Statistical Analysis Plan

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents With Erythropoietic Protoporphyria or X-Linked Protoporphyria

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Prepared By:	Mitsubishi Tanabe Pharma Development America
Version:	V3.0
Date:	16SEP2022

APPROVAL FORM

Statistical Analysis Plan

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BDR	blinded data review
BMI	body mass index
CI	confidence interval
DBE	double-blind extension
DBT	double-blind treatment
DP	decimal places
ECG	electrocardiogram
EPP	Erythropoietic protoporphyria
FAS	full analysis set
ITT	intent-to-treat
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fredrecia's formula
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
ULN	upper limit of normal range
WHO	World Health Organization
XLP	X linked porphyria

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final global master protocol version 4.1 dated 9AUG2021, the final Japan specific protocol (v4.2) dated 24 August 2021, and the final Norway specific protocol (v4.3) dated 24 August 2021, and the final Germany specific protocol (v4.4) dated 24 August 2021 and , and the final Canada specific protocol (v4.5) dated 24 August 2021. The plan covers statistical analysis, tabulations, and listings of the study data to assess the efficacy, safety, and PK of [redacted] and [redacted] doses of MT-7117 compared to placebo.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

The SAP is prepared by MTDA and MTPC data science and reviewed by MTDA clinical study team and MTPC data science following GLB-BST-SOP002 ver.7. The statistical analyses and production of the outputs described in the SAP will be conducted and QCed by [redacted] using SAS version 9.4 or higher. The final analyses and outputs will be approved by MTPC/MTDA Data Science.

This SAP has been approved and signed as Version 1.0 and Version 1.1 for FDA SAP communication. Version 2.0 will be finalized for the Primary Week 26 analysis prior to Week 26 database lock, and Version 3.0 will be finalized for the final analysis prior to the final database lock.

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

For the qualitative exit interview questionnaire, the analysis plan , the dataset and the results will be separately created and reported.

2 STUDY OBJECTIVE AND ENDPOINTS

2.1 Study Objectives

Primary:

- To investigate the efficacy of MT-7117 on time to onset and severity of first prodromal symptoms (burning, tingling, itching, or stinging) associated with sunlight exposure in adults and adolescents with EPP or XLP.

Secondary:

- To investigate the effect on patient-reported quality of life in adults and adolescents with EPP or XLP.
- To investigate the effect on the percentage of responders based on the within-subject meaningful threshold for time to first prodromal symptom in adults and adolescents with EPP or XLP.

- To investigate the effect on number and severity of sunlight-induced pain events (prodrome and phototoxic reactions) in adults and adolescents with EPP or XLP.

Exploratory:

- To investigate the effect on sunlight exposure duration in adults and adolescents with EPP or XLP.
- To investigate the effect on melanin density in adults and adolescents with EPP or XLP.
- To investigate the PK/pharmacodynamic (PD) relationship in adults and adolescents with EPP or XLP.
- [redacted]

Safety:

- To assess the long-term safety and tolerability of MT-7117.

2.2 Estimand

2.2.1 Primary estimand

The primary estimand construction elements for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using treatment policy: Regardless of early discontinuation of study drug due to any reason until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The primary estimand will be based on effectiveness assumption (de-facto) using treatment policy: The treatment effect will be attributable to the subject's initially randomized treatment regardless of treatment discontinuation.

2.2.2 Secondary Estimand

The secondary estimand construction elements to be tested as supportive analysis for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and

1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using hypothetical strategy: If subjects could have treatment completion until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The secondary estimand will be based on efficacy assumption (de-jure) using a hypothetical strategy: The treatment effect will be attributable to the subject's initially randomized treatment if subjects could have stayed on study until the end of the double-blind treatment period.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint for Primary Week26 (DBT) data analysis

- Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 (Visit 7).

To calculate the average daily sunlight exposure time to first prodromal symptom, a 14 day window on or before a timepoint (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26) will be used. For baseline, a 14 day window before Day 1 will be used. A 14 day window will be applied to similar situations for other efficacy endpoints related to sunlight exposure diary.

