16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (Protocol MP1032-CT05) Version 2.0 dated 31-August-2022

Statistical Analysis Plan for Interventional Studies

Sponsor Name: MetrioPharm AG

Protocol Number: MP1032-CT05
Protocol Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PROOF-OF-CONCEPT, PHASE IIA STUDY OF MP1032 PLUS STANDARD OF CARE VS STANDARD OF CARE IN THE TREATMENT OF HOSPITALIZED PATIENTS WITH MODERATE TO SEVERE COVID-19

Protocol Version and Date:
Final 1.0, 09-Feb-2021
Final 2.0, 31-Jan-2022

Syneos Health Project Code: 7019936

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Statistical Analysis Plan Version and Date: Final 2.0, 31-Aug-2022

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	31-Jan-2022	PPD	Initial Release Version
2.0	31-Aug-2022	PPD	Clarification of definitions and derivations, addition of subgroups, addition of table for number of symptoms by visit, addition of table for ECG Interpretation at Screening

I confirm that I have reviewed this document and agree with the content.

Approvals
Syneos Health Approval
PPD

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDRM	Blind Data Review Meeting
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
IDMC	Independent Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EQ	EuroQol
EQ-5D-5L	EuroQol-5D-5L
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HRQoL	Health-related Quality of Life
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ITT	Intention-to-Treat
IWRS	Interactive Web-Response System

Abbreviation	Description
LAR	Legally Authorized Representative
LOCF	Last Observation Carried Forward
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
Min	Minimum
MNAR	Missing Not At Random
N/A	Not Applicable
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
RT-PCR	Reverse-transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SoC	Standard of Care
SpO_2	Saturation of Oxygen

Abbreviation	Description
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
VAS	Visual Analog Scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WI	Work Instruction
WOCBP	Women of Childbearing Potential

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings (TFLs).

2.2. Timings of Analyses

The analysis of efficacy, safety, and pharmacokinetics (PK) is planned after all patients complete the final study visit or terminate early from the study.

An independent Data Monitoring Committee (DMC) will review descriptive summaries of accumulating safety and patient disposition throughout the study in the frequency described in the DMC Charter (refer to Section 15).

3. Study Objectives

3.1. Primary Objective

- To measure the effect of MP1032 plus standard of care (SoC) versus placebo plus SoC on Day 14 on disease progression in patients with moderate to severe coronavirus disease 2019 (COVID-19)

3.2. Secondary Objectives

- To measure the effect of MP1032 plus SoC versus placebo plus SoC on Day 28 on disease progression in patients with moderate to severe COVID-19
- To measure the effect of MP1032 plus SoC versus placebo plus SoC on disease resolution on Day 14 and Day 28
- To measure the effect of MP1032 plus SoC versus placebo plus SoC on the mortality rate and other specific COVID-19 related characteristics
- To assess the safety of MP1032 (eg, adverse events [AEs] and laboratory abnormalities)
- To assess the PK of MP1032 on Day 1 (single dose) and Day 7 (steady state) in a PK subset of patients

3.3. Exploratory Objectives

- To measure the effect of MP1032 plus SoC versus placebo plus SoC on some additional COVID-19 related characteristics
- To evaluate the health-related quality of life (HRQoL) of patients treated MP1032 plus SoC compared with placebo plus SoC
- To evaluate biomarker levels

4. Study Details/Design

4.1. Brief Description

This is a Phase IIa, randomized, double-blind, placebo-controlled, multicenter, proof-of-concept study designed to assess the potential efficacy and safety of 300 mg MP1032 twice daily (BID) plus SoC versus placebo plus SoC in hospitalized adults with moderate to severe COVID-19.

Approximately 40 sites worldwide will participate in this study.

Approximately 140 patients will be screened to randomize approximately 120 patients in 2:1 ratio as follows:

- Arm A (300 mg MP1032 BID plus SoC): approximately 80 patients
- Arm B (placebo BID plus SoC): approximately 40 patients

The stratification factor for randomization will include baseline COVID-19 severity (moderate and severe) and age-class (≤65 years and >65 years). COVID-19 severity will be determined using the following criteria:

- Moderate COVID-19:
  - Positive severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) testing by standard reverse-transcription polymerase chain reaction (RT-PCR) assay or equivalent test
  - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
  - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, saturation of oxygen (SpO_2) >93% (on room air at sea level, if possible), heart rate ≥90 beats per minute
  - No clinical signs indicative of severe or critical COVID-19
- Severe COVID-19:
  - Positive SARS-CoV-2 testing by standard RT-PCR assay or equivalent test
  - Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
  - Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% (on room air at sea level, if possible), partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2)<300, or diagnosed with acute respiratory distress syndrome ([ARDS] according to the Berlin definition; see Table 3 in the Protocol)
  - No criteria met for critical COVID-19

To standardize the assessment of COVID-19 severity, respiratory rate, SpO_2, and heart rate will be measured when the patient is on room air at sea level (ie, no supplemental oxygen, if possible) and at rest for at least 5 minutes. If possible, the site should collect the information from each patient at the same time each day (±1 hour).

Please note: Patients who are receiving oxygen therapy at baseline for a chronic condition (eg, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension [PAH], idiopathic pulmonary fibrosis [IPF], etc.) should be considered as having severe COVID-19 (unless the

patient meets the definition for critical COVID-19). For questions related to COVID-19 severity, the investigator should contact the medical monitor.

Each site will treat all patients with SoC for the duration of the study. The selected SoC will be used in accordance with the hospital's SoC procedures and may include drugs under an emergency use authorization.

This study consists of 3 periods: (1) screening, (2) treatment, and (3) follow-up. During the screening period, each potential patient (or patient's legally acceptable representative) will provide informed consent prior to starting any study-specific procedures. The randomization of patients to treatment groups will be performed centrally by an interactive web-response system (IWRS) using a randomization scheme that will be developed by an unblinded, independent statistician. During the treatment period, randomized patients will be provided their assigned treatment and assessments according to the protocol. All patients will be treated for 28 days, unless the study drug is discontinued, eg, for safety reasons. If the patient is discharged home before Day 28, the study team will provide the patient with the remainder of the blinded study drug kits to take home along with instructions on how to continue treatment at home on the day-of-discharge; for these patients, treatment compliance will be conducted via a diary. If the patient does not feel comfortable to complete the diary, the site will alternatively provide the patient with the option to be called, twice a day, to confirm that the study drug is taken as instructed. The treatment period will end with the Day 28 (End of Treatment Visit) assessments. The follow-up period will end with the Follow-up Visit assessments on Day 60.

Please note: Patients will be assessed while hospitalized. If patients are discharged from the hospital, they will have study visits at Day 14, Day 28, and Day 60 as an outpatient visit. Patients discharged early will continue to receive study drug through Day 28. For discharged patients, Day 14 and Day 28 visits are preferred to be conducted in person at the study site. If restrictions limit the ability of the patient to return to the study site, these visits may be conducted by home healthcare visit or by telephone/virtual call (the patient's caregiver may assist during the telephone/virtual call). For discharged patients, it is sufficient to conduct the Day 60 Follow-up Visit as a telephone/virtual call (the patient's caregiver may assist during the telephone/virtual call) and an outpatient or home healthcare visit is also allowed.

Note: Home healthcare visits are only allowed in countries where home healthcare visits are explicitly permitted by regulatory requirements.

The study duration for an individual patient will be as follows:

- Screening period: up to 7 days
- Treatment period: 28 consecutive days (ie, Day 1 to Day 28)
- Follow-up period: 32 days after Day 28 (ie, Day 60)

As such, the approximate study duration (including screening and the follow-up period) for an individual patient is up to 67 days (±3 days).

An independent DMC will be established by the sponsor or designee to review accumulating study data at regular intervals (as per the DMC charter) throughout the study to ensure the safety of patients and review overall study conduct. The DMC can recommend in writing to the sponsor whether to continue, modify, or stop the clinical study on the basis of safety considerations (see Section 14.8 of the protocol for further details).

No interim analysis is planned.

4.2. Patient Selection

4.2.1. Inclusion Criteria

The inclusion criteria are listed in Section 8.1 of the protocol.

4.2.2. Exclusion Criteria

The exclusion criteria are listed in Section 8.2 of the protocol.

4.3. Determination of Sample Size

The primary efficacy endpoint 'proportion of patients with disease progression on Day 14' is assumed to be 10% in the 300 mg MP1032 BID plus SoC treatment group (Arm A) and 30% in the placebo plus SoC treatment group (Arm B). Using the Chi-square test with type I error alpha=10% two-sided for this proof-of-concept study and 2:1 randomization ratio, 114 patients (76 in Arm A and 38 in Arm B) are required to achieve a statistical power of 83%. Considering about 5% early study terminations, the necessary sample size for randomization results in 120 patients in total (80 in Arm A and 40 in Arm B). If during the conduct of the study the early study termination rate is higher than the estimated 5%, then an increase in the randomized number of patients may be necessary.

Sample size estimation is performed using nQuery 8, Version 8.6.1.0.

A subset of randomized patients will be consented for the collection of blood samples for PK measurements. The PK subset consists of approximately 20 patients from the 300 mg MP1032 BID plus SoC group and approximately 10 patients from the placebo plus SoC group, up to a total of approximately 30 patients.

4.4. Treatment Assignment and Blinding

The randomization of patients to treatment groups will be performed centrally by an Interactive Web-Response System (IWRS) using a randomization scheme that will be produced by an unblinded, independent statistician. During the randomization process, IWRS will assign a randomization number. Each patient will be assigned one kit number at randomization and a second kit number at the Day 14 visit. The study drug kits will contain the respective blinded treatment available at the study site. Further information on IWRS process will be provided in the IWRS Manual.

Approximately 120 patients will be randomly assigned (2:1) as follows:

- Arm A (300 mg MP1032 BID plus SoC): approximately 80 patients
- Arm B (placebo BID plus SoC): approximately 40 patients

The randomization will be performed stratified considering the baseline COVID-19 severity (moderate and severe) and age-class (≤65 years and >65 years) and in blocks.

An unblinded, independent statistician will be assigned to produce the randomization schedule and unblinded tables, figures, and listings for the independent DMC. The unblinded statistician will not otherwise participate in study procedures.

