Statistical Analysis Plan

Protocol Number: MT-7117-A01

A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects with Erythropoietic Protoporphyria

Version 2.0
Date 15 October 2019
NCT number: NCT03520036

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VERSION: **2.0**

DATE: **15OCT2019**

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APPROVAL FORM

STATISTICAL ANALYSIS PLAN

Protocol No. MT-7117-A01

Protocol Title **A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT 7117 in Subjects with Erythropoietic Protoporphyria**

Version 2.0

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Position: Head of CP, MTPC

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Protocol No. **MT-7117-A01**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	AE of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical Study Report
CYP	Cytochrome P450
EC	Ethics committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
EPP	Erythropoietic protoporphyria
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web-based Response System
LFT	Liver function test
LOCF	Last Observation Carried Forward
LS	Least squares
MC1R	Melanocortin 1 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MTDA	Mitsubishi Tanabe Pharma Development America
MTPC	Mitsubishi Tanabe Pharma Corporation
NCS	Not clinically significant
NOAEL	No observed adverse effect level

Abbreviation	Definition
PGIC	Patient Global Impression of Change
PGx	Pharmacogenetic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient-reported Outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PT	Preferred Term
QP	Qualified Person
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
QTcF	Corrected QT interval using Frederica's formula
QTcB	Corrected QT interval using Bazett's formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SNP	Single-nucleotide polymorphism
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
[redacted]	
ULN	Upper limit of normal
WHO	World Health Organization
WMA	World Medical Association

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the MT-7117-A01 final protocol amendment 2 dated Aug. 13, 2019. The plan covers statistical analysis, tabulations and listings of efficacy, safety and PK data to assess the efficacy, safety, and PK of 2 doses of MT-7117 compared to placebo.

The SAP is prepared by MTDA data science and reviewed by MTDA clinical study team and MTPC data science following GLB-BST-SOP002 ver.6. The statistical analyses and production of the outputs described in the SAP will be conducted and QCed by [redacted]. (CRO), using SAS version 9.4 or higher. The final analyses and outputs will be approved by MTPC/MTDA data science.

The summary of exploratory endpoints in Section 2.10 (except for porphyrin and protoporphyrin levels, see Section 7.14) will be presented in a separate report.

1.1 Study Objectives

Primary Objective:

- To investigate the efficacy and safety of MT-7117 on time to onset and severity of prodromal symptoms associated with sunlight exposure in subjects with EPP.

Secondary Objectives:

- To investigate the effect on sunlight exposure duration and tolerance in subjects with EPP
- To investigate the effect on melanin density in subjects with EPP.
- To assess the effect of treatment on quality of life in subjects with EPP.
- To investigate PK in subjects with EPP.

Exploratory Objectives:

- To evaluate skin biopsy samples from EPP subjects for exploratory biomarkers related to pathogenesis of EPP, inflammatory response, and the mode of action of MT-7117.
- To evaluate pharmacogenetics (PGx) including MC1R with single-nucleotide polymorphisms (SNPs), if applicable, as this could lead to pigmentation.
- To evaluate porphyrin and protoporphyrin levels

1.2 Study Design

This is a Phase II, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in subjects with EPP. The study consists of a 2-week screening period, a 16-week double-blind treatment period, and a 6-week follow-up period at Week 22. The total participation period is approximately 24 weeks.

This study is being conducted without regard to seasonality.

The study design is illustrated in Figure 1.

Subjects will attend Screening (Visit 1) up to 2 weeks before Randomization (Visit 2), in order to confirm eligibility and obtain pre-study safety assessments including nevi evaluation. Subjects will also be instructed how to use a sunlight exposure diary.

At Visit 2, subjects meeting eligibility criteria will be randomized in a 1:1:1 ratio to receive either [redacted]-, [redacted] of MT-7117, or matching placebo in a double-blind manner. Baseline average daily sunlight exposure time without prodromal symptom (≤30 min and >30 min) will be used as stratum for the randomization. The first dose will be administered at Visit 2 following baseline assessment including in-clinic sunlight exposure test. Active or placebo tablets will be administered once daily in the morning with food.

Subjects will attend in-clinic visits at Weeks 4, 8, and 12 (Visits 5, 6, and 7, respectively) during which assessments will be performed. In addition, subjects undergo mobile laboratory sample collection at Weeks 1 and 2 (Visits 3 and 4, respectively) to measure liver function markers (AST, ALT, GGT, ALP, direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 16 or early termination (Visit 8). Following the last treatment visit, subjects will attend a follow-up visit at Week 22 or 6 weeks after early termination.