2.3.2 Secondary Efficacy Endpoints for Primary Week26 (DBT) Data Analysis

- Patient Global Impression of Change (PGIC) at Week 26.
- Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period.
- Change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.
- The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26.
- Change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

2.3.3 Exploratory Efficacy Endpoints for Primary Week26 (DBT) Data Analysis

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours).
- Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during the 26-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during the 26-week double-blind treatment period.
- Total number of sunlight-induced pain events defined as phototoxic events during the 26-week double-blind treatment period.
- Total number of sunlight-induced non-prodrome, phototoxic reactions during the 26-week double-blind treatment period.
- Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period on an 11-point Likert scale.
- Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period.
- Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.
- Total number of days subject is exposed to sunlight for any duration without prodromal symptoms during the 26-week double-blind treatment period.
- Total number of days subject is exposed to sunlight for any duration without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind treatment period.
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 26.
- Change from baseline for all total score and total score in each domain of, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference in the PROMIS-57

- Change from baseline in Patient Global Impression of Severity (PGIS) at each visit.
- The percentage of subjects who are responders at Week 26 based on PGIC (Very Much Improved or Much Improved).
- Qualitative exit interview questionnaire about QoL at Week 26.
- Total number of days subjects went outdoors during the 26-week double-blind treatment period.
- Maximum and total severity of phototoxic reaction on an 11-point Likert scale.

2.3.4 Exploratory Efficacy Endpoint for Double Blind Extention (DBE) Data Analysis

- Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at each timepoint.
- Patient Global Impression of Change (PGIC) at each visit.
- Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during each 26-week double-blind extention treatment.
- Change from baseline for all total score and total score in each domain the PROMIS-57 at each visit.
- The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline at each time point.
- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
- Total time (hours) during the 26-week double-blind extention period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total time (hours) during the 26-week double-blind extention period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on an 11-point Likert scale and without phototoxic reactions (pain-free time hours).
- Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during the 26-week double-blind extention period.

- Change from baseline in average daily duration (minutes) of prodromal symptoms during the 26-week double-blind extention period
- Total number of sunlight-induced pain events defined as phototoxic events during the 26-week double-blind extention period
- Total number of sunlight-induced non-prodrome, phototoxic reactions during the 26-week double-blind extention period.
- Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during the 26-week double-blind extention period on an 11-point Likert scale.
- Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during the 26-week double-blind extention period.
- Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.
- 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 the 26-week double-blind extention period
- Total number of days subject is exposed to sunlight for any duration between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on an 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind extention period
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at each timepoint.
- Total number of days subjects went outdoors during the 26-week double-blind extention period
- Change from baseline in Patient Global Impression of Severity (PGIS) at each visit.
- The percentage of subjects who are responders at Week 52 based on PGIC (Very Much Improved or Much Improved).
- Maximum and total severity of phototoxic reaction on an 11-point Likert scale.

2.3.5 Safety Endpoints

- Treatment-emergent adverse events (AEs) (including serious adverse events [SAEs] and adverse events of special interest [AESIs]).
- Physical examination.

- Vital signs (blood pressure, respiratory rate, pulse rate, body temperature and body weight).
- Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin).
- 12-lead ECG at Baseline and EOT.
- Nevi appearance (assessed by a dermatologist or other qualified site staff). Any nevi undergoing change of clinical concern during active treatment will be biopsied for follow up and evaluated by the central pathology lab.

2.3.6 Pharmacokinetics Assessment(s)

- Assessment of plasma PK: Plasma concentrations of MT-7117 will be measured at protocol scheduled visits.

2.3.7 Pharmacogenetics Assessments

- [redacted]

3 STUDY DESIGN

3.1 Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in adults and adolescents with EPP or XLP. The study consists of a 6-week screening period, a 26-week double-blind treatment period, an optional 26-week double-blinded extension (DBE) period, and a 6-week follow-up period at Week 58 (or Week 32 if DBE is not elected). The total participation period is approximately 64 weeks.

The study design is illustrated in Figure 1.

Subjects will attend the screening visit (Visit 1) up to 6 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 an electronic sunlight exposure diary (SED).

At Visit 2, [redacted], or placebo in a double-blind manner. [redacted]

[redacted]

The first dose will be administered at Visit 2 following baseline assessments including an inclinic sunlight exposure test at any time before randomization (Visit 1 or 2), and melanin density determination before randomization (Visit 2). Active or placebo [redacted] will be administered once daily in the morning with or without food.

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

Subjects will attend the end of treatment visit at Week 26 or early termination visit (Visit 7 or Visit 11).

PK will be collected at scheduled visits for ≥18 to ≤75-year-olds. For ≥12 to ≤17-year-old subjects, a total of 9 PK samples at 3 time points will be collected: Day 1 (Visit 2) at 2, 4, 6, and 8 hours post-dose, Week 12 (Visit 6) at pre-dose and 3 hours post-dose, and Week 26 (Visit 7) at pre-dose and 2, and 4 hours post-dose.