In the event that emergency unblinding is required for a given patient because of AEs or concerns for the patient's safety or well-being, the investigator may break the randomization code for the patient via the IWRS, by which the unblinding will be captured. The investigator is responsible for notifying the medical

monitor and/or sponsor of such an event as soon as possible. The unblinding and its cause will also be documented in the electronic case report form (eCRF).

4.5. Administration of Study Medication

All randomized patients will receive study drug from Day 1 to Day 28 according to their assigned treatment and according to the randomization scheme.

Please note: Patients who remain hospitalized after 28 days of consecutive treatment with study drug are not eligible for additional treatments with study drug. Patients will receive 6 capsules in the morning and 6 capsules in the evening (ie, approximately every 12 hours, approximately at the same time every day, and at least 8 hours apart) according to their randomized treatment arm assignment as described below:

- Arm A: MP1032 (300 mg [6 × MP1032 hard gelatin capsules 50 mg] BID) for oral administration
- Arm B: 6 × placebo capsules (ie, matching MP1032 hard gelatin capsules 50 mg) BID for oral administration

In Arm A, the planned total daily dose of MP1032 is 600 mg. In Arm B, the planned total daily dose of MP1032 is 0 mg.

Study drug will be administered to each patient with water (ad libitum) for oral administration. For this study, patients should be, if possible, administered study drug in a fasted state (≥ 4 hours). However, if a patient has eaten prior to their planned administration, the dosing may proceed under a fed state. Patients may eat approximately 30 minutes postdose. The study site should record the date and time of dosing (recorded as the time when the first capsule is administered). For patients in the PK subset, study drug should be administered in fasted state on Day 1 and Day 7, when feasible. If the patient did not receive the study drug in the fasted state, then the amount of food consumed within 4 hours before dosing and 30 minutes after dose administration should be recorded and the PK samples should be collected as planned.

Any missed dose of study drug may be administered as soon as possible and the next scheduled dose may be administered according to the planned schedule as long as the doses are at least 6 to 8 hours apart. If study drug administration is interrupted for >2 days, the investigator should notify the medical monitor to determine if the study drug administration can be resumed.

Patients will be asked to abstain from the following products that may potentially affect their safety and/or the PK profile of the study drug:

- soft or hard drugs (including cannabis) from screening and throughout the study
- smoking or using electronic cigarettes while admitted to the hospital
- consumption of alcohol-based products will be prohibited from screening until the final dose of study drug

4.6. Study Procedures and Flowchart

Table 1: Schedule of Assessments

Study Period	Screening Period		Treatment Period				Follow-up Period	-
Visit Name	Screening[a]	Day 1[a]	Days 2 to 13	Day 14[b]	Day 21[b]	Day 28 (End of Treatment Visit)[b]	Day 60 (Follow-up Visit)[b] / Early Study Termination after Day 28	Day of Discharge / Early Study Termination before Day 28
Study Day (window)	Day -7 to Day -1	Day 1 (NA)	Days 2 to 13 (NA)	Day 14 (±2 days)	Day 21 (±2 days)	Day 28 (±3 days)	Day 60 (±3 days)	Day of Discharge
Informed consent[c]	X	-	-	-		-	-	-
COVID-19 testing[d]	X	X	-	X[e]		X[e]	X[e]	-
Demographics[f]	X	-	-	-		-	-	-
Medical/surgical history[g]	X	X (updates only)	-	-		-	-	-
Inclusion/exclusion criteria	X	X	-	-		-	-	-
Complete physical examination[h]	X	-	-	-		-	-	-
Limited physical examination[h]	-	X	X (only Day 8 [±3 days])[s]	X[e]		X[e]	-	X
Vital signs[i]	X	X	X[j]	X[e]		X[e]	X[e]	X
Height	X	-	-	-		-	-	-
Weight and BMI	X	X	-	X[e]		X[e]	X[e]	X
Clinical laboratory assessments (hematology, blood biochemistry, coagulation, and urinalysis)	X	X	X (only Day 8 [±3 days])[s]	X (Days 14, 21, and 28)[e, u]			-	X
ECG[k]	X	-	-	-		-	-	-
Pregnancy test (WOCBP only)[l]	X	X	-	X		-	-	X (only if discharged before Day 14 or at Early Study Termination before Day 14)
Randomization via IWRS	-	X	-	-		-	-	-

Study Period	Screening Period		Treatment Period				Follow-up Period	-
Visit Name	Screening[a]	Day 1[a]	Days 2 to 13	Day 14[b]	Day 21[b]	Day 28 (End of Treatment Visit)[b]	Day 60 (Follow-up Visit)[b] / Early Study Termination after Day 28	Day of Discharge / Early Study Termination before Day 28
Study Day (window)	Day -7 to Day -1	Day 1 (NA)	Days 2 to 13 (NA)	Day 14 (±2 days)	Day 21 (±2 days)	Day 28 (±3 days)	Day 60 (±3 days)	Day of Discharge
Retrieve the 14-day blinded study drug kit via the study drug kit number assigned by IWRS		X		X[v]				X (only if discharged before Day 14; NA for Early Study Termination)
Blood sample collection for biomarkers	-	X[o]	X (only Day 7)[o]	X (Days 14, 21, and 28)[o]			X[c,o]	-
Administer blinded study drug BID	-		X[t]				-	-
Provide remainder of the assigned blinded study drug kit(s) to the patient along with instructions[m]	-	-	-	-		-	-	X (only if discharged during the treatment period; NA for Early Study Termination)
Provide patient with the diary and train patient on use of the diary[m]	-	-	-	-		-	-	X (only if discharged during the treatment period; NA for Early Study Termination)
COVID-19 symptoms	X	X	-	X		X	X	X
COVID-19 severity[p]	X	X	-	-		-	-	-
Clinical status related to COVID-19 on the NIAID 8-point ordinal scale[q]	X	X	X	X		X	X	X
EQ-5D-5L questionnaire[r]	-	-	-	-		-	X	X (only if discharged/ early terminated

Study Period	Screening Period		Treatment Period				Follow-up Period	-
Visit Name	Screening[a]	Day 1[a]	Days 2 to 13	Day 14[b]	Day 21[b]	Day 28 (End of Treatment Visit)[b]	Day 60 (Follow-up Visit)[b] / Early Study Termination after Day 28	Day of Discharge / Early Study Termination before Day 28
Study Day (window)	Day -7 to Day -1	Day 1 (NA)	Days 2 to 13 (NA)	Day 14 (±2 days)	Day 21 (±2 days)	Day 28 (±3 days)	Day 60 (±3 days)	Day of Discharge
								before Day 60)
Blood sample collection (plasma) for PK (from the PK subset of approximately 30 patients who give optional consent)[n]	-	X	X (only Day 7)[j]			-	-	-
AEs	X							X
Prior and concomitant medications	X							X

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; COVID-19 = coronavirus 2019; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-5L = EuroQol-5D-5L; IEC = independent ethics committee; ICU = intensive care unit; IRB = institutional review board; IWRS = interactive web-response system; LAR = legally authorized representative; NA = not applicable; NIAID = National Institute of Allergy and Infectious Diseases; PK = pharmacokinetic; RT-PCR = reverse transcription-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus type 2; SoC = standard of care; SpO_2 = saturation of oxygen; WOCBP = women of childbearing potential

a. Those patients who are fully eligible (all screening assessments are available) can have Day 1 performed on the same day as screening. If screening and Day 1 are performed on the same day, visit procedures required for both visits do not need to be repeated.
b. Patients will be assessed while hospitalized. If patients are discharged from the hospital, they can have the study visits at Day 14, Day 21, Day 28, and Day 60 as an outpatient visit. Patients discharged early will continue to receive study drug through Day 28. For discharged patients, Day 14 and Day 28 visits are preferred to be conducted in person at the study site. If restrictions limit the ability of the patient to return to the study site, these visits may be conducted by home healthcare visit or by telephone/virtual call (the patient's caregiver may assist during the telephone/virtual call). For discharged patients, it is sufficient to conduct the Day 60 Follow-up Visit as a telephone/virtual call (the patient's caregiver may assist during the telephone/virtual call) or an outpatient or home healthcare visit is also allowed. Please note: In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (eg, telephone calls, letter to the patient's last known mailing address, or local equivalent methods). In cases where the patient's LAR provides informed consent on behalf of the patient, the study site should attempt to contact the LAR. Additionally, the study site should attempt to regain contact with the patient using the alternative contact information provided by the patient/LAR at the time of informed consent. These contact attempts must be documented in the patient's medical records.
c. The patient must give informed consent to participate in the study or, for adults incapable of consenting due to their medical condition (eg, too weak or debilitated, severe shortness of breath) or due to literacy issues, the patient's LAR must be willing give informed consent on behalf of the patient to participate in the study as permitted by local regulatory authorities, IRBs/IECs, or local laws.