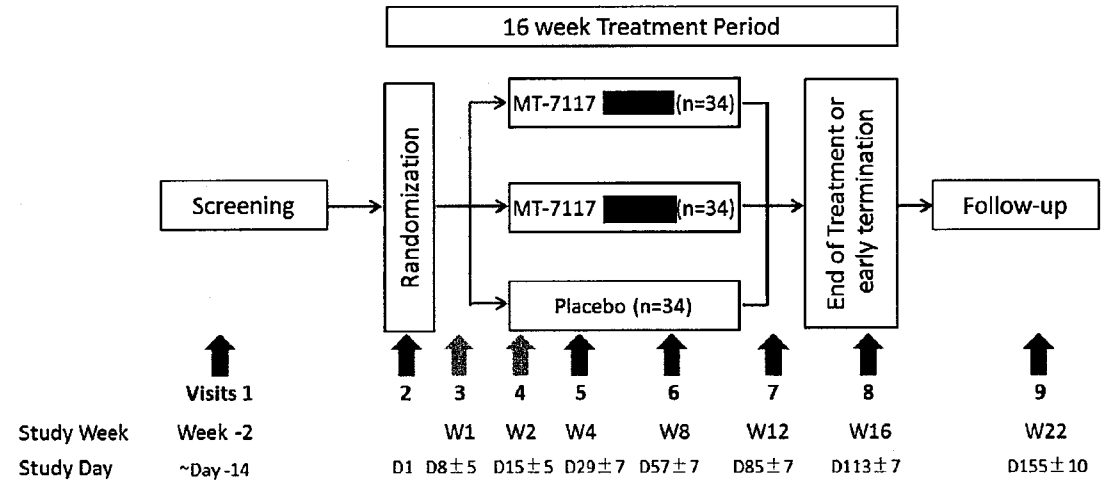


Figure 1 Study Design Schematic

Table 1 Schedule of Assessments

Study Period	Screening	Double-blind Treatment							Follow-up
Visit Number	Visit 1	Visit 2 (Randomization)	Visit 3[f]	Visit 4[f]	Visit 5	Visit 6	Visit 7	Visit 8[n] (EOT)	Visit 9[o] (EOS)
Study Week	Week -2		Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 22
Study Day ± Window	~Day –14[a]	Day 1	Day 8±5	Day 15±5	Day 29±7	Day 57±7	Day 85±7	Day 113±7	Day 155±10
Informed consent[b,c]	X								
Inclusion/exclusion criteria evaluation	X	X							
Demographics	X								
Medical history	X	X							
Randomization		X							
Body weight	X	X			X	X	X	X	X
Height	X								
Physical examination[d]	X	X			X	X	X	X	X
Vital signs[e]	X	X			X	X	X	X	X
12-lead ECG		X						X	
Hematology/coagulation, biochemistry & urinalysis[f]	X	X	X[f]	X[f]	X	X	X	X	X
Blood collection for porphyrin and protoporphyrin levels[g]	X					X		X	
Fitzpatrick skin type assessment	X					X		X	
Pregnancy test[h]	X	X			X	X	X	X	X
PK sampling (blood)[i]		X			X	X	X	X	
Blood sampling for PGx[b]		X							
Pharmacodynamics skin biopsy[c]		X						X	
Dispensing of study		X			X	X	X		

Study Period	Screening	Double-blind Treatment							Follow-up
Visit Number	Visit 1	Visit 2 (Randomization)	Visit 3[f]	Visit 4[f]	Visit 5	Visit 6	Visit 7	Visit 8[n] (EOT)	Visit 9[o] (EOS)
Study Week	Week -2		Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 22
Study Day ± Window	~Day –14[a]	Day 1	Day 8±5	Day 15±5	Day 29±7	Day 57±7	Day 85±7	Day 113±7	Day 155±10
medication									
Medication accountability					X	X	X	X	
Subject Questionnaire for study medication[j]								X	
PROMIS-57		X				X		X	X
PGIC						X		X	X
PGIC 2									X
Sunlight exposure diaries[k]	←								→
Melanin density evaluation		X				X		X	X
In-clinic sunlight exposure test[l]		X						X	
Nevi evaluation[m]		X				X		X	(X)
Exit interview Questionnaire[p]									X
Concomitant medication	←								→
Adverse events	←								→

Abbreviations: ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; PGIC = Patient Global Impression of Change; PGx = pharmacogenetics(s); PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System.

[a] A minimum of 7 days of outside exposure data is required prior to randomization.

[b] Blood samples will be collected for PGx analysis for those subjects who have specifically given informed consent for optional PGx analysis at Visit 2.

[c] Skin biopsy (3 mm × 3 mm punch biopsy) will be performed at Visits 2 and 8 in subjects who have specifically given informed consent for skin biopsy.

[d] Complete physical examination will be performed at Visit 1 and an abbreviated physical examination will be performed at all other time points.

[e] Vital signs include measurement of sitting blood pressure, pulse rate, and body temperature.

[f] At Visits 3 and 4, subjects will have mobile units measure liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin). Blood samples for liver function markers will be shipped to the central laboratory.

[g] Plasma total porphyrins and erythrocyte protoporphyrin will be assessed at Visits 1, 6 and 8. Results reports will be sent to the site for data collection.

[h] For female subjects of child-bearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test will be performed at Visit 2 and Visits 5 through 9.

[i] PK blood samples for MT-7117 will be collected and processed at Visit 2 (pre-dose), Visits 5 through 7 (any time), and Visit 8 (at the visit and 3 to 4 hours after the first PK sample collection [both post-dose]). Date and time of most recent dose, and date and time of PK sample collection will be recorded.

[j] Subjects will be asked whether they receive active or placebo treatment at Visit 8.

[k] Sunlight exposure data, presence of prodromal symptoms and pain, their severity, and their onset/duration will be collected from Visits 1 through 9. Diary training will be performed at the first in-clinic visit during the screening period.

[l] In-clinic sunlight exposure test should be done once before randomization and once at Visit 8.

[m] Nevi evaluation will be performed locally by a dermatologist or qualified site staff. Baseline nevi evaluation will be performed at any time during the Screening period before Randomization. The Nevi evaluation at Visit 9 is to assess for the reversibility if any suspicious nevi changes were observed during treatment as per the investigator's (and/or dermatologist's or other qualified site staff) judgment. Any follow-up will be recorded in the eCRF.

[n] These assessments will be performed at Week 16 or early termination.

[o] All subjects will return to the study site for a follow-up visit at 6 weeks after end of treatment visit (Week 16 or early termination).

[p] The exit interview can be assessed at Visit 9 or as a post study follow-up phone call or online survey.

2. STUDY ENDPOINTS

2.1 Primary Efficacy Endpoints

- Change from baseline in average daily time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 16 (Visit 8).

To calculate the average daily sunlight exposure time to first prodromal symptom, a 14-day window on or before a visit (Week 2, 4, 6, 8, 10, 12, 14, and 16) will be used. For baseline, a 14-day window before Day one will be used. A 14-day window will be applied to similar situations for other efficacy endpoints.

The subjects' diary data will be used to derive this and other endpoints based on sunlight exposure time. The details will be given in section 5.4.1. Minute will be used as unit for duration for this and other endpoints.

2.2 Secondary Efficacy Endpoints

- Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms at Week 16.
- Change from baseline in average daily mean duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. The daily mean duration is considered as multiple periods of sunlight exposure in each day and measurable by sum of duration of each period divided by number of periods.
- Total number of sunlight exposure episodes with prodromal symptoms during 16-week double-blind treatment period.
- The average daily mean intensity of the subject's prodromal symptoms during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during 16-week double-blind treatment period.
- The change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments. Average of 6 skin segments for the change from Baseline and % change from baseline in melanin density at Week 8, 16, and 22.
- Total number of pain events during 16-week double-blind treatment period.

2.3 Other Efficacy Endpoints

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms.
- Total time (hours) during 16-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.

- Total number of days subject is exposed to sunlight for any duration between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset on Saturday without prodromal symptoms at Week 16.
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 16.
- The average daily mean intensity of the subject's pain events during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of pain events during 16-week double-blind treatment period.
- Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity in PROMIS 57.
- Patient Global Impression of Change (PGIC).

2.4 Safety Endpoints

2.4.1 Adverse events (AEs)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0 .

Treatment-emergent AEs (TEAEs) are defined as AEs that newly occurred or worsened in severity on or after the first dose of study double-blinded (DB) treatment. The treatment relationship with the AE is in 2 categories (reasonable possibility, no reasonable possibility). The detail is included in protocol.

2.4.2 Physical examination

The complete physical examination consists of a routine assessment of major body systems:

- Abdominal
- cardiovascular
- general appearance
- head
- eyes
- ears/nose/throat
- lymph nodes
- musculoskeletal

- neck
- neurological
- dermatological
- other

The abbreviated physical examination consists of a routine assessment of the following body systems:

- Abdominal
- cardiovascular
- general appearance
- other

2.4.3 Vital signs

- The vital signs include:
- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Oral Body Temperature (^{0}C)
- Body Weight (kg)

2.4.4 Clinical laboratory examinations

The lab tests are conducted for the following lab categories

- Hematology
- Coagulation
- Biochemistry
- Urinalysis

The liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin) will be collected.

