• Idiopathic portal hypertension	• International normalized ratio increased
• Immune-mediated hepatitis	• Intestinal varices
• Impaired liver function	• Intestinal varices bleeding
• Increased liver stiffness	• Intestinal varices hemorrhage
• Indirect bilirubin increased	• Intra-abdominal venous shunt
• Indirect hyperbilirubinaemia	• Intrahepatic portal hepatic venous fistula
• Indirect hyperbilirubinemia	• Ischemic hepatitis
• Infiltration fatty liver	• Jaundice
• Injury to liver	• Jaundice (excl neonatal)
• Injury to liver with open wound into cavity	• Jaundice cholestatic
• Injury to liver with open wound into cavity, unspecified laceration	• Jaundice hepatocellular
• Injury to liver without mention of open wound into cavity	• Jaundice NOS

Preferred Term	
• Jaundice, unspecified, not of newborn	• Liver cirrhosis
• Kayser-Fleischer ring	• Liver cholestasis
• Kupffer cell decrease	• Liver contusion
• Kupffer cell increase	• Liver damage
• Laceration of liver, major, with open wound into cavity	• Liver damage aggravated
• Laceration of liver, major, without mention of open wound into cavity	• Liver dialysis
• Laceration of liver, minor, with open wound into cavity	• Liver disorder
• Laceration of liver, minor, without mention of open wound into cavity	• Liver enlargement
• Laceration of liver, moderate, with open wound into cavity	• Liver enzyme abnormal
• Laceration of liver, moderate, without mention of open wound into cavity	• Liver failure
• Leucine aminopeptidase increased	• Liver fatty
• LFTs raised	• Liver fatty change
• Liver and pancreas transplant rejection	• Liver fatty degeneration
• Liver and small intestine transplant	• Liver fatty deposit
• Liver biopsy abnormal	• Liver fatty deposition
• Liver cell damage	• Liver fatty infiltration

Preferred Term	
• Liver fatty metamorphosis	• Liver nodule
• Liver fatty phanerosis	• Liver operation
• Liver function test abnormal	• Liver operation NOS
• Liver function test decreased	• Liver pain
• Liver function test increased	• Liver palpable
• Liver function tests abnormal	• Liver palpable subcostal
• Liver function tests abnormal NOS	• Liver repair
• Liver function tests NOS abnormal	• Liver resection
• Liver function tests raised	• Liver retransplantation
• Liver graft dysfunction	• Liver sarcoidosis
• Liver graft function delayed	• Liver scan abnormal
• Liver graft loss	• Liver scan NOS abnormal
• Liver induration	• Liver tender
• Liver inflammation	• Liver tenderness
• Liver injury	• Liver tenderness of
• Liver iron concentration abnormal	• Liver transplant
• Liver iron concentration increased	• Liver transplant failure
• Liver lobectomy	• Liver transplant rejection
• Liver necrosis	• Liver transplantation

Preferred Term	
• Living donor liver transplant	• Molar ratio of total branched-chain amino acid to tyrosine
• Lupoid hepatic cirrhosis	• Monomicrobial non-neutrocytic bacterascites
• Lupus hepatitis	• MRI-PDFF
• Magnetic resonance imaging liver abnormal	• Multivisceral transplantation
• Magnetic resonance proton density fat fraction measurement	• Naevus spider acquired
• MELD score abnormal	• Necrosis hepatocellular
• MELD score increased	• Necrosis liver
• Mesenteric varices	• Necrosis liver focal
• Mesocaval shunt	• Nevus spider acquired
• Metabolic liver injury	• Nodular regenerative hyperplasia
• Metamorphosis fatty liver	• Non-alcoholic fatty liver
• Micronodular cirrhosis	• Nonalcoholic fatty liver disease
• Microvesicular fat disease of liver	• Non-alcoholic steatohepatitis
• Minimal hepatic encephalopathy	• Non-cirrhotic portal fibrosis
• Mitochondrial aspartate aminotransferase increased	• Non-cirrhotic portal hypertension
• Mixed hepatocellular-cholestatic injury	• Nonspecific abnormal results of function study of liver
• Mixed liver injury	• Nonspecific hepatitis
• Model for end stage liver disease score abnormal	• Nuclear magnetic resonance imaging liver abnormal
• Model for end stage liver disease score increased	• Obstructive jaundice

Preferred Term	
• Ocular icterus	• Peritoneal effusion (chronic)
• Oesophageal varices in cirrhosis of liver	• Peritoneal effusion bloody
• Oesophageal varices NOS	• Peritoneal fluid protein abnormal
• Oesophageal varices ruptured	• Peritoneal fluid protein decreased
• Oesophageal varices with bleeding	• Peritoneal fluid protein increased
• Oesophageal varices without mention of bleeding	• Peritoneovenous shunt
• Oesophagogastric devascularisation	• Phanerosis fatty liver
• Oligocholia	• Phosphatase alkaline increased
• Orthotopic liver transplant	• Plasma cholinesterase decreased
• Parenteral nutrition associated cholestasis	• Plasma fibrinogen abnormal
• Parenteral nutrition associated liver disease	• Plasma thrombin abnormal
• Partial hepatectomy	• Plasma thrombin decreased
• Partial splenic embolization	• Plasma thromboplastin abnormal
• Pericardial devascularization	• Plasma thromboplastin decreased
• Perihepatic discomfort	• Pneumobilia
• Perihepatic fluid collection	• Polymicrobial bacterascites
• Perinatal jaundice due to hepatocellular damage	• Portacaval shunt
• Peripancreatic varices	• Portal anastomosis
• Periportal edema	• Portal fibrosis
• Peritoneal effusion	• Portal hypertension

Preferred Term	
• Portal hypertensive colopathy	• Prophylaxis of gastrooesophageal variceal bleeding
• Portal hypertensive enteropathy	• Protein C antigen decreased
• Portal hypertensive gastropathy	• Protein C decreased
• Portal shunt	• Protein S abnormal
• Portal shunt procedure	• Protein S antigen abnormal
• Portal systemic shunt	• Protein S antigen decreased
• Portal systemic shunt procedure	• Protein S decreased
• Portal tract inflammation	• Protein S free decreased
• Portal triaditis	• Protein S total abnormal
• Portal vein cavernous transformation	• Protein S total decreased
• Portal vein dilatation	• Prothrombin abnormal
• Portal vein enlarged	• Prothrombin activity decreased
• Portal vein flow decreased	• Prothrombin consumption increased
• Portal vein pressure increased	• Prothrombin decreased
• Portopulmonary hypertension	• Prothrombin level abnormal
• Prehepatic portal hypertension	• Prothrombin level abnormal NOS
• Primary biliary cholangitis	• Prothrombin level decreased
• Primary biliary cirrhosis	• Prothrombin ratio decreased
• Primary liver transplant nonfunction	• Prothrombin time abnormal
• Prophylaxis of gastroesophageal variceal bleeding	• Prothrombin time abnormal NOS

Preferred Term	
• Prothrombin time ratio abnormal NOS	• Raised liver function tests
• Prothrombin time ratio decreased	• Regenerative siderotic hepatic nodule
• Prothrombin time increased	• Rejection acute hepatic
• Prothrombin time prolonged	• Rejection chronic hepatic
• Prothrombin time ratio abnormal	• Renal and liver transplant
• Prothrombin time ratio high	• Retention sulfobromophthalein
• Prothrombin time ratio increased	• Retinol binding protein decreased
• Prothrombin time ratio low	• Retrograde portal vein flow
• Prothrombinopenia	• Reye's syndrome
• PT increased	• Reynold's syndrome
• PT prolonged	• Scan liver NOS abnormal
• Pure intrahepatic cholestasis	• Scleral icterus
• Quick's value decreased	• Serum alkaline phosphatase elevated
• Radiation hepatitis	• Serum bilirubin increased
• Radiation-induced liver disease	• Serum cholinesterase decreased
• Raised bilirubin	• Serum glutamic-oxaloacetic ta increased
• Raised INR	• Serum glutamic-oxaloacetic transaminase increased
• Raised LFTs	• Serum glutamic-pyruvic ta increased
• Raised liver enzymes	• Serum glutamic-pyruvic transaminase increased

Preferred Term	
• Serum transaminase increased	• Steatosis hepatic
• SGOT increased	• Stomal varices
• SGPT increased	• Subacute fulminant hepatitis
• Single pass albumin dialysis	• Subacute hepatic failure
• Skin coloring yellow	• Subacute hepatic necrosis
• Skin colouring yellow	• Subacute liver disease
• Small-for-size liver syndrome	• Subicteric
• Spider angioma	• Sugiura procedure
• Spider naevi	• Sulfobromophthalein retention
• Spider nevi	• Sulphobromophthalein retention
• Spider nevus	• Supratherapeutic INR
• Splenic varices	• Syncytial giant cell hepatitis
• Splenic varices bleeding	• Syndrome hepatorenal
• Splenic varices hemorrhage	• Telangiectases acquired
• Splenorenal shunt	• Tenderness liver
• Splenorenal shunt procedure	• Thrombin clotting time abnormal
• Splenorenal varices	• Thrombin clotting time prolonged
• Spontaneous intrahepatic portosystemic venous shunt	• Thrombin decreased
• Steatohepatitis	• Thrombin time abnormal

Preferred Term	
• Thrombin time prolonged	• Unconjugated bilirubinemia
• Thromboplastin decreased	• Unspecified chronic liver disease without mention of alcohol
• Todd's cirrhosis	• Unspecified disorder of liver
• Total bile acids increased	• Unspecified injury to liver with open wound into cavity
• Total hepatectomy	• Unspecified injury to liver without mention of open wound into cavity
• Toxaemia of liver	• Urine ammonia increased
• Toxemia of liver	• Urine bilirubin increased
• Toxic acute liver disease	• Urobilin urine absent
• Transaminase glutamic-oxalacetic increased	• Urobilin urine present
• Transaminase glutamic-pyruvic increased	• Urobilinogen appeared
• Transaminase NOS increased	• Urobilinogen negative
• Transaminase value increased	• Urobilinogen urine decreased
• Transaminases abnormal	• Urobilinogen urine increased
• Transaminases increased	• Urobilinogen urine positive
• Transaminitis	• Varices esophageal
• Transjugular intrahepatic portosystemic shunt	• Varicose veins of abdominal wall
• Ultrasound liver abnormal	• Vascular spider
• Unconjugated bilirubinaemia	• White nipple sign

Preferred Term	
• X-ray biliary abnormal	• Yellow ocular colouring
• X-ray hepatobiliary abnormal	• Yellow skin
• Yellow ocular coloring	

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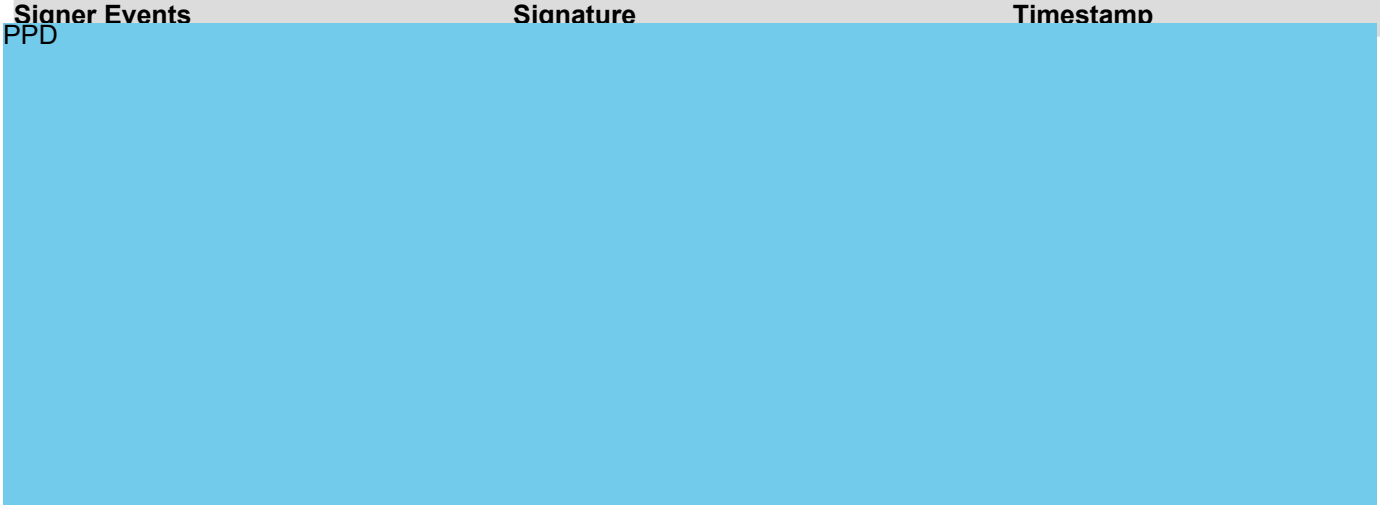
PPD



In Person Signer Events	Signature	Timestamp
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/28/2021 5:26:08 PM
Certified Delivered	Security Checked	7/28/2021 8:04:05 PM
Signing Complete	Security Checked	7/28/2021 8:07:28 PM
Completed	Security Checked	7/29/2021 5:46:00 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

Electronic Record and Signature Disclosure created on: 3/3/2020 2:03:57 PM
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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.
Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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