d. At the screening visit, the local laboratory may perform COVID-19 testing by standard RT-PCR assay or equivalent test. At screening, a positive test must be available in order for the patient to be randomized on Day 1. If the patient has a previous confirmation of SARS-CoV-2 (within 7 days of Day 1), the SARS-CoV-2 test at screening is not required. On Day 1, Day 14, Day 28, and Day 60, samples will be sent to the central laboratory for COVID-19 testing by standard RT-PCR assay. The result of the COVID-19 tests (positive/negative) must be documented in the eCRF. Further details will be described in the laboratory manual. Please note: If COVID-19 tests are performed at unscheduled time points (eg, according to SoC), findings (ie, positive/negative result) must be recorded in the eCRF.
e. Not all assessments will be able to be performed if the Day 14, Day 28, and/or 60 visits are conducted via a telephone/virtual call (the patient's caregiver may assist during the telephone/virtual call). If the assessment can be conducted via a telephone/virtual call, the study site should record the details; otherwise, the missed assessment will not be considered a protocol deviation. If the visit is conducted by a home healthcare nurse, these assessments should be conducted, if possible; if the assessment can be conducted via home healthcare nurse, the study site should record the details; otherwise, the missed assessment will not be considered a protocol deviation. These assessments must be conducted if the visit is conducted at the study site. All efforts should be made to collect clinical laboratory assessments on Day 14 (± 2 days) and Day 28 (± 3 days). Please note: In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (eg, telephone calls, letter to the patient's last known mailing address, or local equivalent methods). In cases where the patient's LAR provides informed consent on behalf of the patient, the study site should attempt to contact the LAR. Additionally, the study site should attempt to regain contact with the patient using the alternative contact information provided by the patient/LAR at the time of informed consent. These contact attempts must be documented in the patient's medical records.
f. Demographics will include sex, age, race, and/or ethnicity.
g. Medical/surgical medical history includes all active and chronic diseases (eg, asthma and COPD), and any diseases diagnosed in the past 1 year (before screening) that the investigator considers clinically significant. Additional pre-existing conditions present at the time when informed consent is given and up to the time of first dosing (Day 1) are to be regarded as concomitant. Medical history will include documentation of social behaviors, including use of tobacco, nicotine (including use of electronic cigarettes), and soft or hard drugs (including cannabis), as well as alcohol consumption, if applicable. Smoking history also must be documented as part of medical history and includes: never, light (<100 cigarettes/lifetime), active smoker, and former smoker (quit date). History of number packs/day, number of smoking years, and quitting time for former and active smokers must also be documented. Additionally, the investigators will document at screening the patient's Charlson score via the Charlson Comorbidity Index (see Section 12.1 of protocol for further details).
h. A complete physical examination will be performed at screening. Physical examinations will be performed by a physician, nurse, or other appropriately trained staff. The complete physical examination includes: head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems. A limited physical examination to verify continued patient eligibility and to follow-up regarding any change in medical history will be performed at the visits indicated above. Symptom-driven, limited physical examinations may be performed as clinically indicated during the study (according to SoC).
i. Vital signs include systolic and diastolic blood pressure, heart rate, respiration rate, SpO_2, and body temperature. All vital signs will be measured after the patient has been resting for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Moreover, additional vital signs may be performed as needed in case of any cardiac AE.
j. For patients who remain hospitalized only.
k. A 12-lead, resting ECG will be obtained locally at screening. At screening, the investigator must examine the ECG traces for clinically significant abnormalities that could exclude the patient from the study. ECGs should always be obtained in supine position after adequate rest (≥5 minutes).

l. For WOCBP, a serum sample for pregnancy testing must be collected at screening and a urine sample for pregnancy testing must be collected before the first dose on Day 1. Pregnancy tests must be negative for the patient to be randomized and treated. A urine pregnancy test will be repeated on Day 14 (± 7 days). If the patient is discharged before Day 14, urine pregnancy test at day of discharge should be done, and urine pregnancy test at Day 14 is not required. If the patient is discharged after Day 14, urine pregnancy test should be done at Day 14, and urine pregnancy test at day of discharge is not required (whichever comes first). Patients with a positive pregnancy test will be discontinued from study drug.

m. Only for patients discharged before Day 28. If the patient does not feel comfortable to complete the diary, the site will alternatively provide the patient with the option to be called, twice a day, to confirm that the study drug is taken as instructed.

n. Plasma PK samples will be collected via sparse sampling from approximately 30 patients (who give optional consent) in a 2:1 ratio to assess the PK of MP1032 on Day 1 (single dose) and Day 7 (steady state). A total of 16 samples will be collected relative to the first dose on Day 1 and the first dose on Day 7. Samples on Day 1 and Day 17 will be collected predose (within 10 minutes before the first daily dose) and postdose at 10 minutes, 20 minutes, 30 minutes, 60 minutes, 120 minutes, 8 hours (before next dose), and 24 hours before the next morning dose (if applicable), if possible. Patients who provide consent for the PK sampling, but are no longer hospitalized on Day 7, will not have Day 7 PK samples collected.

o. Blood samples to be obtained on Day 1 (before the first study drug administration) and Days 7, 14, 21, 28, and 60 (when possible). Blood samples for biomarkers must be collected on Days 7, 14, 21, 28, and 60 if a patient is still hospitalized. If a patient is discharged, the study site should arrange an outpatient visit (ie, at the study site) to accommodate the collection of blood samples for biomarkers on Days 7, 14, 21, 28, and 60.

p. To standardize the assessment of COVID-19 severity, respiratory rate, SpO_2, and heart rate will be measured when the patient is on room air at sea level (ie, no supplemental oxygen, if possible) and at rest for at least 5 minutes. If possible, the site should collect the information from each patient at the same time each day (±1 hour).

q. Record the patient's clinical status related to COVID-19 on the NIAID 8-point ordinal scale and also record the date and time for each individual component of the NIAID 8-point ordinal scale including: invasive or non-invasive mechanical ventilation/ECMO start/stop, high-flow/mask oxygen start/stop, supplemental oxygen start/stop (nasal cannula, liter flow [and its conversion to FiO_2], other delivery services), hospital discharge (whether with limitations or without limitations), hospitalization type (eg, transfer to ICU) start/stop, and (if applicable) death, cause of death (including relatedness to COVID-19), and date/time of death. If possible, the site should collect the information from each patient at the same time each day (±1 hour).

r. The EQ-5D-5L (Appendix 2 of protocol) is only required for discharged patients and at the following visits: day of discharge, Day 60, and Early Termination visit (if applicable). The EQ-5D-5L is not required for patients who remain hospitalized until study end.

s. The limited physical examination and clinical laboratory assessments on Day 8 (± 3 days) will be collected in all patients who remain hospitalized. If the patient is discharged before Day 8 (± 3 days), the site should arrange to have the physician assess the patient via a telephone/virtual call. If the physician determines during the telephone/virtual call that the limited physical examination and clinical laboratory assessments are clinically indicated, then the site should arrange for an outpatient visit to collect these assessments.

t. For all patients (except on Day 1 and Day 7 for patients in the PK subset): Patients should not eat within the 30 minutes before planned study drug administration and within the 30 minutes after study drug dosing, when feasible. However, if a patient has eaten within the 30 minutes before their planned study drug administration, study drug dosing may proceed. The study site should record the date and time of dosing (recorded as the time when the first capsule is administered). For patients in the PK subset on Day 1 and Day 7 only: Patients should not eat within the 4 hours before planned study drug administration and within the 120 minutes after study drug dosing, when feasible. Thus, study drug should be administered in fasted state (≥ 4 hours), when feasible. However, if a patient has eaten within the 4 hours before their planned administration, study drug dosing may proceed. The patient's fed or fasted state, as well as food intake (yes/no) within the 120 minutes after study drug dosing should be recorded. The PK samples should be collected as planned regardless of the patients' fasted/fed state. The study site should record the date and time of dosing (recorded as the time when the first capsule is administered).

u. The clinical laboratory assessments on Day 21 will be collected in all patients who remain hospitalized. If the patient is discharged before Day 21, the site should arrange to have the physician assess the patient via a telephone/virtual call. If the physician determines during the telephone/virtual call that the clinical laboratory assessments are clinically indicated, then the site should arrange for an outpatient visit to collect this assessment.
v. The +2 day window does not apply to the retrieval of the 14-day blinded study drug kit as the second kit must be distributed at the latest on Day 14.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

- Proportion of patients with disease progression on Day 14. Disease progression is defined as the proportion of patients who are not alive or who have respiratory failure. Respiratory failure is defined as patients who have a score of 2, 3 or 4 on the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale (see below).

5.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of this study are:

- Proportion of patients with disease progression on Day 28. Disease progression is defined as the proportion of patients who are not alive or who have respiratory failure. Respiratory failure is defined as patients who have a score of 2, 3 or 4 on the NIAID 8-point ordinal scale (see below).
- Proportion of patients with disease resolution on Day 28. Disease resolution is defined as patients who are alive and have a score of 6, 7, or 8 on the NIAID 8-point ordinal scale.
- All-cause mortality rate at Day 28
- Change of clinical status related to COVID-19 on Day 28 compared with baseline according to the following NIAID 8-point ordinal scale:
  1. Death
  2. Hospitalized, on invasive ventilation (mechanical ventilator and/or Extracorporeal Membrane Oxygenation ECMO)
  3. Hospitalized, on non-invasive ventilation or high-flow oxygen devices
  4. Hospitalized, requiring supplemental oxygen
  5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (COVID-19 related or otherwise)
  6. Hospitalized, not requiring supplemental oxygen and no longer requires ongoing medical care (used if hospitalization was extended for infection-control reasons)
  7. Not hospitalized, limitation on activities, and/or requiring home oxygen
  8. Not hospitalized, no limitations on activities

Please note: Patients requiring oxygen before COVID-19 and returning to baseline oxygen use will be considered improved (ie, not requiring supplemental oxygen). Patients with a limitation on activities before COVID-19 and returning to baseline activity will be considered improved. In case of death before Day 14 or Day 28, the patient will be considered with the NIAID score for death (score of 1) on the date of death in the analysis.

5.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints of this study are:

- Proportion of patients with disease resolution on Day 14. Disease resolution is defined as patients who are alive and have a score of 6, 7, or 8 on the NIAID 8-point ordinal scale (as listed above).
- All-cause mortality rate at Day 14 and Day 60
- Change of clinical status related to COVID-19 on Day 14 compared with baseline according to the NIAID 8-point ordinal scale (as listed above)
- Proportion of patients requiring invasive ventilation (mechanical ventilator and/or ECMO), or who are not alive on Day 14 or Day 28
- Proportion of patients in each category of the NIAID 8-point ordinal scale
- Time to (first) improvement of at least 1 category on the NIAID 8-point ordinal scale (until Day 28). Patients who did not improve at least 1 category on the NIAID scale or deaths before Day 28 will be censored at Day 28.
- The odds ratio between MP1032 and SoC and placebo and SoC of the number of patients with clinical status improvement from baseline on the NIAID 8-point ordinal scale (ie, an improvement of at least 1 category) at Day 14 and Day 28
- Total duration of hospitalization (from baseline to discharge; with death censored on the last day of the observed period – at Day 28 or Day 60, respectively)
- Proportion of patients alive and testing negative for COVID-19 on Day 14, Day 28 and Day 60

5.4. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints of this study are:

- Change in saturation of oxygen (SpO_2)/fraction of inspired oxygen (FiO_2) ratio (for patients alive) on Day 14 or Day 28 compared with baseline
- Total number of days in the intensive care unit (ICU)
- Duration of invasive mechanical ventilation and/or ECMO
- Time to recovery from COVID-19 symptoms (stuffy or runny nose, sore throat, red or irritated eyes, shortness of breath, cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, and number of times of vomit, times of diarrhea, sense of smell, sense of taste in the last 24 hours) at Day 14, Day 28, and Day 60
- Change from discharge in the EuroQol (EQ) index value and EQ visual analog scale (VAS) based on the EuroQol-5D-5L (EQ-5D-5L) questionnaire at Day 60

5.5. Pharmacokinetic Endpoints

- MP1032 plasma concentrations and PK parameters (if possible) including maximum observed plasma concentration, area under the concentration-time curve, elimination parameters, apparent body clearance, apparent volume of distribution, trough concentration, average observed plasma concentration at steady state, and other relevant PK parameters assessed via MP1032 plasma exposure on Day 1 and Day 7 in a PK subset of patients.

5.6. Pharmacodynamic Endpoints

- Change from baseline in biomarker levels potentially including, but not limited to, cytokines (eg, C-reactive protein, interleukin [IL]-1β, IL-6, tumor necrosis factor-α, and IFN-γ), and other coagulation/inflammatory biomarkers (eg, D-dimer and ferritin)

5.7. Safety Endpoints

- Safety and tolerability assessed by:
  - Cumulative incidence of treatment-emergent AEs (summarized by seriousness, severity, relationship to the study medication, outcome, and duration)
  - Vital sign parameters
  - Clinical laboratory parameters
  - Physical examination findings

6. Analysis Sets

6.1. Screened / Randomized Set

The Screened Set will include all patients who give informed consent and are screened. Unless specified otherwise, this set will be used for summaries of patient disposition.

The Randomized Set will include all patients randomized. Unless specified otherwise, this set will be used for all patient listings with exception of the listing presenting screening failures and the respective reason(s) for screen failure.

6.2. Safety Set

The Safety Set (SS) will include all randomized patients who receive at least 1 dose of study drug. The treatment group assignment in the SS will be defined by the treatment actually received. The SS will be used for the analysis of safety.

6.3. Intention-To-Treat Set

The Intention-To-Treat Set (ITT) corresponds with the randomized set and will include all randomized patients, irrespective of any deviation from the protocol or premature discontinuation from study drug or withdrawal from study. The treatment group assignment will be designated according to initial randomization. The ITT will serve as the basis for the analysis of efficacy and summary of demographics and baseline characteristics.

6.4. Per Protocol Set

The Per Protocol Set (PPS) will include all patients from ITT who received at least 1 dose of study drug and who do not have any major protocol deviations affecting the efficacy assessments. Patients will be analyzed according to randomized treatment. The PPS will be used for supportive analyses of efficacy.

The final identification and categorization of all protocol deviations and the final definition of the analysis populations including the PPS will be performed in the Blind Data Review Meeting (BDRM) prior to database lock (following Syneos Health SOP 3911).

6.5. Pharmacokinetic Analysis Set

The Pharmacokinetic analysis set (PKS) will include all the patients who have been administered active study drug and have at least 1 postdose evaluable plasma concentration after Day 1 dose.

6.6. Protocol Deviations

Protocol deviations will be identified periodically throughout the trial following the 'Protocol Deviation and Non-compliance Management Plan' (Syneos Health SOP and WI, 3101 and 3101.W02). Final definition of protocol deviations and categorization into minor / major will be performed in the BDRM prior to database lock and unblinding.

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator and the study statistician, and finalized before database lock during the BDRM. Also the determination whether a major protocol deviation has an impact on the assessment of the primary efficacy, and the determination of the patient sets will be finalized in the BDRM following SOP 3911.

7. Estimands

7.1. Primary Efficacy Endpoint

The main estimand for the primary efficacy endpoint is defined as follows:

- Treatment: 300 mg MP1032 BID plus SoC in Arm A and placebo BID plus SoC in Arm B. If a patient terminates the study treatment, but still remains in the study and is followed up, then the patient will continue to receive either SoC alone or SoC+additional treatment. These treatments are defined with regards to intercurrent events as 'other treatments'.
- Population: Of all patients defined by the study inclusion / exclusion criteria, the analysis population will include all randomized patients (ITT population).
- Variable: A binary variable indicating disease progression (respiratory failure) when having completed Day 14 assessment or died prior to Day 14. Respiratory failure is defined as patients who have a score of 2, 3 or 4 on the NIAID 8-point ordinal scale.
- Intercurrent events: All events leading to study treatment discontinuation and/or switch to other treatment prior to Day 14 will be handled using the treatment-policy strategy (ie, the observed NIAID score at Day 14 will be used for definition of the failure in such patients).
- Population-level summary: Common risk difference resulting from the Mantel-Haenszel (MH) test considering the 4 strata out of the combinations of the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years) at baseline.

Missing data on Day 14 resulting from study termination prior to Day 14 are not expected. However, in case it happens, such monotone missings will be imputed by multiple imputation using information from similar patients of the same treatment group assuming 'missing at random' (MAR) mechanism. Missing post-baseline data for patients randomized but not treated will be imputed by the respective baseline value (baseline observation carried forward, BOCF). Intermediate missing data of Day 14 (ie, NIAID assessments prior Day 14 and at Day 28 are available, but only Day 14 is missing) will be imputed by Last-observation-carried-forward (LOCF). The comparison between the treatment groups will be performed on the ITT after imputation of missing values using MH test for common risk difference considering the 4 strata resulting from the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years). 95% confidence interval (CI) will be provided for the risk difference.

A second estimand for the primary efficacy endpoint will be defined similar to the main estimand but with the only difference that the intercurrent event study drug discontinuation due to AE or due to lack of efficacy will be treated using the composite strategy as 'disease progression', but the intercurrent event of study drug discontinuation due to other reasons will be still treated with the treatment-policy strategy. The imputation strategy as described for the main estimand will be used for the second estimand also. Similar sensitivity analyses as for the main estimand will be applied for the second estimand.

7.2. Key Secondary Efficacy Endpoint 1

The main estimand for the key secondary efficacy endpoint 1 is defined as follows:

- Treatment: 300 mg MP1032 BID plus SoC in Arm A and placebo BID plus SoC in Arm B. If a patient terminates the study treatment, but still remains in the study and is followed up, then the patient will continue to receive either SoC alone or SoC+additional treatment. These treatments are defined with regards to intercurrent events as 'other treatments'.
- Population: Of all patients defined by the study inclusion / exclusion criteria, the analysis population will include all randomized patients (ITT population).

- Variable: A binary variable indicating disease progression (respiratory failure) when having completed Day 28 assessment or died prior to Day 28. Respiratory failure is defined as patients who have a score of 2, 3 or 4 on the NIAID 8-point ordinal scale
- Intercurrent events: All events leading to study treatment discontinuation and/or switch to other treatment prior to Day 28 will be handled using the treatment-policy strategy (ie, the observed NIAID score at Day 28 will be used for definition of the failure in such patients).
- Population-level summary: Common risk difference resulting from the MH test considering the 4 strata out of the combinations of the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years).

Missing data on Day 28 resulting from study termination prior to Day 28 (monotone missings) will be imputed by multiple imputation using information from similar patients of the same treatment group assuming 'MAR mechanism. Missing post-baseline data for patients randomized but not treated will be imputed by BOCF. The confirmatory comparison between the treatment groups will be performed on the ITT after imputation of missing values using MH test for common risk difference considering the 4 strata resulting from the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years). 95% confidence interval (CI) will be provided for the risk difference.

A second estimand for the first key secondary efficacy will be defined similar to the main estimand but with the only difference that the intercurrent event study drug discontinuation due to AE or due to lack of efficacy will be treated using the composite strategy as 'disease progression', but the intercurrent event of study drug discontinuation due to other reasons will be still treated with the treatment-policy strategy. The imputation strategy as described for the main estimand will be used for the second estimand also. Similar sensitivity analyses as for the main estimand will be applied for the second estimand.

7.3. Key Secondary Efficacy Endpoint 2

The main estimand for the key secondary efficacy endpoint 2 is defined as follows:

- Treatment: 300 mg MP1032 BID plus SoC in Arm A and placebo BID plus SoC in Arm B. If a patient terminates the study treatment, but still remains in the study and is followed up, then the patient will continue to receive either SoC alone or SoC+additional treatment. These treatments are defined with regards to intercurrent events as 'other treatments'.
- Population: Of all patients defined by the study inclusion / exclusion criteria, the analysis population will include all randomized patients (ITT population).
- Variable: A binary variable indicating 'disease resolution' when having completed Day 28 assessment. Disease resolution is defined as patients who are alive and have a score of 6, 7, or 8 on the NIAID 8-point ordinal scale.
- Intercurrent events: All events leading to study treatment discontinuation and/or switch to other treatment prior to Day 28 will be handled using the treatment-policy strategy (ie, the observed NIAID score at Day 28 will be used for definition of the disease resolution in such patients). Death prior to Day 28 will be considered as non-resolution of disease (or failure) using the composite strategy.
- Population-level summary: Common risk difference resulting from the MH test considering the 4 strata out of the combinations of the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years).

Missing data on Day 28 resulting from study termination prior to Day 28 (monotone missings) will be imputed by multiple imputation using information from similar patients of the same treatment group assuming 'MAR mechanism. Missing post-baseline data for patients randomized but not treated will be imputed by BOCF. The confirmatory comparison between the treatment groups will be performed on the

ITT after imputation of missing values using MH test for common risk difference considering the 4 strata resulting from the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years). 95% confidence interval (CI) will be provided for the risk difference.

A second estimand for the second key secondary efficacy endpoint will be defined similar to the main estimand but with the only difference that the intercurrent event study drug discontinuation due to AE or due to lack of efficacy will be treated using the composite strategy as 'non-resolution of disease (or failure)', but the intercurrent event of study drug discontinuation due to other reasons will be still treated with the treatment-policy strategy. The imputation strategy as described for the main estimand will be used for the second estimand also. Similar sensitivity analyses as for the main estimand will be applied for the second estimand.

7.4. Key Secondary Efficacy Endpoint 3

The main estimand for the key secondary efficacy endpoint 3 is defined as follows:

- Treatment: 300 mg MP1032 BID plus SoC in Arm A and placebo BID plus SoC in Arm B. If a patient terminates the study treatment, but still remains in the study and is followed up, then the patient will continue to receive either SoC alone or SoC+additional treatment. These treatments are defined with regards to intercurrent events as 'other treatments'.
- Population: Of all patients defined by the study inclusion / exclusion criteria, the analysis population will include all randomized patients (ITT population).
- Variable: A binary variable indicating life status (death due to any reason or alive) at Day 28.
- Intercurrent events: All events leading to study treatment discontinuation and/or switch to other treatment prior to Day 28 will be handled using the treatment-policy strategy (ie, the life status at Day 28 will be used in such patients).
- Population-level summary: Common risk difference of the all-cause mortality rate resulting from the MH test considering the 4 strata out of the combinations of the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years).

Missing data of the life status at Day 28 resulting from study termination prior to Day 28 are not expected. However, in case they happen, such missings will be imputed by death. The confirmatory comparison between the treatment groups will be performed on the ITT after imputation of missing values using MH test for common risk difference considering the 4 strata resulting from the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years). 95% confidence interval (CI) will be provided for the risk difference.

7.5. Key Secondary Efficacy Endpoint 4

The main estimand for the key secondary efficacy endpoint 4 is defined as follows:

- Population: Of all patients defined by the study inclusion / exclusion criteria, the analysis population will include all randomized patients (ITT population).
- Variable: Clinical status related to COVID-19 measured on the NIAID 8-point ordinal scale on Day 28 compared to the baseline assessment, ie, change from baseline of NIAID score.
- Intercurrent events: All events leading to study treatment discontinuation and/or switch to other treatment prior to Day 28 will be handled using the treatment-policy strategy (ie, the NIAID score at Day 28 will be used for such patients).
- Population-level summary: Risk difference between the treatment groups of the changes from baseline in the NIAID score as assessed in the ANCOVA model with the 2 randomization

stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years) as independent variables additionally to the treatment variable, and the baseline value of the NIAID score as covariate.

Missing data on Day 28 resulting from study termination prior to Day 28 will be imputed by multiple imputation using information from similar patients of the same treatment group assuming MAR mechanism. Missing post-baseline data for patients randomized but not treated will be imputed by BOCF. The confirmatory comparison between the treatment groups will be performed on the ITT after imputation of missing values using the ANCOVA model considering the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years) as independent variables and the baseline assessment of NIAID as covariate. 95% confidence interval (CI) will be provided for the risk difference.

8. General Aspects for Statistical Analysis

8.1. General Methods

SAS® version 9.4 or higher will be used for all statistical analyses and tabulations.

In general, summaries will present data by treatment group and overall for each scheduled assessment time where appropriate. Efficacy, PK and PD summaries will be presented by treatment group, only.

Unless stated otherwise, descriptive summaries will be presented as follows: Continuous and ordinal variables will be summarized by the number of patients (N), mean, standard deviation, median, minimum, and maximum for actual values and change from baseline. Additionally, for ordinal data, the number and percentage of patients in each category will be presented. Binary and categorical variables will be summarized by treatment group by presenting the number and percentage of patients in the categories.

Statistical tests for comparison between treatments for all defined estimands and endpoints of efficacy will be performed using a two-sided alpha level of 10%. No adjustment for multiple testing will be applied in this descriptive proof-of-concept study. Additionally, 95% confidence intervals will be provided.

Adverse events and medical history will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the most recent WHO Drug Dictionary version. The actual version of MedDRA and WHO drug used will be noted in the footnote of the respective output. Unless otherwise specified, summaries will be presented for each treatment and overall.

If there are multiple assessments collected for the same scheduled time, the last available assessment before start of study treatment will be used as baseline value and the first assessment at the respective post-baseline visit will be used for post-baseline summarization, except for COVID-19 test results where the last assessment at the post-baseline visit will be used for post-baseline summarization.

All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings.

Data collected at unscheduled visits will be included in the data listings but will not be included in the analyses or in treatment summaries except unscheduled COVID-19 test results.

8.2. Key Definitions

Baseline is defined as the last non-missing value prior to the start date and time of the study drug. For non-treated patients, baseline is defined as the last non-missing value from the Screening and Day 1 visits.

Study Day 1 is defined as the first day of study drug administration. Study day will be calculated as date of event/collection – first dose date of the study + 1 for all assessments after start of study drug, and as date of event/collection – first dose date of the study for all assessments prior to start of study drug.

8.3. Missing Data

Missing data will be imputed for the primary efficacy and key secondary efficacy variables as described in sections 7 and 10.

Missing or incomplete dates in safety data: In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation and sorting based on dates and for consideration in summary tables, the following method will be used: The most conservative approach will be systematically considered

(ie, if the onset date of an AE/concomitant medication is missing or incomplete, it is assumed to have occurred during the study treatment, ie, the AE will be considered as TEAE, except if the partial onset date indicates differently). A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

Missing TEAE relationship will be imputed by 'related' for summary tables.

8.4. Visit Windows

For visit windows see Table 1: Schedule of Assessments in Section 4.6 of this SAP.

8.5. Pooling of Centers

Summaries will be provided pooled for all centers by treatment group if not indicated otherwise.

8.6. Subgroups

Descriptive summaries of efficacy for the primary efficacy endpoint and for the key secondary efficacy endpoints will be repeated on the subgroups of COVID-19 severity (moderate and severe), age-class (≤65 years and >65 years), vaccination status (vaccinated and not vaccinated), patients taking Dexamethasone and/or Remdesivir during treatment with study drug, and obesity risk factor (BMI <30.0 kg/m^2 and BMI >=30.0 kg/m^2). Additionally, baseline characteristics will be summarized for these subgroups.

9. Demographic, Other Baseline Characteristics and Medication

9.1. Patient Disposition and Withdrawals

Patient disposition data will be listed. Summary tables reflecting the number of patients for the following will be presented:

- Screened and randomized patients
- ITT, PPS, SS and PKS
- Patients who completed 14 days of treatment
- Patients who early terminated and did not complete 14-days of study treatment with reasons for early treatment termination
- Patients who completed the 28-days treatment period
- Patients who early terminated the 28-days study treatment period with reasons for early treatment termination
- Patients who early terminated the study treatment but are followed up until Day 28
- Patients who early terminated the study treatment but are followed up until Day 60
- Patients who completed the study including the follow-up period (Day 60), after having completed study treatment
- Patients who early terminated the study after having completed the treatment period with reasons for early study termination

Screen Failure subjects will be listed with reason for failure.

9.2. Demographic and Baseline Characteristics

Demographic characteristics such as sex, age, race, ethnicity, height, weight and BMI at screening will be summarized for ITT and SS, by treatment and overall. Number and percentage of patients with age ≤65 years and >65 years and number and percentage of patients in the disease severity moderate and severe will be presented by treatment group and overall for the ITT and the SS. Additionally, demographic characteristics will be summarized for each country by treatment group and overall for the ITT. In case of identification of relevant heterogeneity in the distribution between countries, supportive analyses of efficacy for comparison between the treatments will consider country (or at least region) as nominal variable within the respective model. Demographic characteristics will be listed for all randomized patients.

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

9.3. Medical and Surgical History

Medical and surgical history will be coded using current version of MedDRA®. Medical and surgical history will be listed for all randomized patients. Medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall.

9.4. Other Baseline Characteristics

NIAID at baseline will be summarized by number and percentage of patients in each category by treatment group and overall for ITT and SS.

9.5. Medication

Prior medication is defined as any medication which has an end date prior to the date of first dose of study drug administration.

Concomitant medication is defined as any medication which starts before the last dose of study drug and has an end date after the date of first dose of study drug administration or missing.

The original verbatim terms collected in the eCRF for prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD current version).

Listings will include the therapeutic (ie, the second level of Anatomical Therapeutic Chemical [ATC] classification system code that is corresponding to the first 3 figures), preferred name (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by treatment group, patient ID, chronological start date, stop date, therapeutic class, preferred name and verbatim name and will contain all randomized patients.

A frequency table of the number and percentage of patients will be provided for prior medications and concomitant medications by therapeutic class and preferred name for each treatment group and overall on the ITT.

Non-drug therapies collected on the eCRF will be listed and summarized by number and percentage of patients.

9.6. Extent of Exposure

Number and percentage of patients who received study treatment for the first 14 days, and who completed all 28 days of study treatment will be presented by treatment group and overall. The total duration of treatment and the total number of capsules received within the first 14 days and within 28 days will be summarized by treatment group on the SS and ITT, as appropriate. A listing presenting all above defined variables of extent of exposure will be presented for the randomized patients.

9.7. Treatment Compliance

During hospitalization, the administration of the study drug will be performed by the investigator (or qualified blinded designee) to ensure compliance. If the patient is discharged home before Day 28, the study team will provide the patient with the remainder of the assigned blinded study treatment kit(s) to take home along with instructions to continue treatment at home; for these patients, treatment compliance will be assessed via a diary. If the patient does not feel comfortable to complete the diary, the site will alternatively provide the patient with the option to be called twice a day, to confirm that the study drug is taken as instructed. Patients are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Investigators will maintain records that adequately document that the patients were provided with the correct study treatment kit(s) and reconcile the products received from the drug dispensing center.

Treatment compliance in % will be calculated as

(Total number of capsules taken / 12) / treatment duration (days) x 100%

The treatment compliance will be calculated for the first 14 days of treatment and for the whole 28 days treatment and will be summarized by treatment group and overall on the SS and ITT, as appropriate.

Noncompliance is defined as taking <80% or >120% of study drug. The number and percentage of patients with non-compliance will be presented by treatment group and overall on the SS and ITT, as appropriate.

A listing including all above defined variables of treatment compliance will be presented for the randomized patients.

10. Efficacy

All efficacy endpoints will be summarized using descriptive statistics by treatment group and by visit, as appropriate: Binary and categorical endpoints will be summarized by treatment group by presenting the number and percentage of patients in each category. Continuous and ordinal endpoints will be described by mean, standard deviation, median, minimum, and maximum for actual values and change from baseline. Additionally, for ordinal data, the number and percentage of patients in each category will be presented. Statistical tests for the comparison between treatments will be performed using a two-sided alpha of 10%.

10.1. Primary Efficacy Estimands and Analysis

The main estimand and the second estimand for the primary efficacy endpoint that is defined as a binary variable indicating disease progression (death or respiratory failure) at Day 14 will be compared between the treatment groups based on the common risk difference resulting from the MH test considering the 4 strata out of the combinations of the 2 randomization stratification factors disease severity (moderate versus severe) and age-class (≤65 years versus >65 years).

Missing data on Day 14 resulting from study termination prior to Day 14 are not expected. However, in case they happen, such monotone missings will be imputed by multiple imputation using information from similar patients of the same treatment group assuming the missings are MAR. Missing post-baseline data for patients randomized but not treated will be imputed by BOCF. Intermediate missing data of Day 14 (ie, NIAID assessments prior Day 14 and at Day 28 are available, but only Day 14 is missing) will be imputed by LOCF. The comparison between the treatment groups will be performed on the ITT after imputation of missing values using the MH test. 95% confidence interval (CI) will be provided for the risk difference. A sensitivity analysis for the main estimand and the second estimand will be performed by imputation of missing values at Day 14 with 'progression' assuming that missings happen not at random (MNAR). A table with number and type/reason of missing values in the primary efficacy variable will be provided by treatment group on the ITT.

All above described analyses will be repeated on PPS as supportive analysis. Additionally a logistic regression model with treatment and the 2 stratification factors as covariables will be applied on the ITT as supportive analysis.

10.2. Key Secondary Efficacy Estimands and Analyses

10.2.1. Key Secondary Efficacy Endpoint 1

Similar MH analyses as for the main estimand of the primary efficacy endpoint will be applied to the main estimand and the second estimand of the first key secondary efficacy endpoint, which is defined as a binary variable indicating disease progression (death or respiratory failure) at Day 28. Prior to the analysis, missing data will be imputed as described in Section 7.2 of this SAP. A sensitivity analysis for the main estimand and the second estimand will be performed by imputation of missing values at Day 28 with 'progression' assuming MNAR. A table with number and type / reason of missing values in the first key secondary efficacy variable will be provided by treatment group on the ITT.

10.2.2. Key Secondary Efficacy Endpoint 2

Similar MH analyses will be applied to the main estimand and the second estimand of the second key secondary efficacy endpoint, which is defined as a binary variable indicating disease resolution (alive and have a score of 6, 7 or 8 on NIAID) at Day 28. Prior to the analysis, missing data on Day 28 will be imputed as described in Section 7.3 of this SAP. A sensitivity analysis for the main estimand and the second

estimand will be performed by imputation of missing values at Day 28 with 'no disease resolution' assuming MNAR. A table with number and type / reason of missing values in the second key secondary efficacy variable will be provided by treatment group on the ITT.

10.2.3. Key Secondary Efficacy Endpoint 3

A similar MH approach as described above will be applied also to the main estimand of the third key secondary efficacy endpoint, which is the all-cause mortality at Day 28. No missing data of life status on Day 28 is expected. However, in case of missing information life status will be imputed by death.

10.2.4. Key Secondary Efficacy Endpoint 4

The main estimand of the fourth key secondary efficacy endpoint 'Change of clinical status related to COVID-19 on Day 28 compared with baseline on the NIAID 8-point ordinal scale' will be compared using the risk difference between the treatment groups resulting from the analysis of covariance (ANCOVA) model with treatment and the 2 binary stratification factors severity and age-class as independent factors and the baseline value of NIAID as independent covariate. Prior to the analysis, missing data on Day 28 will be imputed as described in Section 7.5 of this SAP. A sensitivity analysis for the main estimand will be performed by imputation of missing values at Day 28 in both treatment groups using information from similar patients of the placebo group assuming MNAR. A table with number and type / reason of missing values in the fourth key secondary efficacy variable will be provided by treatment group on the ITT.

All above described analyses for the key secondary endpoints will be repeated on PPS as supportive analyses. Additionally a logistic regression model with treatment and the 2 stratification factors as covariables will be applied on the ITT as supportive analysis.

10.3. Other Secondary Efficacy Endpoints

No estimands are defined for other secondary efficacy endpoints. Missing life status will be imputed by death, however other missing data will not be imputed for the analysis of other secondary efficacy endpoints. Other secondary efficacy endpoints will be summarized and analyzed on the ITT.

The proportion of patients with disease resolution at Day 14 and the all-cause mortality rate at Day 14 and Day 60 will be analyzed using similar MH methods as described above for disease resolution at Day 28. Additionally, the cumulative proportion of patients with disease resolution will be plotted over time.

A similar ANCOVA approach as described above (10.2.4.) will be applied for the analysis of the change of clinical status related to COVID-19 on Day 14 compared with baseline on the NIAID 8-point ordinal scale. The endpoints considering the proportion of patients requiring invasive ventilation (mechanical ventilator and/or ECMO) or who are not alive, the proportion of patients in each NIAID category, and the proportion of patients alive and testing negative for COVID-19 on Day 14, Day 28 and Day 60, respectively, will be compared between the treatment groups using MH tests. Overall survival, time to (first) improvement of at least 1 category on the NIAID scale and total hospitalization duration (from baseline to discharge; with death censored on last day of the observed period - at Day 28 or Day 60, respectively - depending on the analyses) will be summarized using Kaplan-Meier estimates and will be compared between treatment groups using logrank tests. Additionally, Cox proportional hazards model will be applied with treatment and the 2 stratification factors as independent variables.

The odds ratio between MP1032 + SoC and placebo + SoC of the number of patients with clinical status improvement from baseline on the NIAID 8-point ordinal scale (ie, an improvement of at least 1 category)

at Day 14 and Day 28 will be analyzed using a logistic regression with consideration of the 2 stratification factors.

10.4. Exploratory Efficacy Endpoints

No estimands are defined for exploratory efficacy endpoints. Exploratory efficacy endpoints will be summarized by descriptive statistics on the ITT, only. No statistical comparison will be performed. Some exploratory efficacy endpoints are defined in a subgroup of the randomized patients: potential bias resulting from this aspect will be considered in the interpretation of respective summaries by treatment.

The time to recovery of all at baseline present COVID-19 symptoms (stuffy or runny nose, sore throat, red or irritated eyes, shortness of breath, cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, and number of times of vomit, times of diarrhea, sense of smell, sense of taste in the last 24 hours) will be presented by Kaplan-Meier estimates and figure. The change from baseline will be presented in shift tables for each single symptom with the number and percentage of patients in each category at post-baseline assessment time-point compared to baseline for each treatment group. Number of symptoms will be summarized by visit and treatment group.

Total number of days in ICU and duration of invasive mechanical ventilation, and/or ECMO will be descriptively summarized by treatment group using mean days with 90% confidence intervals and additionally by median days and quartiles. To consider death sufficiently unfavorable in these measures, in case of death the duration of the respective measure will be considered with the longest duration possible. Eg, if a summary of the first 28 days is presented, then death prior to Day 28 will be considered as duration 28 days, and if the summary includes also follow-up period until Day 60, then death prior to Day 60 will be considered as duration 60 days. Both summaries (up to Day 28 and up to Day 60) will be provided.

Saturation of oxygen (SpO2)/fraction of inspired oxygen (FiO2) ratio (for patients alive) will be summarized for actual values and change from baseline by treatment and visit.

For HRQoL assessments at discharge and Day 60, the EQ index value and the EQ VAS, both based on the EQ-5D-5L questionnaire will be calculated and summarized by visit and treatment group. Additionally, the change at Day 60 from discharge will be summarized by treatment group. For countries without a published index value set, the published value set from the geographically closest country will be used.

11. Pharmacokinetics

The Pharmacokinetic Analysis Set will be used for the analyses specified in this section.

This SAP describes the method of deriving PK using non-compartmental analysis applying appropriate software, ie, Phoenix™ WinNonlin® (Version 8.0 or higher, Certara Corporation), and all other analyses and summaries using SAS® (Version 9.4 or higher, SAS Institute Inc.), which will be presented in CSR.

The PK analyses will be conducted for MP1032 in plasma and will include a listing, summary, figure of concentrations, and derived PK parameters as described below.

11.1. PK Sampling Schedule

The PK sampling schedule of MP1032 in plasma on Day 1, and Day 7 is mentioned in Table 1 Section 4.6. In summary, PK samples will be collected via sparse sampling from a PK subset of approximately 30 patients (who give optional consent) in a 2:1 ratio (approximately 20 patients from the 300 mg MP1032 BID plus SoC group and approximately 10 patients from the placebo group plus SoC group) to assess the PK of MP1032 on Day 1 (single dose) and Day 7 (steady state). A total of 16 samples (approximately 4.9 mL per time point for a total of approximately 78.4 mL) will be collected relative to the first dose on Day 1 and the first dose on Day 7. Samples on Day 1 and Day 7 will be collected predose (within 10 minutes before the first daily dose) and postdose at 10 minutes, 20 minutes, 30 minutes, 60 minutes, 120 minutes, 8 hours (before next dose), and 24 hours before the next morning dose (if applicable), if possible. Patients who provide consent for the PK sampling, but are no longer hospitalized on Day 7, will not have Day 7 PK samples collected.

11.2. Plasma PK Endpoint

The following PK parameters will be calculated by standard non-compartmental methods with MP1032 plasma concentrations, using up to 8 hours post-dose, on Day 1 and Day 7 for fasting condition (or fed, if fasting not possible):

AUC0-inf:	Area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t} + C_t/K_{el}$, where C_t is the last observed non-zero concentration.
AUC0-t:	Area under the concentration-time curve from time zero to the last non-zero concentration. The calculation of AUC_{0-t} will be done using the linear trapezoidal method using linear trapezoidal linear interpolation.
C_{max}:	Maximum observed concentration.
C_{last}:	Last observed concentration.
t_{max}:	Time of observed C_{max}.
$T_{½\,el}$:	Elimination half-life, calculated as ln (2)/K_{el}.
Residual area:	Residual area, calculated as 100*(1- AUC_{0-t} / AUC_{0-Inf}).
	If Residual Area is >20%, then AUC_{0-Inf} is considered unreliable; due to which all related PK parameters of AUC_{0-Inf} (Cl/F, V_z/F, Residual area, and AUC_{0-Inf}) will be flagged in individual listings, and excluded from summary statistics if residual Area is >20%.
Kel:	Elimination rate constant. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed plasma concentration versus time

profile in the terminal elimination phase. Best fit method will be used to calculate the K_{el} from at least 3 post C_{max} concentration data points excluding the C_{max}. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), as well as the R_{sq} adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported. R_{sq} adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. If the K_{el} cannot be measured (eg: fewer than 3 non-zero concentrations in the terminal elimination phase), then K_{el}, and its related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, $AUC_{0\text{-}Inf}$, Residual area, $T_{½\ el}$, Cl/F, and V_z/F) will not be reported for PK profiles. If the R_{sq} adjusted is <0.8, then K_{el}, and its related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, $AUC_{0\text{-}Inf}$, Residual area, $T_{½\ el}$, Cl/F, and V_z/F) will be will be included and flagged in the listings but will not be included in the summary statistics.

Cl/F — Apparent total body clearance (Cl/F), estimated as Dose/$AUC_{0\text{-}Inf}$ (Day 1 only).

V_z/F — Apparent volume of distribution (V_z/F), estimated as Dose/(K_{el} x $AUC_{0\text{-}Inf}$) (Day 1 only).

For Day 2 (or 24 hours after Day 1), Day 7, and Day 8 (or 24 hours after Day 7):

C_{trough}: Pre-dose concentration (Day 2, 7, and 8).

11.3. Presentation of Concentration Data

11.3.1. Handling of Missing Data

Missing concentration data for all patients who are administered study drug will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

11.3.2. Handling of the Difference between the Scheduled (nominal time) and the Actual Sampling Times (actual time)

For all sampling times, the actual sampling times relative to dosing are calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in hours and rounded off to three decimal digits are used, except for pre-dose samples occurring prior to dosing, which are reported as zero (0.000), regardless of the time difference. Scheduled sampling times are presented in concentration tables. If the actual time of sampling is missing, the nominal time is used.

11.3.3. Listing and Presentation of Individual PK Data

- The sampling time of pre-dose samples relative to dosing is treated as zero for all sampling periods separately;
- All concentrations are presented in original units as reported by Bioanalytical lab, eg, ng/mL;
- All concentrations that are below the lower limit of quantification (BLQ) will be set to zero;

- Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug;
- No further imputation will be applied to any missing values.

Individual PK concentration data will be listed by patient ID, time point and treatment (in relevant concentration units).

The individual plasma concentrations for MP1032 will be presented graphically on both the linear and semi-logarithmic scales of Day 1, and Day 7 separately.

11.3.4. Summary of PK Concentrations

For PK concentration summary, the following rules apply:

- PK concentrations BLQ in pre-dose samples and in samples taken before the time of the first quantifiable value are set to zero;
- The PK concentrations BLQ after quantifiable concentration are set to zero;
- The sampling time of pre-dose samples relative to dosing will be treated as zero;
- Drug concentrations will be summarized by nominal time point;
- Descriptive statistics will be performed;
- No further imputation is applied to any missing values.

Plasma MP1032 concentrations will be summarized descriptively by study day, time point and treatment (in relevant concentration units) using descriptive statistics (n, number and percent of patients with BLQ, arithmetic mean, geometric mean, SD, arithmetic and geometric coefficient of variation (CV) %, minimum, median and maximum) presented according to the following reporting precision.

Variable	Summarized with:
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Arithmetic Mean, Geometric Mean, Median	4 significant digits or as needed based on actual measured values
SD	5 significant digits or as needed based on actual measured values
CV%, and Geometric CV%	1 decimal place or as needed based on actual measured values

Mean ± SD plasma concentration-time profiles for MP1032 of all patient on linear and log-linear scales will also be presented.

11.4. PK Parameters Derivation

For the derivation of PK, the following rules will apply:

- All plasma concentrations BLQ will be imputed with a value of zero;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- Actual blood sampling times will be used to derive PK parameters. If the actual blood sampling is not present, then that time point will not be considered for PK analyses.

- If the pre-dose sample is not present, then that patient will not be considered for PK derivation;
- No further imputation will be applied to any missing values.

All PK parameters will be listed.

11.4.1. PK Parameters Summarization

PK parameters and concentrations data will be summarized using the following descriptive statistics:

Variable	Summarized with:
PK concentration at each time point	n, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
AUCs, C_{max}, C_{trough}, CL/F, and V_z/F	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
$T_{½\ el}$, K_{el}	n, arithmetic mean, SD, CV%, minimum, median, maximum
t_{max} (actual time)	n, minimum, median, and maximum

Note: CV% = SD/mean in %; n = No. of observations.

For PK tables and listings, the final reportable results or data will be presented by rounding off to two decimal digits, except for the following situations (this applies to individual data and descriptive statistics):

- K_{el} and R_{sq} adjusted data: rounded off to four decimal digits.
- Pharmacokinetic parameters related to time such as t_{max}, $K_{el\ Lower}$, and $K_{el\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.

Concentration versus time data: reported as they appear in corresponding dataset.

11.5. Exploratory Relationship between Plasma exposure, and Biomarker (Exposure-Response relationship)

Any possible correlation between plasma exposure (C_{max}, or AUC_{0-t}) and biomarkers (eg, change from baseline in cytokines, or other coagulation/inflammatory biomarkers) using Day 7 if available, may be explored applying exposure-response scatterplots. Further correlation analysis (eg, utilizing a combination of Spearman and Pearson correlation) may be applied if exposure-response scatterplots reveal any robust relationships. Tables will be then produced for calculated correlation coefficient, confidence intervals for Pearson coefficient in addition to p-value, to demonstrate the validity of correlation.

12. Pharmacodynamics

Biomarker levels potentially including, but not limited to, cytokines (eg, C-reactive protein, interleukin [IL]-1β, IL-6, tumor necrosis factor-α, and IFN-γ), and other coagulation/inflammatory biomarkers (eg, D-dimer and ferritin) will be summarized by actual values and changes from baseline by treatment group and visit on the SS. The change in biomarker levels will be evaluated with any change of COVID-19 clinical status by presenting summary tables of the change in biomarker levels from baseline stratified by COVID-19 status by treatment group.

13. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed based on adverse event (AE) or adverse drug reactions (ADR) reports, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

13.1. Adverse Events / Adverse Drug Reactions

All AEs will be coded using the most recent MedDRA Version.
Each AE will be assigned a grade which refers to the severity of the AE based on the Common Terminology Criteria for Adverse Events version 5.0. The Common Terminology Criteria for Adverse Events v5.0 displays grades 1 through 5 with unique clinical descriptions of the severity for each AE. Tables for the classification of the AE severity and relationship to the drug are provided in Tables 6 and 7 in Section 12.6.1 of the protocol.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the event should be noted in the eCRF. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates) in the eCRF: the assessment of an AE in several records will be called as 'episodes' of one AE.

A treatment-emergent AE (TEAE) is an AE that starts or worsens at any time after initiation of study drug until the end of the follow-up period at Day 60. Events with missing onset dates will be considered as TEAEs. If a patient experiences >1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the corresponding summary tables. In case that for one AE, several AE episodes with eg changing severity are reported, an aggregation of all respective episodes to one AE will be performed prior to summarization. The worst severity and the worst relationship will be assigned to the aggregated AE.

Listings presenting all AEs including all episodes of one AE will be produced for TEAEs and non-TEAEs with the flagging of SAEs. Listings of serious TEAEs, TEAEs leading to study drug withdrawal, and TEAEs leading to death will be presented in the table section of the outputs. Additionally, in the listing TEAEs starting in the treatment period and TEAEs starting in the follow-up period or starting after the initial treatment has stopped will be flagged

An overall summary will be provided of the number and percentage of patients reporting AEs, TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs leading to study drug withdrawal and TEAEs leading to death. In the overall summary, additionally, the number and percentage of patients with at least one severe TEAE, with at least one moderate TEAE but no severe TEAE and with only mild TEAEs will be provided. For patients with any serious TEAE and for patients with any related serious TEAE exposure-adjusted events rates will be calculated and compared between treatment groups using the risk ratio [(300 mg MP1032 BID plus SoC) / (placebo plus SoC)] with respective 95% CI. This comparison will also be performed for the rate of re-hospitalization which is considered a serious AE.

The number and percentage of patients with TEAEs / treatment-related TEAEs / serious TEAEs / and TEAEs leading to study drug withdrawal will be summarized by SOC and PT for each treatment group, and total. In these tables, the incidence of TEAEs by SOC and PT will also be included. TEAEs will also be summarized by SOC and PT for maximum intensity and maximum relationship to study drug for each treatment group and total. Additionally, separate tables of TEAEs by SOC and PT will be provided for

TEAEs starting in the treatment period and for TEAEs starting in the follow-up period or after the study drug administration has stopped.

13.2. Laboratory Evaluations

Clinical laboratory data of local laboratories will be presented in separate tables for each laboratory test type (hematology, blood chemistry, coagulation, urinalysis). Each laboratory parameter will be presented with the number and percentage of patients with values below, within, or above the normal range at each time point by treatment group and overall. Additionally, a shift table of the number and percentage of patients with normal and abnormal, and clinically significant abnormal values at each scheduled post-baseline visit compared to the normal, abnormal, and clinically significant abnormal categorization at baseline will be provided by treatment group. A listing of clinically significant abnormal values will be provided in the tables section.

Summary tables of actual values and changes from baseline can be presented for continuous laboratory parameters only after 'normalization' of the local laboratory assessment as supposed by Chuang-Stein (see reference 1 and 2) using one reference laboratory based on the following formula

$$s = L_s + (x - L_x)\frac{U_s - L_s}{U_x - L_x}$$

where s = the transformed individual laboratory value considering the normal range of the reference laboratory, x = the original laboratory value, L_x and U_x are the lower and upper limits or normal range of the local laboratory for the respective parameter, L_s and U_s are the lower and upper limits of the selected reference laboratory. For calculating summary statistics, results of <x or <=x will be imputed as x/2 and results of >x or >=x will be imputed as x.

Pregnancy test results will be listed only for randomized female patients.

13.3. Vital Signs

Vital signs will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute, bpm), respiration rate (breaths per minute), SpO_2, and body temperature (°C). Summary tables of the actual values and changes from baseline will be provided for each vital sign parameter at each scheduled visit by treatment group, and in total.

Additionally, body weight and BMI will be summarized with actual values and change from baseline at each scheduled visit by treatment group, and in total.

Vital signs data, body weight and BMI will be listed for randomized patients.

13.4. ECG

The overall interpretation of ECG at screening will be summarized by treatment group and overall and listed for all randomized patients.

13.5. Physical Examination

Abnormal physical examination results will be summarized by presenting number and percentage of patients for each body system by treatment group and overall for all scheduled visits. All physical examination data will be listed for the randomized patients.

14. Health Economics

Not applicable.

15. Interim Analyses or IDMCs

There will be no interim analysis in the study.

An independent DMC will be established by the sponsor or designee to review accumulating study data at regular intervals (as per the DMC charter) throughout the study to ensure the safety of patients and review overall study conduct. Additional data may be reviewed that are related to efficacy, but the DMC will only be reviewing data for risk-benefit purposes. Members will include experts in drug safety and/or medical specialist and biostatistics, who are not participating in this study and do not have affiliation with the investigators or the sponsor. The DMC can recommend in writing to the sponsor whether to continue, modify, or stop the clinical study on the basis of safety considerations. The pre-specified study stopping rules for the trial are defined as follows:

- death (not including disease progression) in any patient in whom the cause of death is judged to be related to the study drug by investigator
- the occurrence in any patient of a SAE whose causal relationship (ie, without a plausible alternative explanation) to the study drug is judged to be related by investigator
- two occurrences of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by investigator.

The DMC's specific duties will be fully described in a DMC charter. The list of the outputs that will be produced for the DMC will be attached to the charter. An unblinded team from Syneos Health Biostatistics will perform the analyses as described in Section 4.4 of this SAP to maintain the blinding of the study.

16. Changes from Analysis Planned in Protocol

Not applicable

17. Reference List

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

2. Chuang-Stein C. Some issues concerning the normalization of laboratory data based on reference ranges. Drug Information Journal 2001; 35(1): 153-156.

3. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Step 5; Date for coming into effect: 30Jul2020; EMA.

18. Programming Considerations

18.1. General Considerations

- A separate SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format pdf
- Numbering of TFLs will follow ICH E3 guidance

18.2. Table, Figure, and Listing Format

18.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (eg, μ). Certain subscripts and superscripts (eg, cm^2, C_{max}) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate

18.2.2. Headers

- All output will have the following header at the top left of each page:
  - MetrioPharm AG, Protocol MP1032-CT05 (Syneos Health study number <*xxx*>)
  - Draft/Final Run <*date*>

- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (ie, the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

18.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (ie, Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be one blank line between the last title and the solid line.

- Table x.y.z
- First Line of Title
- Second Line of Title if Needed
- (Full Analysis Set)

18.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) or in the row headings, if applicable. This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

18.2.5. Body of the Data Display

18.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (eg, counts) will be right-justified; and

- Numbers containing fractional portions will be decimal aligned.

18.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

- Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).
- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. P-values above 0.999 will be presented as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (eg, 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the

denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values that cannot be estimated will be reported as '-'

- The percentage of patients will normally be calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

18.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time

- Missing data will be represented on patient listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (–JUL2000). Dates that are missing because they are not applicable for the patient will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (eg, 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

18.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (eg, treatment mean change from baseline) values will be displayed on the Y-axis

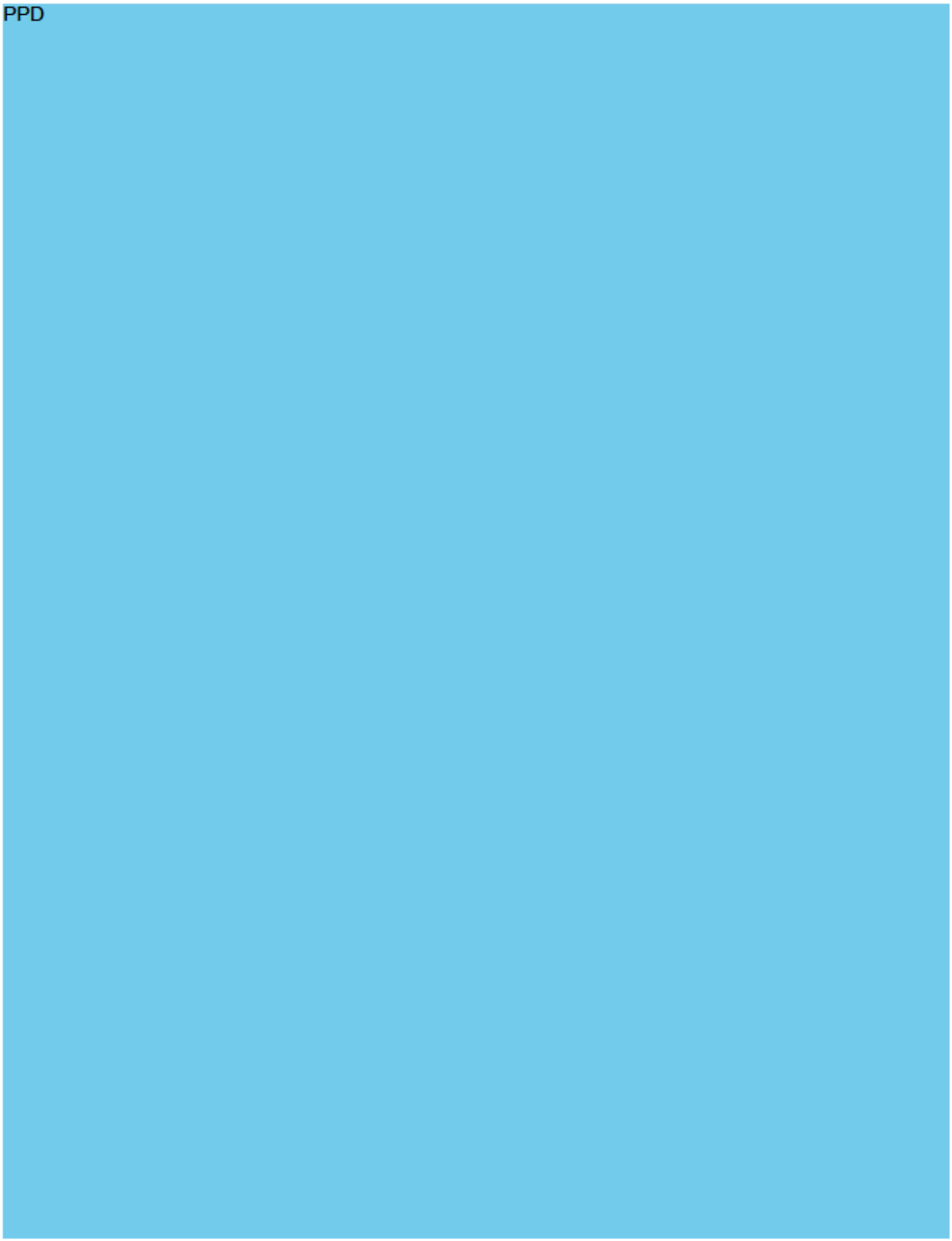
18.2.6. Footnotes

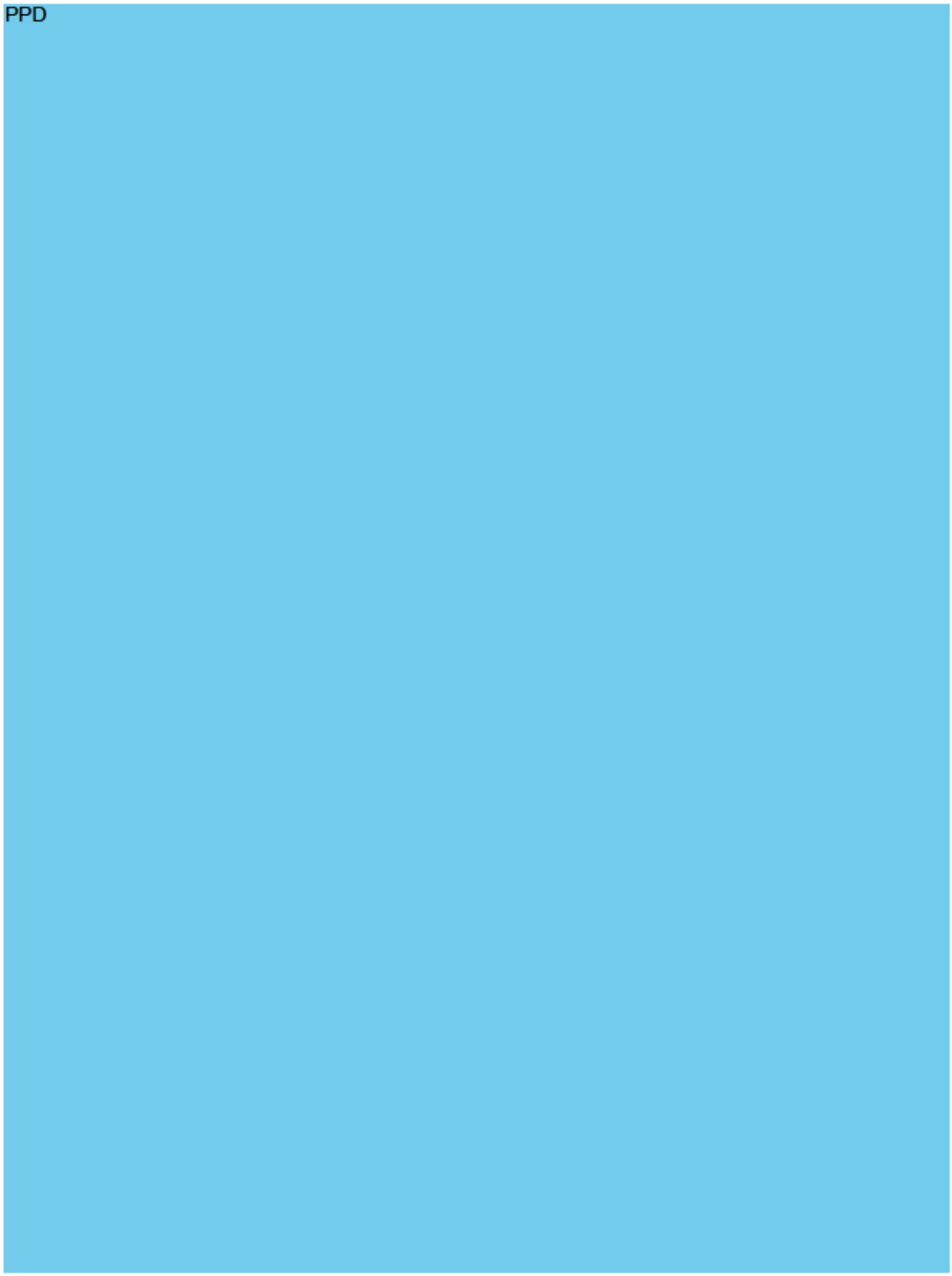
- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible
- Patient specific footnotes are avoided, where possible
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (ie, 'Program: myprogram.sas Listing source: 16.x.y.z')
- Sources and / or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

19. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.


PPD


PPD