Subjects will be offered participation in a 6-month extension where all participants are on active drug but are double-blinded to dose starting immediately after the end of the 26-week doubleblind treatment period. If study subjects elect to participate in the 26-week DBE after end of Visit 7 (EOT/Rand), subjects will remain blinded and subjects will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] or [redacted] in 1:1 ratio for the 26 weeks DBE period. [redacted] the [redacted] dose will be administered without re-randomization.

During the DBE, subjects will attend an in-clinic visit at Week 39 (Visit 10) where measurements will be performed. In addition, subjects may undergo mobile laboratory or in-clinic visits for sample collection at Weeks 28 and 32 (Visits 8 and 9, respectively) to measure liver function markers (AST, ALT, GGT, ALP, direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 52 or early termination visit (Visit 11). Following the last treatment visit, subjects will attend a follow-up visit at Week 58 (Week 32 if DBE is not elected) or 6 weeks after early termination visit.

Subjects who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. If a patient decides to completely withdraw consent/assent from the study, every attempt should be made to have the patient complete an early termination visit (Visit 7 or Visit 11).

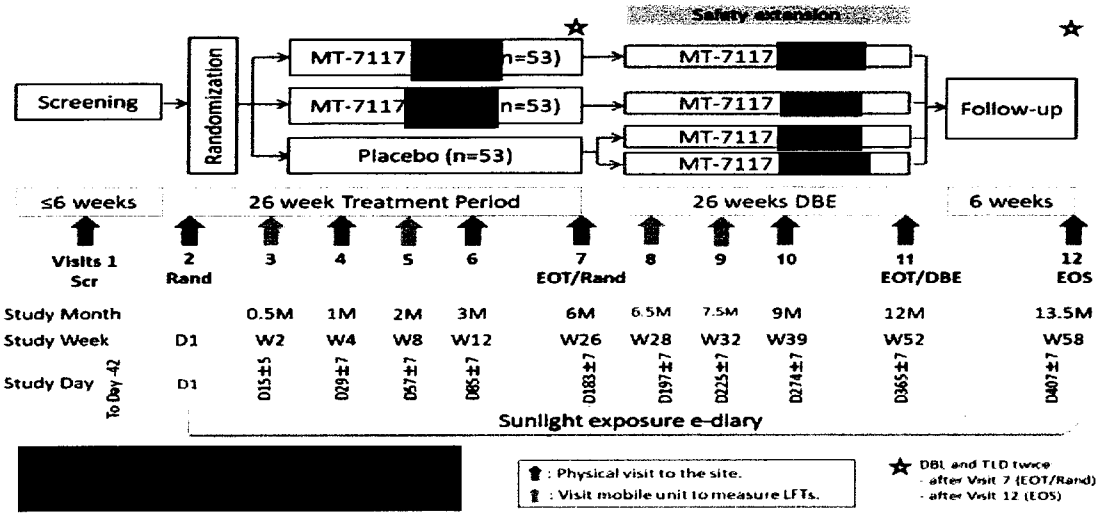


Figure 1 Study Design Schematic

3.2 Schedule of Study Procedures

Study assessments and corresponding event schedules are summarized in the time and events schedule. The schedule of assessment in the global master protocol is shown in Table 1. The schedules of assessment for each country specific (Japan, Norway, Germany and Canada) are referred to each country specific protocol.

Table 1 Schedule of Assessments

Study Period	**Screening**	**Double-blind Treatment**						**Double-blind Extension**				**Follow-up**
Visit Number	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3[g]**	**Visit 4**	**Visit 5[g]**	**Visit 6**	**Visit 7[n] (EOT/ Rand)**	**Visit 8[g]**	**Visit 9[g]**	**Visit 10**	**Visit 11[q] (EOT/ DBE)**	**Visit 12[r] (EOS)**
Study Week	**Week -6 to Week 0**		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 26**	**Week 28**	**Week 32**	**Week 39**	**Week 52**	**Week 32 or 58**
Study Day ± Window	**Day -42 to Study Day[a]**	**Day 1**	**Day 14±5**	**Day 29±7**	**Day 57±7**	**Day 85±7**	**Day 183±7**	**Day 197±7**	**Day 225±7**	**Day 274±7**	**Day 365±7**	**Day 407±7**
Informed consent/assent[b]	X											
Inclusion/exclusion criteria evaluation	X	X										
Demographics	X											
Medical history	X	X										
Randomization		X					X[f]					
Body weight	X	X		X		X	X			X	X	X
Height	X											
Physical examination[c]	X	X		X		X	X			X	X	X
Vital signs[d]	X	X		X		X	X			X	X	X
12-lead ECG[e]	X						X				X	
Hematology/coagulation, biochemistry & urinalysis[g]	X	X	X[g]	X	X[g]	X	X	X[g]	X[g]	X	X	X
Blood collection for porphyrin and protoporphyrin levels[h]	X			X		X	X			X	X	
Fitzpatrick skin type	X			X		X	X			X	X	

assessment[s]												
Pregnancy test[i]	X	X		X		X	X			X	X	X
PK sampling (blood)[j]		X		X		X	X			X	X	
Blood sampling for PGx[b]		X										
Dispensing of study medication		X		X		X	X			X		
Medication accountability				X		X	X			X	X	
Subject Question for study medication[k]							X					
PROMIS-57		X				X	X			X	X	X
PGIC				X			X				X	
PGIS		X		X		X	X			X	X	X
EOT/Exit interview questionnaire[l]							X					
Sunlight exposure diaries[m]	←											→
In-clinic sunlight exposure test[n]		X					X				X	
Melanin density evaluation		X		X		X	X				X	X
Nevi evaluation[o]	X			X		X	X			X	X	X
Concomitant medication	←											→
Adverse events	←											→

Abbreviations: DBE= double-blinded extension; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; 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/assent for optional PGx analysis at Visit 2.

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

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

[e] ECG will be assessed at Visit 7 for subjects who do not elect DBE. For subjects who elect DBE, ECG will be assessed at Visit 11.

[f] All study subjects who elect to participate in the 26-weeks DBE will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 or in 1:1 ratio for the 26 weeks DBE period. For subjects with , the dose will be administered without re-randomization.

[g] At Visits 3, 5, 8, and 9, subjects may have mobile units or in-clinic visits to 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.

[h] Plasma total porphyrins and erythrocyte protoporphyrin will be assessed at Visits 1, 4, 6, 7, 10, and 11.

[i] 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 Visits 2, 4, 6, 7, 10, 11, and 12.

[j] For subjects who are ≥18 to ≤75: PK blood samples for MT-7117 will be collected and processed at Visit 2 (pre-dose), Visits 4, 6, 10, and 11 (any time), and Visit 7 (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. Subjects who are ≥12 to ≤17 years old will have 9 PK samples at 3 time points collected. Visit 2 at 2, 4, 6, and 8 hours post-dose, Visit 6 at pre-dose and 3 hours post-dose, and Visit 7 at pre-dose and 2, and 4 hours post-dose.

[k] Subjects will be asked whether they believe they received active or placebo treatment.

[l] EOT/Exit interview will only be performed in selected countries.

[m] Sunlight exposure data, presence of prodromal symptoms and sunlight-induced phototoxic reactions, their severity, and their onset/duration will be collected from Visits 1 through 12. Diary training will be performed at the first in-clinic visit during the screening period.

[n] In-clinic sunlight exposure test should be done once before randomization and once at Visit 7. For subjects who elect DBE, the test is also performed at Visit 11.

[o] 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 (Visit 1 or 2). The Nevi evaluation at Visit 12 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. Nevi assessment will be described in a separate document.

[p] These assessments will be performed at Week 26 or early termination from the double-blind treatment period. If the visit is due to early termination, no double-blinded extension study medication is to be dispensed.

[q] These assessments will be performed at Week 52 or early termination from the double-blinded extension period.

[r] All subjects will return to the study site for a 6-week follow-up visit at Week 58 (Week 32 if DBE is not elected) or 6 weeks after early termination. For discontinued subjects who will not revisit the clinic, the site will perform scheduled phone calls for the collection and source documentation for safety information (AEs, concomitant medication, and date of last dose of medication).

[s] Fitzpatrick skin type assessment should be done once before randomization.

3.2.1 Screening Phase

Screening assessments will be performed up to 42 days prior to Day 1 of the double-blind treatment period. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

3.2.2 Rescreening

If a subject has not met all eligibility criteria at the end of the Screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1-time following consultation with the Sponsor and Medical Monitor.

Rescreened subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new screening window will begin. The rescreened subject will be reassigned a new unique Subject Identifier and the previous Subject Identifier will be noted. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including ICF, must be repeated.

If the subject does not meet eligibility criteria for laboratory tests, the subject may undergo repeat laboratory tests up to 2 additional times during the 6-week Screening period. Repeat of laboratory tests is not considered rescreening.

3.3 Sample Size and Power Considerations

For the primary estimand, the sample size of 159 is expected to provide adequate power for the comparisons between MT-7117 and placebo for change from baseline in the average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 based on the MT-7117-A01 study. The calculation of sample size assumes a 2-sided alpha level of 0.05 and a 20% dropout rate up to Week 26. The sample size of 42 completers per treatment group will provide 91% and 79% power to detect an effect size of 0.72 and 0.66 in the average daily time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26 (ie, an absolute treatment difference of 57 mins between MT-7117 [redacted] vs placebo, 52 mins between MT-7117 [redacted] vs placebo, and a standard deviation [SD] of 79.3 mins). The sample size of 42 completers was calculated by SAS simulation using the fixed sequence testing procedure in order to confirm the power affected by multiplicity adjustment in treatment comparison for primary endpoint. Taking into account for a 20% dropout rate up to Week 26, total sample size of 159 was calculated.

Due to the rapid enrollment rate in the last few months of the enrollment period after COVID-

19 restrictions were lifted in many countries, a total of 184 subjects were enrolled.

4 PLANNED ANALYSIS

The following analyses related to the objectives will be done twice in this study, Primary Week 26 Analysis and Final Analysis.

4.1 Primary Week 26 Analysis

Primary Week 26 analysis will take place when the last subject completes Week 26 visit or follow-up period after DBT early termination and includes all subject data collected until then except for ongoing DBE or Follow up data. The avaiable data in this analysis is as below;

Subject Type	Subject's Status on the date of LPLV for DBT			Primary Week 26 Analysis			
	DBT Period (26 weeks)	DBE Period (26 weeks)	Follow up (6 weeks)	DBT data	DBE data	Follow-up data	FU Type
A	Completed	Completed or Discontinued	Completed	X	X	X	DBE
B	Completed	Completed or Discontinued	No data	X	X		
C	Completed or Discontinued	No data	Completed	X		X	DBT
D	Completed or Discontinued	Ongoing in either DBE or FU / No data		X			

Note: X is "Included" in Primary W26 Analysis

After Week 26 database lock, the primary efficacy analysis will be conducted. No alpha adjustment for final analysis is needed, as this Week 26 efficacy analysis will be the primary efficacy analysis. The results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study. This detail was described in "MT-7117-G01 Blinding and Unblinding Plan Version 1.2 final.docx".

4.2 Final Analysis

Final Analysis will take place when the patient data collected up to the time the last subject completes the last visit of Week 58 visit, unless last subject is lost to follow-up. This analysis will include all of the data in Primary Week 26 Analysis, and may include updated to partial or imcomplete data previously included in Primary Week 26 Analysis.

5 ANALYSIS POPULATIONS

5.1 Randomized (RAND) Population

The randomized (RAND) population includes all randomized subjects.

5.2 Safety (SAF) Population

For the DBT data analysis
Safety Population 1 (SAF1) includes all randomized subjects who received at least 1 dose of study medication after randomization.

For the DBE data analysis
Safety Population 2 (SAF2) includes all randomized subjects who received at least 1 dose of study medication during DBE period.

The safety populations will be used for all safety analyses. The subject actual treatment received will be used for safety analyses. For subjects who took more than one treatment, the highest dose level will be used for safety analyses.

5.3 Intent-to-treat (ITT) population

For the DBT data analysis
Intent-to-treat population 1 (ITT1) includes all randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.

For the DBE data analysis
Intent-to-treat population 2 (ITT2) includes all randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment during DBE period.

The ITT populations will be used for all efficacy analyses. The subject randomized treatment will be used for efficacy analyses.

5.4 Pharmacokinetic (PK) population

Pharmacokinetic (PK) population for the primary Week 26 analysis includes all randomized subjects who receive at least 1 dose of MT-7117 and who have at least 1 postdose value for plasma concentration at time point to be included in the PK analysis without important protocol deviations which may affect the PK of MT-7117.
PK population for the final analysis includes all randomized subjects who receive at least 1 dose of MT-7117 and who have at least 1 postdose value for plasma concentration at time point to be included in the PK analysis without important protocol deviations which may affect the PK of MT-7117.

6 STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics

Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis population 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).
Unless otherwise specified, all data will be summarized by analysis visits and treatment group.

6.2 Statistical Tests

Unless otherwise specified, all formal statistical tests of treatment effects will be done at two-sided significance level of 0.05. