TITLE PAGE

STUDY NUMBER CNMAu8.202

REPAIR-PD

A PHASE 2, OPEN LABEL, SEQUENTIAL GROUP, INVESTIGATOR BLINDED STUDY OF MAGNETIC RESONANCE SPECTROSCOPY (31P-MRS) TO ASSESS THE EFFECTS OF CNM-Au8 FOR THE BIOENERGETIC IMPROVEMENT OF IMPAIRED NEURONAL REDOX STATE IN PARKINSON'S DISEASE (PD)

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER CNMAu8.202

REPAIR-PD

A PHASE 2, OPEN LABEL, SEQUENTIAL GROUP, INVESTIGATOR BLINDED STUDY OF MAGNETIC RESONANCE SPECTROSCOPY (^{31}P-MRS) TO ASSESS THE EFFECTS OF CNM-Au8 FOR THE BIOENERGETIC IMPROVEMENT OF IMPAIRED NEURONAL REDOX STATE IN PARKINSON'S DISEASE (PD)

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This study will be conducted in compliance with the Protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

DOCUMENT HISTORY

Version Number	Author	Date	Change
V0.1	S. Ligozio	04May2021	new
V1	S.Ligozio	19May2021	Final, incorporating sponsor comments from 207 SAP, added descriptive statistical testing to PGI/CGI

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Signature Page

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GLOSSARY AND ABBREVIATIONS

Abbreviation	Definition
^{31}P-MRS	^{31}P Magnetic Resonance Spectroscopy
ACS	Abnormal clinically significant
ADP	Adenosine Diphosphate
AE	Adverse event
APDM	Ambulatory Parkinson's Disease Monitoring
ANCS	Abnormal not clinically significant
ATP	Adenosine Trinucleotide Phosphate
ATP (avg)	ATP average
Au	Gold
AUC [0-24]	Area under the plasma concentration-time curve for 24 hours
BL	Baseline
BMI	Body Mass Index
C-SSRS	Columbia Suicide Severity Rating Scale
Cmax	Maximum observed plasma concentration
CGI	Clinician Global Impression
CNS	Central Nervous System
CSF	Cerebral spinal fluid
CSR	Clinical Study Report
ECG	Electrocardiogram
EOS	End of study
GPC	Glycerophosphocholine
GPE	Glycerolphosphoethanolamine
ITT	Intent-to-treat
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
NAD	Nicotinamide adenine dinucleotide
NAD+	Oxidized form of nicotinamide adenine dinucleotide
NADH	Reduced form of nicotinamide adenine dinucleotide
PC	Phosphocholine
PCr	Phosphocreatine
PD	Parkinson's Disease
PDE	Phosphodiesters
PDF	Portable document file
PE	Phosphoethanolamine
PGI	Patient Global Impression
PME	Phosphomonoesters
PI(t)	Total Inorganic phosphate
PI(in)	Intracellular inorganic phosphate

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Abbreviation	Definition
PI(ex)	Extracellular inorganic phosphate
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
TEAE	Treatment-emergent adverse event
Tmax	Time to reach Cmax
TUG	Timed Up and Go
UDPG	Uridine diphosphate glucose
UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organization

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to ensure that the statistical methodologies implemented in Protocol CNMAu8.202 (Repair-PD) are complete and appropriate, allowing for valid conclusions regarding the study objectives. Results obtained from the analyses outlined in this document will be included in the final clinical study report (CSR) for this protocol. Any deviations from this SAP will be documented in the final CSR.

The pharmacokinetic (PK), pharmacodynamic, and ambulatory Parkinson's Disease monitoring (APDM) data will be analyzed outside of this SAP. Therefore, analyses planned for these data will be described in a separate analysis plan.

1.1 Study Design

This is a single-center open label, sequential group, investigator-blinded study of the central nervous system (CNS) metabolic effects, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in subjects who have been diagnosed with Parkinson's Disease (PD) within three years of their screening visit. Subjects will be screened over a 6-week period. Subjects who meet the inclusion criteria and none of the exclusion criteria will be enrolled into the clinical study.

This study will consist of up to two treatment cohorts, with each cohort consisting of up to fifteen subjects. Both cohorts will share identical study schedules (See Table 1). Investigators and subjects will remain blinded to the study dose. The Sponsor may choose to discontinue the study following the completion of the first cohort. In the case that two cohorts are conducted, each will be analyzed separately following the completion of each respective cohort.

The primary efficacy outcome measure will be assessed based upon data obtained at each subject's final treatment period study visit (originally planned as the Visit 4, Week 12 study visit). Due to the ongoing COVID-19 pandemic, some participants may remain on study treatment for greater than 12 weeks, if Institutional restrictions or safety concerns prevent the completion of the planned visits per the study schedule (see Table 1). At the end of the study, subjects will complete an end of study (EOS) visit four weeks following their last study visit before exiting the study. All subjects who are discontinued from treatment will be asked to complete an EOS assessment. Participants who electively terminate their participation prior to completion of the 12-week visit will be asked to return for an abbreviated EOS visit 4-weeks following their last dose of study medication. All subjects will receive once daily oral treatment over twelve consecutive weeks during the treatment period.

There will be three study periods per treatment cohort:

(1) A 6-week screening period (Screening Period);

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(2) A 12-week treatment period (Treatment Period);

(3) A 4-week follow-up period (End-of-Study Assessment).

The visit schedule is shown in Table 1 below.

Table 1. Time and Events Schedule

Time and Events Schedule	Visit	-1	0	1	2	3	4	5
	Phase	Screening	Baseline	Treatment Period				EOS
	Week	-6	0	2	4	8	12	16
	Day	-42 to -1	1[a]	14 [a]	28 [a]	56 [a]	84 [a]	112 [b]
ICF Signed		X						
Eligibility Review		X	X					
Medical History		X						
ConMed/Prior Med Assessment		X	X	X	X	X	X	X
Physical Examination		X	X		X	X	X	X
Height Assessment		X						
Weight Assessment		X	X				X	
Urine Drug Test		X						
HIV/Viral Hepatitis Screen		X						
Serum Pregnancy Test [c]		X						
Urine Pregnancy Test [c]			X		X	X	X	
Vital Signs		X	X		X	X	X	X
12-lead ECG [d]		X	X		X	X	X	X
Clinical Laboratory (Blood)		X	X		X	X	X	X
Urinalysis		X	X		X	X	X	X
MMSE		X						
Treatment Assignment			X					
Dispense/Return Drug			X		X	X	X	
PK Sampling (Whole Blood)					X[e]	X[e]	X[f]	X[e]
PD Sampling (Whole Blood, Plasma)			X[e]		X[e]	X[e]	X[e]	
CSF Sampling (optional)			X				X	
Adverse Events		X	X	X	X	X	X	X
Anxiolytic Administration			X				X	
^{31}P-MRS			X				X	
MDS-UPDRS			X		X	X	X	
PGI			X		X	X	X	
CGI			X		X	X	X	
C-SSRS		X	X	X	X	X	X	X
APDM Instrumented Tests			X				X	
Phone call				X				

a. Scheduled Visit ± 4 days for Visit 1-4. For Visit 0 (Baseline), the ^{31}P-MRS and PD CSF assessments may be completed over a -7 day window prior to Day 1. All assessments must be completed prior to administration of first study drug dose.
b. Timing for the EOS assessment should occur at four weeks (±3 days) from last dose regardless of early termination or completion of the trial.
c. For females of child bearing potential only.
d. Electrocardiogram (ECG) intervals will be summarized and presented descriptively. ECG rhythm will be interpreted by the Investigator as normal (N), abnormal not-clinically significant (aNCS), or abnormal clinically

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significant (aCS). Triplicate values will be collected at Baseline and averaged for comparison to single assessments at subsequent visits.

e. Whole blood for PK and PD will be taken pre-dose only (~1 hour prior to the dose of study drug).
f. Whole blood for PK will be taken at pre-dose (T_0) and at 1, 2, 4, and 6 hours after dosing for the visit. The exact time at which the patient took his/her previous day's study drug dose must be recorded in order to impute a 24-hour trough value ($T_{24\text{-imputed}}$).

1.2 Study Objectives

To assess the CNS metabolic profile and safety of CNM-Au8 for the treatment of PD:

- Metabolic effects will be assessed as an improvement of ^{31}P-MRS assessment of brain tissue ratio of oxidized form of nicotinamide adenine dinucleotide/reduced form of nicotinamide adenine dinucleotide (NAD+/NADH) concentrations and various additional bioenergetic and phospholipid membrane markers.

- Safety will be assessed via adverse events, serious adverse events, discontinuations due to adverse events, and changes in the Columbia Suicide Severity Rating Scale (C-SSRS), clinical laboratory results, and vital signs.

2. Study Populations

The following analysis populations are to be used for this study:

- Intent to Treat Population (ITT) – The Intent to Treat population will consist of all screened subjects who were assigned a treatment assignment number.

- Safety Population – The Safety population will consist of subjects in the ITT population who received at least one dose of study drug.

- Per Protocol Treatment Population – The Per Protocol Treatment population will consist of subjects in the Safety population who have completed at least 12 weeks of treatment, have Week 12 ^{31}P-MRS measurements, and who have an overall treatment compliance between 80-120%. Participants remaining on treatment longer than 12 weeks due to the COVID-19 pandemic who return to the Institution for completion of the Week 12 visit outside the specified visit window will be included in this population.

3. Statistical Methodology

All study data will be presented in listings, tables and/or figures. Continuous variables will be summarized using descriptive statistics (i.e., mean, standard deviation (SD), minimum, median, and maximum). Categorical variables will be summarized using frequency counts and percentages.

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All summaries, statistical analyses, and individual subject data listings described below will be performed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC). A study-wise Type I error (alpha) of 0.05 will be used for the study. P-values will be 2-sided and descriptive in nature.

Reporting precision in the tables will be to one decimal place for percentages and typically one decimal place more than the precision of the variable when collected/reported for the mean and median. The SD will be presented to one decimal place more than the mean, and the minimum and maximum will be presented to the same precision as the reported value or follow the mean/median precision if derived. Missing values will not be considered in percentage calculations, unless stated otherwise. In these cases, footnotes will specify the percentage denominator definition, or the denominator used will be presented with the summary. P-values will be presented to 4 decimal points. If a p-value is less than or equal to 0.0001, it will be reported as <0.0001. The table shells will specify if there is a deviation from the precision noted here. Data listings will be sorted by subject, dose level, and visit (if applicable). Tables, listings, and figures will be in portable document format (PDF) files.

Baseline will be defined as the last non-missing measurement prior to dosing. Repeated or unscheduled assessments will not be summarized in the tables unless they are part of a baseline derivation, a worst value summary, or the scheduled assessment is missing/invalid, in which case the first non-missing post-baseline value after the scheduled assessment will be used for data analysis.

3.1 Determination of Sample Size

Ren et. al. assessed the feasibility of repeated ^{31}P-MRS scans in a cohort of 7 healthy volunteers (aged 55.7 ± 6.2 years) at UT Southwestern with scans approximately two weeks apart (unpublished data, Ren et al. 2019). The ratio of the NAD+/NADH baseline average value for the healthy volunteer cohort was 4.09 ± 0.78, while the repeat ^{31}P-MRS assessment was 4.11 ± 0.79. The standard deviation of the difference from baseline to week 2 was 0.28, while the coefficient of variation was 5.8% ± 4.8%, demonstrating consistent ^{31}P-MRS NAD+/NADH reproducibility.

For sample size estimates, assuming a common SD of 0.42 for the change from Baseline to Week 12, an evaluable sample size of 11 patients per cohort will have 80% power to detect a mean difference of 0.41 (e.g., approximately 10% change versus baseline). Allowing for up to two drop-out per cohort (~15%) brings the planned sample size to at least 13 participants per cohort.

3.2 Handling of Missing Data

Incomplete dates will be imputed as follows:

If the incomplete date is a start/onset date:

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(1) if the month and year are present, then the first day of the month will be used for day.

(2) if only the year is present, then the first day of January will be used for month and day.

If the incomplete date is an end date:

(1) if the month and year are present, then the last day of the month will be used for day.

(2) if only the year is present, then the last day of December will be used for month and day.

If the reported year is the same as the informed consent year and the imputed date is invalid using the rules above (no day or month), then the informed consent date will be used.

Missing dates will not be imputed.

Missing data will not be imputed for endpoints, and data will be summarized at the visits reported in the database. Drop-outs (i.e., those participants without post-baseline ^{31}P-MRS scan data) will not be imputed and will not be included in the ^{31}P-MRS efficacy analyses for the Per Protocol Treatment population.

3.3 Subject Characteristics

3.3.1 Disposition

Subject disposition will be summarized by treatment on all subjects. The number of screen failures, assigned treatment, included in each population, completing the study and discontinuing from the study as well as the reasons for discontinuation will be presented. Disposition will be presented in data listings.

3.3.2 Demographics and Baseline Characteristics

Demographic data such as age, gender, race, ethnicity, height, weight, body mass index (BMI), and childbearing potential, will be summarized by treatment and presented in data listings. Demographic summaries will be presented for ITT, Per Protocol Treatment, and Safety populations.

3.3.3 Parkinson's Disease History and Medical History

Parkinson's Disease and medical history are collected during the screening visit.

The age at diagnosis of PD, the number of years since onset of symptoms, the diagnostic criteria (presence of resting tremor, bradykinesia, rigidity, and response to dopaminergic therapy), length of dopaminergic therapy and whether the dopaminergic therapy was stable in the last 6 weeks will be summarized on the ITT, Per Protocol Treatment, and Safety populations.

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Medical history will be coded using Medical Dictionary of Regulatory Activities (MedDRA) version 21.0. Medical history will be presented in a data listing.

3.3.4 Prior and Concomitant Medications

Medications taken before and during the study will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 March 2021. Incomplete dates will be imputed (See Section 3.2). If a medication started and ended before the first dose of study drug, then it is considered a prior medication. Medications that are ongoing at or started after the first dose of study drug are considered concomitant medications. All medications will be presented in a data listing.

3.4 Efficacy Analyses

^{31}P-MRS scans will be performed at the baseline and Week 12 visits. Because Week 12 ^{31}P-MRS scans may have been delayed due to COVID-19 related research restrictions, they will be considered for the Week 12 primary endpoint regardless of the actual timing.

The ^{31}P-MRS NAD^+/NADH ratio is measured by a *partial volume coil* that images the parietal and occipital lobes as a single value with respect to the fraction (%) of the nicotinamide adenine dinucleotide (NAD) signal measured as either the oxidized (NAD^+) or reduced form (NADH). All other ^{31}P-MRS reported data are measured by a *full volume coil* (e.g., whole brain coil, bird cage coil) with reported values consisting of the means for all evaluable voxels (approximately 600 voxels at 2 cm^3).

The primary endpoint is the mean change from baseline to Week 12 in the ratio of NAD^+ to NADH (NAD^+/NADH) on the Per Protocol Treatment population. Secondary endpoints include the mean change from baseline to Week 12 from the *partial volume coil* for the fraction (%) of NAD^+, and the fraction (%) of NADH.

The exploratory endpoints include additional measures of brain bioenergetics and brain membrane component precursors as measured by ^{31}P-MRS, the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), APDM measurements of gait, balance, and mobility, and patient and clinician reported outcomes will be assessed by global impression (CGI and PGI).

All efficacy analyses will be conducted on the Intent to Treat and Per Protocol Treatment populations. All efficacy parameters will be presented in data listings.

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3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in the average NAD^+/NADH brain ratio from baseline to Week 12 using the *partial volume coil* ^{31}P-MRS data on the Per Protocol Treatment Population. A paired t-test will be used to analyze the mean change from baseline.

3.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints using the *partial volume coil* ^{31}P-MRS data are the mean change in the NAD+ brain fraction (%) from baseline to Week 12 and the mean change in the NADH brain fraction (%) from baseline to Week 12. A paired t-test will be used to analyze the mean change from baseline for each endpoint. Secondary Efficacy Endpoints will be assessed heirchially with NAD+ brain fraction (%) followed by NADH brain fraction (%).

3.4.3 Exploratory Efficacy Endpoints

3.4.3.1 ^{31}P-MRS Markers of Brain Bioenergetics and Membrane Component Precursors

Exploratory analyses will include: (i) regression of the percent changes at the end of study compared to the baseline values, and (ii) mean change from baseline (BL) to end of treatment (Week 12), as follows:

- Regression of the mean change in average tissue concentration as measured by ^{31}P-MRS (a) *full volume coil* and (b) *partial volume coil* peak area (integral of peak signal area) by metric for the treatment group, for the percent (%) change from BL to Week 12 (end of treatment) compared to the BL subject values.

- Mean change in average tissue concentration as measured by ^{31}P-MRS (a) *full volume coil* and (b) *partial volume coil* peak area (integral of peak signal area) by metric for the treatment group for the mean change from baseline and percent (%) change from baseline to Week 12.

The regression analyses, along with percent changes from baseline to Week 12, will be presented for the following phosphorous metabolites and phosphorous indices:

- NAD(u) (i.e., combined NAD+, NADH pool, including uridine diphosphate glucose (UDPG) overlap)

- Alpha (α) adenosine trinucleotide phosphate (ATP)

- Gamma (γ) ATP

- Beta (β) ATP

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- Intracellular inorganic phosphate (Pi $^{(in)}$)
- Extracellular inorganic phosphate (Pi $^{(ex)}$)
- Phosphoethanolamine (PE)
- Phosphocholine (PC)
- Glycerolphosphoethanolamine (GPE)
- Glycerophosphocholine (GPC)
- Uridine diphosphate glucose

Phosphocreatine (PCr) is used as a normalization factor for each ^{31}P-MRS imaged voxel and will be reported as a value of one (1) for all participants and not analyzed.

The following variables will be calculated programmatically based on the ^{31}P-MRS coil reported metrics described above:

- NAD(only): NAD signal only, defined as NAD(u) less UDPG
- Phosphomonoesters (PME): defined as the sum of PC + PE
- Phosphodiesters (PDE): defined as the sum of GPE + GPC
- Average ATP (ATP(avg)): defined as the average of alpha, beta, and gamma ATP
- PC/PE ratio: defined as the ratio of PC to PE
- $Pi^{(in)}/Pi^{(ex)}$ ratio: defined as the ratio of $Pi^{(in)}$ to $Pi^{(ex)}$
- Total inorganic phosphorous (Pi(t)): defined as the sum of $Pi^{(in)} + Pi^{(ex)}$
- Energy Consumption Index[1]: defined as Pi(t) divided by ATP(avg)
- Energy Consumption Index[2]: defined as Pi(ex) divided by ATP(avg)
- Membrane Phospholipid Index: defined as PME divided by PDE
- pH will be calculated as $pkA + \log_{10} [(Pi(in)$ *[for the PPM value only]* $- D_a)/(D_b - Pi(in))]$, where the constants pKA = 6.75, D_a=3.27, D_b = 5.63

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- Adenosine diphosphate (ADP) (μM) will be calculated as 0.15085/ ((1.66*10^9) * (1*10^(0-pH)))*1000*2.8

Values will also be reported and analyzed for each phosphorous metabolite described above for:

- Average mean change and percent change from Baseline to Week 12 for the Magnitude of each phosphorous peak (e.g., the maximum height of the phosphorous peak)

- Average mean change and percent change from Baseline to Week 12 for the PPM shift

3.4.3.2 MDS-UPDRS

The MDS-UPDRS will be collected at baseline and Weeks 4, 8, and 12. The Unified Parkinson's Disease Rating Scale (UPDRS) is a rating tool used to gauge the course of Parkinson's disease in patients. The UPDRS is composed of four parts: part I assesses behavioral problems; part II assesses patients' perceptions of their ability to carry out activities of daily living; part III covers the motor evaluation of disability; part IV covers treatment complications.

The change from baseline for the total score and each part of the MDS-UPDRS will be summarized. A paired t-test will be used to test for differences.

3.4.3.3 APDM Measurements of Gait, Balance, and Mobility

APDM Mobility Lab and wearable Opal sensors will be utilized to assess for gait abnormalities and postural instability, conditions that worsen with disease severity and can both be used as indicators of fall risk. Assessments include a Timed Up and Go (TUG) test, a 2-Minute Walk test, and in Instrumented Postural Sway test conducted with both eyes open and eyes closed.

APDM assessments are performed at baseline and Week 12. Changes from baseline will be summarized post-hoc in a separate statistical analysis plan.

3.4.3.4 Patient Global Impression Scale

The PGI of severity will be performed at baseline, Weeks 4, 8, and 12. Subjects will mark the response that best describes their symptoms at each visit and their change from baseline.

Frequencies and percentages will be used to summarize the responses for each visit by dose. Additionally, the change from baseline will be summarized. The severity responses will be numbered sequentially: 0=Normal, 1=Mild, 2=Moderate, 3=Severe. The change responses will be numbered such that any positive or negative change will be evident: 3=Very much better, 2=Much better, 1=A little better, 0=No change, -1=A little worse, -2=Much worse, -3=Very much worse.

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The PGI severity responses will be analyzed using a paired t-test. The PGI change responses will be analyzed using a one sample t-test.

3.4.3.5 Clinical Global Impression Scale

The CGI severity will be performed at baseline, Weeks 4, 8, and 12, and the CGI of change will be performed on the post-baseline visits. The severity scale is a measure of the subject against the clinician's patient population.

The results will be presented using frequencies and percentages by visit. Additionally, the change from baseline will be summarized. The severity responses will be numbered sequentially: 0=Normal, not at all, 1=Borderline ill, 2=Mildly ill, 3=Moderately ill, 4=Markedly ill, 5=Severely ill, 6=Among the most extremely ill patients. The change responses will be numbered such that any positive or negative change will be evident: 3=Very much improved, 2=Much improved, 1=Minimally improved, 0=No change, -1=Minimally worse, -2=Much worse, -3=Very much worse. The CGI severity responses will be analyzed using a paired t-test. The CGI change responses will be analyzed using a one sample t-test.

3.5 Pharmacokinetic and Pharmacodynamic Endpoints

Samples for the measurement of whole blood concentrations of gold (Au) will be collected before (pre-dose) administration of the investigational drug product during the Week 4, 8, 12, and EOS visits. At the Week 12 visit, whole blood for PK will be taken at 1, 2, 4, and 6 hours after dosing as well. The data will be used to construct a composite whole blood concentration-time profile for the Week 12 visit over the treatment period. The Week 12 data will be used to estimate the maximum observed plasma concentration (Cmax) of Au and time (Tmax) and the area under the curve over the 24-hour dosing interval (AUC [0-24]). The 24-hour trough value will be imputed.

Samples for the measurement of pharmacodynamic data will be collected before (pre-dose) study drug administration at the baseline visit and following the PK collection during the Week 4, 8, and 12. An optional cerebrospinal fluid or cerebral spinal fluid (CSF) collection at the baseline (pre-dose) and Week 12 visit.

Summaries and analyses on these data will be described in a separate analysis plan.

3.6 Safety Analyses

Safety summaries will be descriptive and performed on the Safety population. No statistical comparisons will be performed.

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Safety assessments include extent of exposure, incidence of adverse events (AE), clinical laboratory results, physical examinations, vital signs, electrocardiogram results (ECG), and Columbia Suicide Severity Rating Scale. All safety parameters will be presented in data listings.

3.6.1 Extent of Exposure

The duration of treatment will be summarized by dose. Treatment duration will be derived as follows: Date of Last Dose – Date of First Dose +1.

If the date of last dose is missing, then it will be imputed to the last available date of study visit.

Study duration will also be summarized and is defined as the total number of days in the study (date of last visit – date of informed consent +1).

Compliance will also be summarized at each visit and overall by dose. Drug accountability will be collected at Weeks 4, 8, and 12. Subjects are expected to consume 2 bottles per day. Therefore, the expected number of used bottles will be calculated for each subject based on the number of days between each visit (current visit date - previous visit date + 1). Compliance at each visit will be derived as follows: (Number of Used Bottles/2 x number of days between each visit) x 100. The overall compliance will be the total number of used bottles divided by the total number of expected used bottles multiplied by 100. For participants who remain on their assigned treatment longer than 12-weeks due to ongoing safety or Institutional restrictions related to COVID-19, overall compliance will include all unscheduled study drug dispensations.

3.6.2 Adverse Events

Adverse events will be collected throughout the study and coded using MedDRA version 21.0. A treatment emergent adverse event (TEAE) is defined as any event that starts on or after the first dose of study drug.

An overall summary of adverse events will be tabulated for:

- the number of subjects with an adverse event
- the total number of adverse events
- the number of subjects with TEAEs
- the number of subjects with TEAEs related to study drug
- the number of subjects with deaths due to a TEAE
- the number of subjects with serious adverse events (SAE) that are treatment emergent

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- the number of subjects with a TEAE leading to discontinuation of study drug

Treatment emergent adverse events will be summarized by system organ class and preferred term for each dose. Related TEAEs, SAEs, TEAEs leading to discontinuation, and TEAEs by severity (mild, moderate, severe) will also be summarized by system organ class and preferred term.

Subjects with more than one event in a system organ class will be counted once within the class and once for each preferred term. Subjects with more than one event with the same preferred term will be counted once, and if the summary is by severity, the subject's most severe event will be counted.

3.6.3 Clinical Laboratory Tests

Laboratory tests will be assessed at screening, baseline, and Weeks 4, 8, 12, and 16 (EOS). Tests with numeric results for hematology, chemistry, and urinalysis will be summarized using descriptive statistics (number of subjects, mean, SD, standard error of the mean (SEM), median, minimum, and maximum) for each visit by dose. Tests with subjective results will be displayed in data listings only.

Table summaries will be presented for observed and change from baseline values. Values flagged as Low, Normal, Abnormal, or High using the laboratory reference ranges will be summarized using shift tables comparing the Week 4 – 12 and EOS values to baseline.

3.6.4 Physical Examinations

A full physical examination will be performed at screening, baseline, and Weeks 4, 8, 12, and 16 (EOS). Clinically significant findings during a physical examination after the baseline visit will be reported as adverse events. Results from the physical examinations will be presented in a data listing.

3.6.5 Vital Signs

Vital signs will be measured at screening, baseline, and Weeks 4, 8, 12, and 16 (EOS). Observed and change from baseline values for systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each visit by dose.

3.6.6 Electrocardiogram

12-Lead ECG will be measured at screening, baseline, and Weeks 4, 8, 12, and 16 (EOS). The baseline measurements will be performed in triplicate and the values averaged for summary. The worst response for the Investigator's interpretation of the ECG will be used in the baseline summary, and a shift table will be used to present the changes from baseline to each post baseline

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visit. Observed and change from baseline values for the numeric parameters will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) by dose for each visit.

3.6.7 Columbia Suicide Severity Rating Scale

The C-SSRS will be given at baseline, Weeks 4, 8, 12 and 16 (EOS). The post screening assessments will be in relation to how they feel in comparison to their last visit. The results will be listed.

4. Interim Analysis

No formal interim analysis will be performed. In the case that two cohorts are conducted, each will be analyzed separately following the completion of each respective cohort.

5. Tables, Listings, Figures

A table of contents for the tables, listings, and figures will be presented in a separate document as the list of summaries or numbering may change after finalization of this document. If additional summaries are added that are not described in this document, then this SAP will be amended, or an addendum will be created.

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6. REFERENCES

There are no references for this document.