The lab test names are listed in the table below.

Table 2 Routine Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell count	White blood cell count and differential
Biochemistry:	
Aldosterone	Cholesterol
Alkaline phosphatase	Triglycerides
Aspartate aminotransferase	High density lipoprotein-cholesterol
Alanine aminotransferase	Low density lipoprotein-cholesterol
Gamma-glutamyl transpeptidase	Protein (total)
Potassium	Albumin
Sodium	Creatine kinase
Chloride	Creatinine
Inorganic phosphate	Ferritin
Glucose	
Bilirubin (direct and total)	
Blood urea nitrogen	
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalized ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood	
Microscopic examination[a]	

[a] Performed only if required, based on urinalysis results

2.4.5 ECG parameters

The 12-lead ECG will be performed and the following parameters will be collected.

- Heart rate(bpm)
- PR(msec)
- RR(msec)
- QRS(msec)
- QT(msec)
- QTcF (msec)
- QTcB(msec)

The ECG interpretation (abnormal / normal and clinically significant / not clinically significant) will be collected.

2.4.6 Nevi appearance

- Nevi appearance is assessed by a dermatologist. Any nevi that enlarge or otherwise undergo changes that are of clinical concern during active treatment will be biopsied for follow up.
- Any suspicious nevi found during assessment (Y,N)
- Any clinically significant findings (Y,N)

2.5 Pharmacokinetics (PK) Evaluations

Plasma concentrations of MT-7117 will be sampled then analyzed at randomization visit, Week 4, 8, 12, and 16 visits.

2.6 Demographic and Other

2.6.1 Demographic and Baseline Characteristic

The following subject demographic and baseline characteristic are collected.

- Age (years)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Baseline average sunlight exposure duration without prodromal symptoms
- Baseline average daily duration of pain
- Seasonality (Randomized between Mar 1 and Aug 31 inclusive, other)

2.6.2 Medical History

The subjects Medical, medication, smoking, alcohol, psychiatric disease and surgical history will be recorded. Medical/surgical history includes any medical condition or surgical history before Screening. In addition, the detailed history of hepatic disease or injury (e.g., viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, or biliary tract disease) will be recorded.

2.6.3 Prior or Concomitant Medications

Prior medications are defined as any medication taken before Screening.

Any prior medication, including prescription and over-the-counter medications, taken within 1 month before Screening will be recorded on the eCRF. Information recorded will include: name of medication, dose, duration of and reason for use.

Concomitant medication is defined as any medication, other than study medication, which is taken during the study after Screening, including prescription, over-the-counter medications, herbals, dietary supplements, and recreational drugs. All concomitant medications taken while the subject is participating in the study will be recorded.

The prior and concomitant medication data will be coded using World Health Organization Drug Dictionary (WHO-DD).

2.7 Fitzpatrick Skin Type Assessment

The Fitzpatrick scale test will be completed at screening, Week 8, and 16.

The Fitzpatrick scale (also Fitzpatrick skin typing test; or Fitzpatrick phototyping scale) is a numerical classification schema for human skin color, developed in 1975 by Thomas B. Fitzpatrick as a way to estimate the response of different types of skin to ultraviolet light.

Fitzpatrick scale test is presented in protocol Appendix 2.

2.8 Subject Questionnaire for Study Medication

Subject will be asked whether they receive active or placebo treatment at Week 16 or early termination. The results will be recorded on the eCRF.

2.9 Protocol Deviations

Protocol deviations will be documented, reviewed and determined in the blinded data review meeting (BDRM). Protocol deviations potentially influencing the evaluation of the primary endpoint will be defined as major deviations in order to define PP population in Section 4.3. The major protocol deviations will be selected in this meeting.

At least the following will be included as major protocol deviations:

- I/E criteria violation with significant impact on efficacy
- Overall drug compliance is less than 80% or greater than 120%
- Taking wrong treatment

The BDRM meeting minutes will serve as the main document for protocol deviations.

2.10 Exploratory Endpoints

- Biomarker assessments using pharmacodynamics skin biopsy samples for those subjects who have given their consent
- PGx analysis including MC1R, with SNPs for those subjects who have given their consent
- Porphyrin and protoporphyrin levels

2.11 Exit interview and PGIC_2

Questionnaires for exit interview and PGIC_2 at follow up visit are added in protocol amendment 2. Due to the late stage of the study, limited subjects have chance to finish these questionnaires. These data will not be included in the clinical data base.

3. PLANNED ANALYSES

3.1 Interim Analyses

An interim analysis is not planned for this study.

3.2 Final Analysis

The final analysis will be conducted with unblinded data after database lock.

All the planned efficacy and safety analyses in this SAP will be performed by [redacted]. (CRO).

4. ANALYSIS POPULATION(S)

4.1 Safety (SAF) Population

Safety (SAF) Population includes all randomized subjects who received at least 1 dose of study medication. The safety population will be used for all safety analyses. The subject Actual treatment received will be used for safety analyses. For subjects took more than one treatment, the highest dose level will be used for safety analyses.

4.2 Intent-to-treat (ITT) population

Intent-to-treat (ITT) population: includes all randomized subjects who have at least 1 dose of study medication and who have at least 1 post-baseline efficacy assessment. The ITT population will be used for all efficacy analyses. The subject randomized treatment will be used for efficacy analyses.

4.3 Per-protocol (PP) population

Per-protocol (PP) population: includes all ITT subjects who do not have any major protocol deviations which have significant impact on primary analysis and complete Week 16 (the end of double-blind treatment period). The PP population will be used for primary analyses. The subject randomized treatment will be used for efficacy analyses.

4.4 Pharmacokinetic (PK) population

Pharmacokinetic (PK) population includes all randomized subjects who receive at least 1 dose of MT-7117 and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of MT-7117.

5. GENERAL CONSIDERATIONS

5.1 Number of digits to report (present in TFL)

Table 3 Number of decimal places (DP) or significant digits (SD)

Statistic	Specification	Apply to
Minimum, maximum	same number of DPs as the data provided in the datasets	All original, i.e. non-derived, data provided in the datasets
mean, median, confidence intervals	one more DP than the raw data	All
SD	one more DP than the raw data	All
Percentages	1 DP	All
p-values	3 DP	All
Odds Ratio	2DP	All
Rate	2DP	All

5.2 Significance level and confidence interval

The statistical tests will be performed as two-sided with significance level of 5%.

The two-sided confidence intervals will be determined with a confidence level of 95%.

5.3 Descriptive statistics values to calculate

Where appropriate, variables will be summarized descriptively (frequency and percent will be summarized for categorical variables; mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by analysis visit and by treatment group.

The denominator for the percentages will be the total number of subjects in the treatment group and Analysis Set being presented, unless otherwise specified (e.g. on some occasions,

percentages may be calculated out of the total number of subjects with available data at a particular visit and/or time point).

Summary statistics required for PK or related data are described in relevant sections later.

5.4 Derived variables and data convention

5.4.1 Derived variables for diary data

For this study, only the sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset is considered and collected. The following wording is not repeated.

The subjects will record in their diaries for the sunlight exposure periods (start/end time), prodromal symptom periods, and pain periods. The subjects' sunlight exposure start and end times will be compared with their state capital cities sunrise and sunset times. The sunlight exposure time beyond the interval (from 1 hour post sunrise to 1 hour pre-sunset) will be excluded from the analyses unless it is specified in a different way.

The analysis windows are defined in the table below. The nominal day for each week relative to the first dose day will be used. Day1 is the first dose day.

Table 4 Analysis Visit Window for diary data

Analysis Visit	Nominal day	Window
Baseline	-1	Day -14 to -1
Week 2	14	Day 1 to 14
Week 4	28	Day 15 to 28
Week 6	42	Day 29 to 42
Week 8	56	Day 43 to 56
Week 10	70	Day 57 to 70
Week 12	84	Day 71 to 84
Week 14	98	Day 85 to 98
Week 16	112	Day 99 to 112
Week 22 (FU)		the latest 1 to 14 days before FU not overlapping with the Double-Blind Period.

5.4.1.1 The average daily time to first prodromal symptom associated with exposure to sunlight

The following is the procedure to calculate the average daily time to first prodromal symptom associated with exposure to sunlight.

1. If the sunlight exposure time is beyond the interval (from 1 hour post sunrise to 1 hour pre-sunset), then this time is excluded by comparing the sunrise/sunset time.
2. The time to first prodromal symptom associated with exposure to sunlight in a day is calculated. It is the sum of the sunlight exposure time before the first prodromal symptom occurred in the day. If a subject had sunlight exposure but no prodromal

symptom in a day, the sum of the sunlight exposure time for the day is used as the sunlight exposure time to the first prodromal symptom.

3. A diary day is qualified if the subject had non-zero duration of sunlight exposure in the day.
4. The average daily sunlight exposure time to the first prodromal symptom at a time point (Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, and 22) is the average of the sunlight exposure time to the first prodromal symptom of qualified days in the corresponding 14-day window. At least 1 day diary data is required for each 14 day window to be qualified for this calculation.
5. The minute is used as the unit for calculation of the duration. The Duration will not be rounded. However, in data presentation for listings, the duration will be rounded to integer. HH:MM can be used when the duration is more than 60 minutes. For tables, the duration will be rounded to integer for minimum and maximum and to one decimal place for mean, SD, median and confidence intervals.

5.4.1.2 The average daily duration of sunlight exposure without prodromal symptoms

The following is the procedure to calculate the duration of sunlight exposure without prodromal symptoms. The analysis windows are defined in the table 4.

1. Step 1 in section 5.4.1.1 will be applied.
2. The duration of sunlight exposure without prodromal symptoms in a day is calculated. It is the sum of the duration of sunlight exposure periods deducting the prodromal symptom presenting time covered in each period.
3. Step 3 to 5 in Section 5.4.1.1 will be applied.

The following endpoint is derived when applying the rule above without the step 1.

5.4.1.2.1 The average daily duration of sunlight exposure regardless of time of day without prodromal symptoms

5.4.1.3 The average daily mean duration of sunlight exposure without prodromal symptoms

The following is the procedure to calculate the average daily mean duration of sunlight exposure without prodromal symptoms. The analysis windows are defined in the table 4

1. Step 1 in section 5.4.1.1 will be applied.
2. The duration of sunlight exposure without prodromal symptoms in a day is calculated. It is the sum of the duration of sunlight exposure periods deducting the prodromal symptom presenting time covered in each period. This sum of duration is divided by the number of sunlight exposure periods as the average daily mean duration.
3. Step 3 to 5 in Section 5.4.1.1 will be applied.

5.4.2 Definition of baseline

Unless otherwise specified, the baseline values are the last available assessment before the first dose of randomized treatment.

5.4.3 Definition of (percent) change from baseline

For numerical variables, change from baseline will be calculated as the post-baseline value minus the baseline value. If percent change from baseline is required, then percent change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100. If baseline value cannot be determined for a particular variable, the change from baseline and percent change from baseline will not be calculated.

5.4.4 Analysis visits for the non-diary data

The analysis visits will be derived for the non-diary data. The analysis windows are different from the windows used for diary data.

Unless stated otherwise, the analysis visit windows for by visit summary in efficacy and safety endpoints are defined in the table below.

Table 5 Analysis Visit Windows for the non-diary data

Analysis visit	Nominal day	Window
Screening	Day -14	By Day -14
Day 1	First dose day	NA
Week 1	Day 8	Day 3 to 11
Week 2	Day 15	Day 12 to 22
Week 4	Day 29	Day 23 to 42
Week 8	Day 57	Day 43 to 71
Week 12	Day 85	Day 72 to 99
Week 16	Day 113	Day 100 to 134
Week 22 (FU)	Day 155	NA
End of treatment (EOT)	Week 16 study visit or study early termination visit	

The analysis visits are derived according to the following criteria:

- The unscheduled visits are not used for the deriving.
- If a study visit is the only one in an analysis visit window, this study visit becomes the derived analysis visit.
- If there are multiple visits in an analysis visit window, the closest visit to the nominal day becomes the analysis visit. In the event that two visits are the closest visits to the nominal day and equally distanced to the nominal day, the visit after the nominal day becomes the derived visit.
- The follow-up visit will not be derived. The study visit will be used.

- Unscheduled visits and retests (same visit number assigned), will not be displayed in by-visit summary tables, but will be included in the data listings.
- The deriving analysis visit is not applicable to the data not depending on study visit, for example, the AE data.

5.4.5 BMI

BMI (kg/m^2) = Body weight (kg)/{Body height (m)}^{2}

Round off the second decimal place and report the value to the first decimal place.

5.4.6 Medical history and Adverse events

All medical history and adverse events will be coded from the verbatim terms reported by the investigator term using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or the later version.

5.4.7 Adverse reactions

Adverse reactions are defined as adverse events that are determined to have a "reasonably possible" causal relationship to the study drug.

5.4.8 Duration of the AE and time to the AE

Duration of the AE and time to the AE occurrence from start of study medication will be calculated and presented in days, where AE duration = AE stop date – AE start date + 1 and the time to the AE occurrence = AE start date – first DB dose date + 1.

5.4.9 Prior and Concomitant medications

Prior and concomitant medications are medications other than Study treatment. They are derived by comparing their start and stop dates with the first treatment dose date.

Prior medications are those which stopped prior to first dose of double-blind study medication. Concomitant medications are medications that started prior to, on or after date of first dose of double-blind study medication and ended on or after date of first dose of double-blind study medication. This includes medications deemed as ongoing at the end of study.

5.4.10 Study Treatment Exposure

The duration of exposure is calculated as the total number of days that the subject has been treated with double-blind study medication— that is, from the treatment start date to the date of their EOT visit. For subjects lost to follow up, the treatment end date is taken to be the date of their last visit. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Duration of exposure (days) = EOT visit date – first treatment distribution date +1.

5.4.11 Study Treatment Compliance

Compliance with double-blind study medication—based on the drug accountability data—will be calculated as the number of days subjects take study medication divided by the duration of exposure in days, expressed as a percentage.

Study medication compliance will be calculated as follows:

$$\frac{\text{duration of exposure (days)} - \text{number of days subject miss the medication}}{\text{duration of exposure in days}} \times 100\%$$

The subjects should take one dose daily per protocol.

6. SAMPLE SIZE AND POWER CONSIDERATIONS

The sample size for this study is not based on a formal statistical calculation since this is an exploratory clinical study for a rare disease and no formal data is available to support estimation for the primary endpoint. However, a sample size of 34 subjects per treatment group is considered to be adequate to meet the objectives of the study.

7. STATISTICAL METHODOLOGY

7.1 Blinded Data Review

Prior to database lock, a blinded data review meeting (BDRM) will be conducted. Protocol deviations, protocol defined analysis populations will be confirmed during the meeting. Additional data handling rules may be introduced as results of data review. Should additional data handling rules be confirmed during the meeting, they will be incorporated into the analyses planned in this SAP.

PK data that are considered "invalid" will be flagged in the listing. The PK data handling will be assessed during BDRM prior to database lock and in the investigation of PK data handling assessment after unblinding. A separate PK data handling document will be produced to cover both pre- and post- unblinding decisions. If PK sample handling errors or other factors are identified after data unblinding, and these errors have led to unexpected erroneous data, then these erroneous data will be regarded as "invalid".

7.2 Disposition of Subjects

The number of subjects who completed or prematurely discontinued from the study, the reasons for discontinuation, and the number of subjects in each analysis population will be summarized by treatment group.

The number of subjects who enter screening will be summarized, and the percentage of these subjects who fail to meet entry criteria will be reported for total subjects. Screen failures will be summarized in total and by each reason for screen failure.

The data listing for Subject disposition will be generated.

7.3 Demographic and Other Baseline Characteristics

The subject demographic and baseline characteristic will be summarized by treatment in table and presented in data listing for the ITT population.

7.4 Medical History

The subjects Medical and surgical history will be summarized by treatment, SOC and PT in table and presented in data listing for the safety population.

The number and percentage of subjects who had at least one medical history or surgical history will be presented. For each medical history or surgical history term the count and percentage of subjects will be presented.

In the above tables, SOC is sorted by International order; then within SOC, PT is sorted by descending counts under Overall Total column, then descending counts under Placebo column, then alphabetic order for PTs with the same count.

7.5 Prior or Concomitant Medications

The prior and concomitant medications will be summarized in table separately by treatment group and presented in data listing for the SAF population. The data will be coded using World Health Organization Drug Dictionary (WHO-DD). The summaries will be by ATC level 2 and preferred name and treatment.

The number and percentage of subjects who had at least one prior or concomitant medication will be presented. For each prior or concomitant medication term, the number and percentage of subjects will be presented.

7.6 Fitzpatrick skin scale test

Fitzpatrick scale test will be summarized in table by treatment and visit.

The Fitzpatrick skin type will be summarized with number and percentage and the Fitzpatrick total score will be summarized with descriptive statistics (N, mean, SD, median, minimum, and maximum).

7.7 Prohibited medication

The prohibited medications coded by the protocol Appendix 1 Table 14.1-1 will be summarized in table by treatment and presented in data listing for the safety population. The data will be coded using World Health Organization Drug Dictionary (WHO-DD). The summaries will be by ATC level 2 and preferred name and treatment.

7.8 Study Treatment Exposure

Duration of exposure and total dosed days will be summarized in table by treatment and presented in data listing for the safety population.

7.9 Treatment Compliance

Compliance to Double-Blind study medication will be presented for the safety population in table by treatment.

The range 80% <= compliance <= 120% will be used to define a subject being treatment compliant.

All study medication administration and accountability data will be listed by subject.

7.10 Protocol Deviations

The major protocol deviations will be summarized in tables by treatment and presented in data listings as well.

7.11 Efficacy Assessments

7.11.1 Primary Efficacy Analysis

The primary treatment comparisons of interest are the change from baseline in average daily time to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset for the two MT-7117 doses ([redacted], and [redacted]) compared with placebo at Week 16 (Visit 8).

To assess the treatment effect at Week 16, change from baseline in average daily (minutes) time to first prodromal symptom associated with exposure to sunlight between 1 hour post sunrise and 1 hour pre-sunset at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 will be analyzed using mixed-effect model for repeated measures (MMRM).

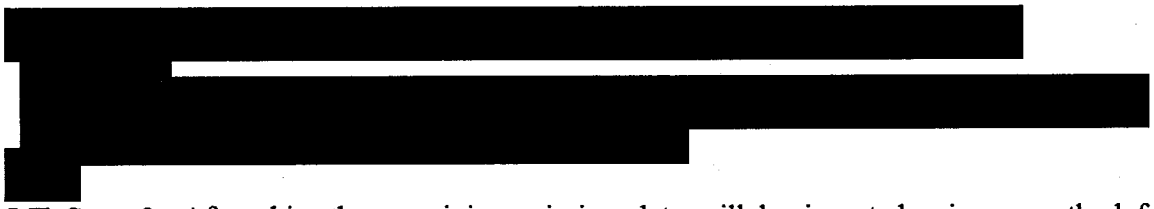
The analysis model included fixed categorical terms for treatment, randomization strata (the baseline average daily sunlight exposure time without prodromal symptoms (≤30 min or >30 min)), visit, and treatment by visit interaction together with continuous covariate terms for the corresponding baseline and the corresponding baseline by visit interaction. An unstructured correlation structure will be used to model the within-subject variance covariance errors. Should convergence of the model fail (due to the small numbers of subjects in this study), a Toeplitz correlation matrix will be used if appropriate, or else AR(1) correlation matrix will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, adjusted (least squares [LS]) means and standard errors will be produced by treatment and visit. Difference in adjusted means at each visit (each MT-7117 dose vs. placebo) with standard errors, 95% CIs and associated P-values will also be produced. All available data from all patients will be used in the primary analysis without any imputation. The figure of LS mean with standard error will be plotted from this MMRM.

A supportive analysis will be performed the same way for the primary endpoints using the PP population.

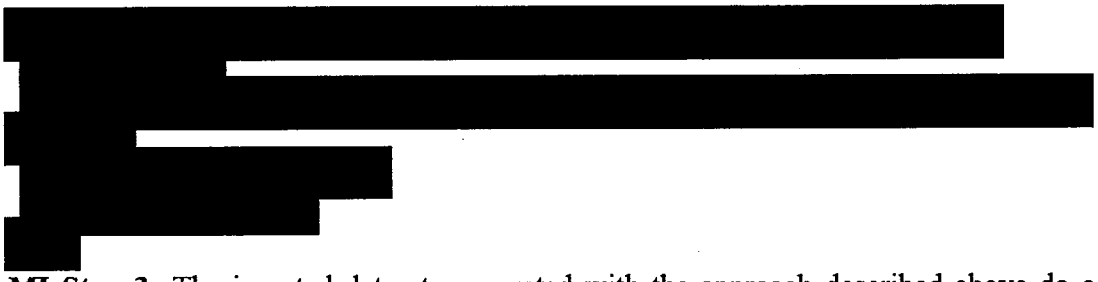
Non-parametric analysis will be performed in order to confirm the robustness for the above parametric model. The change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post sunrise and

1 hour pre-sunset at each visit (Weeks 2, 4, 6, 8, 10, 12, 14 and 16) from two treatments being compared will enter the corresponding analysis. The point estimates and two-sided 95% confidence intervals for the difference between the treatment groups will be obtained using the Hodges-Lehman estimator corresponding to Wilcoxon's rank sum test. The paired comparison between each MT-7117 arm with placebo will also be performed using this non-parametric analysis method. **This non-parametric analysis will be performed with multiple imputation (MI) method in the following steps, assuming missing at random.**

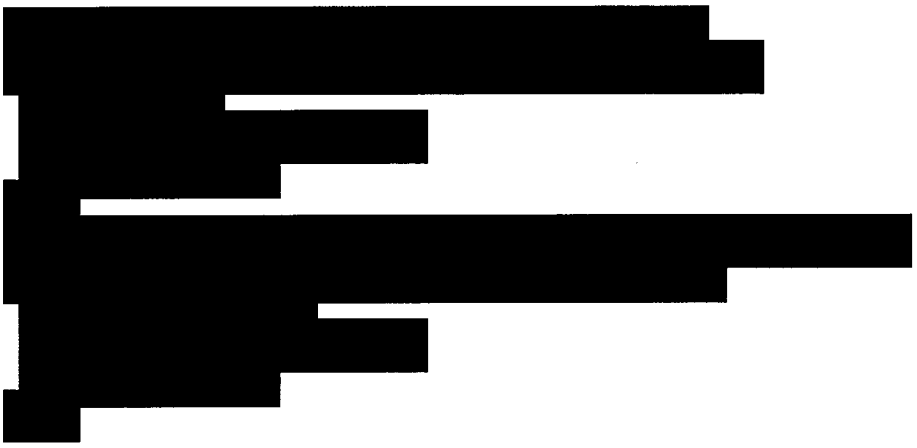
MI Step 1: Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. The MI procedure in SAS will be used for this purpose and this first MI step is planned to be repeated 1000 times, creating different datasets with a monotone missing data structure. Seed value of 1995 will be used in the MI procedure. The following SAS code will be used to generate the monotone missing data pattern:



MI Step 2: After this, the remaining missing data will be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the created dataset with a monotone missing data pattern, the MI procedure in SAS will be used to impute missing values based on a sequential procedure reflecting the monotone missing data pattern. Patients with the first missing value occurring at Week 2 will have their missing Week 2 value replaced by an imputed value from a regression model with treatment group and the baseline value as explanatory variables. In the next step, patients with their Week 4 value missing will have their missing Week 4 value replaced by an imputed value from a regression model with treatment group, baseline value and Week 2 value as explanatory variables. Similar procedure will be used to replace the missing values at Week 4, 6, 8, 10, 12, 14 and 16.The following example SAS code will be used to make the imputation with the MAR assumption:



MI Step 3: The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the sensitivity analysis for the primary efficacy endpoint. The Hodges-Lehman estimator to obtain the point estimates and two-sided 95% confidence intervals for the difference between the treatment groups with paired comparison for Week 2, 4, 6, 8, 12, 14 and 16 will be run on each of the 1000 generated imputed datasets. Finally, the MIANALYZE procedure in SAS will be applied to combine the results from these analyses to derive an overall estimate of the treatment differences at Week 2, 4, 6, 8, 10, 12, 14, 16 according to the following code. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated. The following example SAS code will be used:



The primary efficacy endpoint will also be summarized using descriptive statistics and presented in data listing.

7.11.2 Analysis of Secondary and Other Efficacy Endpoints

The following continuous secondary and other efficacy endpoints will be analyzed using MMRM similar to the analyses for the primary endpoint.

- Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted.
- Change from baseline in average daily mean duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. The daily mean duration is considered as multiple periods of sunlight exposure in each day and measurable by sum of duration of each period divided by number of periods.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during 16-week double-blind treatment period.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted.
- Change from baseline in average daily duration (minutes) of pain events during 16-week double-blind treatment period.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.

- The figure of LS mean with standard error will be plotted.

- Change from baseline in average daily mean intensity of the patient's prodromal symptoms during 16 week double-blind treatment period.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted.
- Change from baseline in average daily mean intensity of the patient's pain events during 16 week double-blind treatment period.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted.
- Change from baseline for all total score and total score in each domain of Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to Participate in Social Roles and Activities, Pain Interference, Pain intensity in PROMIS-57.
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction.
  - The figure of LS mean with standard error will be plotted by all total score and total score in each domain of PROMIS-57.
- PGIC
  - The model will include fixed categorical terms for treatment, randomization strata, visit, and treatment by visit interaction.
  - The figure of LS mean with standard error will be plotted.

The following secondary endpoint will be listed and summarized by treatment and planned time point using descriptive statistics. The value of melanin density, change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments and average of 6 skin segments will be plotted by treatment. For average of 6 skin segments for the value of melanin density, change from Baseline and % change from baseline in melanin density at Week 8, 16, and 22, will be analyzed using MMRM similar to the analyses for the primary endpoint.

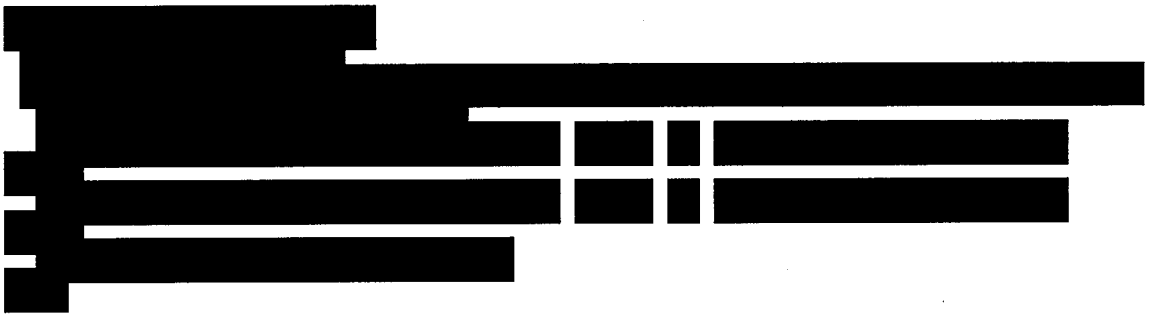
- The change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments.
- Average of 6 skin segments for the change from Baseline and % change from baseline in melanin density at Week 8, 16, and 22.

The value of melanin density, change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments and average of 6 skin segments will be plotted by treatment.

The following endpoints will be analyzed using a negative binomial regression model with log link will be fitted. The model will include treatment and the baseline average daily sunlight exposure time without prodromal symptoms (≤30 min or >30 min) as fixed effect, and baseline total number of sunlight exposure episodes with prodromal symptoms as the covariate. The estimated incidence rate (IR) and its 95% confidence interval for each treatment group, incidence rate ratio (IRR) of each active MT-7117 treatment group versus placebo, 95% confidence interval of the IRR together with relevant p-values will be reported.

- Total number of sunlight exposure episodes with prodromal symptoms during 16-week double-blind treatment period.
- Total number of pain events during 16-week double-blind treatment period.

The following example SAS code will be used;



The following endpoints will be summarized using descriptive statistics and Wilcoxon's rank sum test.

- Total number of days subject is exposed to sunlight for any duration between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms during 16-week double-blind treatment period.

The following endpoint will be analyzed using ANCOVA or ANOVA model.

- Change from baseline for In-clinic sunlight exposure time (minutes) to the first prodromal symptoms.
  - The model will include fixed categorical terms for treatment, randomization strata, together with continuous covariate terms for baseline value.
- Change from baseline in Average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset on Saturday without prodromal symptoms at Week 16. The average value is calculated for Saturdays within the windows defined in section 5.4.
  - The model will include fixed categorical terms for treatment, randomization strata, together with continuous covariate terms for baseline value.
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 16
  - The model will include fixed categorical terms for treatment, randomization strata, together with continuous covariate terms for baseline value.

- Total time (hours) during 16-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
  - The model will include fixed categorical terms for treatment, randomization strata.

7.11.3 Other Analyses

- The change from baseline in average daily time to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset (Change in time to first prodromal) vs. Change from baseline in melanin density:
  - Relationship of:
    - Change in time to first prodromal versus Change from baseline in average of 6 skin segments in melanin density
    - Change in time to first prodromal versus %Change from baseline in average of 6 skin segments in melanin density
    - Change in time to first prodromal versus Change from baseline in melanin density by each skin segment
    - Change in time to first prodromal versus %Change from baseline in melanin density by each skin segment

Plots

The relationship of primary endpoint versus melanin density will be explored graphically by providing scatter plots with loess and linear regression curves. **The matching data of change in time to first prodromal and melanin density at Week 8, 16 and 22 will be pooled into this relationship analysis.**

7.12 Safety Assessments

7.12.1 Adverse Events

The treatment emergent adverse events (TEAEs) are defined as AEs that newly occurred or increased in severity on or after the first dose of study medication.

The hepatic AEs will be selected from available TEAEs reviewed by the Clinical and Drug safety team. Then Clinical and Drug safety team will provide a list of hepatic AEs in Excel format to Data Science team. The list on Excel format will be used with clinical database to generate the hepatic AE table and listing.

The TEAEs are summarized for subjects with at least one TEAE, at least one treatment emergent adverse reaction, at least one serious TEAE, at least one serious treatment emergent adverse reaction, at least one TEAE leading to drug withdrawn, at least one treatment emergent adverse reaction leading to drug withdrawn, at least one hepatic AE, at least one Adverse Events of Special Interest (AESI) and fatal TEAE.

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment and overall. For this table, SOC is sorted by International order; then within SOC, PT is sorted by descending counts under MT-7117

Total group, then descending counts under Placebo group, then alphabetic order for PTs with the same count.

The AE summaries will be presented for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship
- Treatment emergent adverse reactions by SOC and PT
- Treatment emergent adverse reactions by SOC, PT and severity
- Serious TEAEs by SOC and PT
- Serious treatment emergent adverse reactions by SOC and PT
- TEAEs leading to drug withdrawn by SOC and PT
- TEAEs by SOC and PT for TEAEs with frequency >= 3% in total MT-7117 group
- Treatment Emergent Hepatic AEs by SOC and PT

For each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum intensity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility, no reasonable possibility). If intensity or relationship is found to be missing the most severe occurrence will be imputed for that particular summary.

All AEs for each subject, including multiple occurrences of the same event, will be listed.

Deaths that occur during the study will be listed in a data listing. The data listings for serious TEAE and TEAE leading to drug withdrawn will be generated as well.

7.12.2 Laboratory Tests

Lab test values and changes from baseline will be summarized descriptively by treatment and visit.

The lab tables will be generated for each Lab categories (Hematology, Coagulation, Biochemistry and Urinalysis).

All laboratory data will be listed with clinically relevant values flagged (L=Lower than lower limit of normal range, H=Higher than upper limit of normal range or A=Abnormal).

The number and percentage of subjects with lab values out of normal range for each lab test will be summarized in table by treatment. The percentage will be based on the number of subjects of safety population in the corresponding group.

In addition, following clinical relevant ranges (and flags) will also be considered for summary table. The count and percent of subjects meeting the criteria will be presented. The percentage will be based on the number of subjects of safety population in the corresponding group.

- ALT and/or AST $\geq 3 \times$ Upper Limit of Normal Range (ULN), 4xULN, 6xULN, 10xULN
- AST and/or ALT $\geq 3 \times$ ULN with Total bilirubin $\geq 2 \times$ ULN
- Total bilirubin $\geq 2 \times$ ULN

- Creatinine >= 2 × ULN
- ALP ≥ 3 × ULN
- Hy's Law (ALT or AST > 3 x ULN and TBL > 2 x ULN and Alkaline phosphatase < 2 x ULN)

The figure of mean (or median) and standard error value of ALT, AST, Total bilirubin and Alkaline phosphatase by visit will be plotted.

7.12.3 Vital Signs

Vital signs data and their change from baseline will be summarized descriptively in tables by treatment and analysis visit.

All vital sign data will be listed.

7.12.4 ECGs

ECG parameter values and changes from baseline will be summarized descriptively by treatment and analysis visit.

For ECGs, number and percentage of subjects meeting the criteria listed below will be presented in tables:

- Baseline QTc <450 msec and >500 msec at EOT
- Baseline QTc <450 msec and 500 msec ≥ QTc > 480 msec at EOT
- Baseline QTc <450 msec and 480 msec ≥ QTc > 450 msec at EOT
- Change from baseline at EOT in QTc > 30 msec
- Change from baseline at EOT in QTc > 60 msec

These criteria will be applied to both QTcB and QTcF.

Shift tables will present the changes in clinically relevant categories from baseline to EOT. The categories are Normal, Abnormal-not-clinically significant and Abnormal-clinically significant.

All ECG parameters and findings will be listed.

7.12.5 Physical Examinations

Physical examination data will be summarized descriptively (number and percentage of the subjects) in tables by treatment and analysis visit.

All physical examination data will be listed.

7.12.6 Nevi appearance

Nevi appearance will be summarized descriptively (number and percentage of the subjects) in tables by treatment and analysis visit for subjects' suspicious nevi found:

- Any suspicious nevi found during assessment (Y,N)
- Any clinically significant findings (Y,N).

Nevi appearance data will be listed.

7.12.7 Other Safety Assessments

As post hoc analysis, the data collected in the questionnaires for exit interview and PGIC_2 at follow up visit will be presented in data listing. The summary tables will be generated if the available data is enough.

7.13 Pharmacokinetics Assessment

Plasma MT-7117 data will be listed for each subject and scheduled visit and treatment period with the same precision as provided by the bioanalytical laboratory. PK sample collection times, most recent dosing times, as well as derived actual sampling time relative to the most recent dose will be provided in a listing. The actual sampling time relative to the most recent dose will be calculated in hours and rounded to 2 DP. Plots of individual concentration vs actual sampling time will be presented overlaid with treatment in different symbols for each treatment by visit, or overlaid with visits.

The analysis plan for the PPKPD will be in a separate document. and the results will be separately reported.

7.14 Exploratory endpoint

Porphyrin and protoporphyrin levels will be listed and summarized by treatment using descriptive statistics. The summary of other exploratory endpoints in Section 2.10 will be presented in a separate report.

7.15 Statistical/Analytical issues

7.15.1 The Sunrise and Sunset Time to Use

The primary and some secondary efficacy endpoints are derived from the diary data where sunshine exposure time between 1 hour post sunrise and 1 hour pre-sunset are used. For the subjects exposed to sunlight within the US, the sunrise and sunset time of the fifty states are used. For the subjects expose to sunlight outside of the US, the sunrise and sunset time of corresponding country or areas are used.

The source data of sunrise and sunset time is from the website of the United States Naval Observatory (USNO) Astronomical Applications Department. The accurate sunrise and sunset times for each US state and territory (*or arbitrary non-US location*) on each day in 2018 and 2019 will be used (http://aa.usno.navy.mil/data/docs/RS_OneYear.php).

The fifty US States' sunrise and sunset time are available from the time the subjects' enrolled. With the study going on, the subjects' geographical locations for sunlight exposure will be checked from time to time. The sunrise and sunset time for the countries, cities, and areas will be added into SDTM as needed. The last time new sunrise and sunset time will be added is 5 weeks before the last subject last visit in the study. In the event that any subjects had sun exposure outside of US after that; the time 6:00 and 18:00 will be used as sunrise and sunset time. This is a close approximation of the average sunrise and sunset time for the current accumulated study data in the US.

7.15.2 Data Handling of eDiary records

(1) If a record has "-0:00" as start/end time, the time will be treated as missing.

(2) If there is inconsistency between start date and end date of a record for prodromal symptom, the following handling rule will be adapted.

- If recorded end date is later than start date, the record will be divided per day.
- If recorded start date is later than end date, the record will not be used for analysis.

(3) If there are duplicated eDiary records, a record with the latest record time will be used.

7.15.3 Data Handling of Dropouts or Missing

Missing data will not be imputed in the summary at each time point.

For AE start and/or end date missing or partial missing, the AE will be treated as TEAE if it cannot be determined a non-TEAE.

For prodromal symptom start/end date missing or partial missing, complete with the following handling rule;

1. For the end date of prodromal symptom missing or partial, the earliest datetime of following two datetime will be used as the end datetime.
   - Start datetime of next sunlight exposure record
   - 23:59 of the day of linked sunlight exposure record

2. For the start date of prodromal symptom missing or partial, the latest datetime of following three datetime will be used as the end datetime.
   - End datetime of prior sunlight exposure record.
   - End datetime of prior prodrome symptom record
   - 0:00 of the day of linked sunlight exposure record

7.15.4 Data Handling of PK data and melanin density data

The PK data and melanin density data handling will be confirmed during blinded data review (BDR). PK data that are considered "invalid" will be flagged in the listing. Due to the nature of PK data, some issues may only be discovered after PK data are unblinded. Should new issues be identified post unblinding, and new data handling rules would have to be applied, a separate PK data handling document will be produced to provide detailed rationale and decision making. If there is clear evidence that PK sample handling errors or other factors are identified after data unblinding and these errors have led to unexpected erroneous data, then these erroneous data will be regarded as "invalid", full explanations will be given in the PK data handling document.

7.15.5 Multiple Comparison/Multiplicity

There is no adjustment for multiplicity for this study.

7.15.6 Subgroup Analysis

The subgroup analyses for Primary endpoints will be performed for the following subgroups using primary efficacy analysis.

- Gender (Male, Female)
- Age group (age < 65, age >= 65)
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Race (White, Black or African American, Asian, others)
- BMI (BMI <30, BMI ≥30 kg/m^2)
- Baseline average daily time to first prodromal symptom associated with exposure to sunlight (≤30 min and >30 min)
- Seasonality (Randomized between Mar 1 and Aug 31 inclusive, other)

8. CHANGES FROM THE PROTOCOL

There are no changes to the statistical analyses that are described in the protocol.

9. VALIDATIONS

The tables, figures, and listings (TFLs) planned in this SAP will be produced by [redacted]. (CRO) using SAS software version 9.4 (or above). The TFLs will be quality checked by statistics team in MTDA/MTPC using SAS software version 9.3 (or above) and will be approved by MTDA.

10. PROGRAMMING AND DATA PRESENTATION CONVENTIONS

Listings will be presented in treatment, subject, visit (where applicable) and date (where applicable) order. Listings and Tables will be produced (landscape in MS Word) in Courier font and pitch 8.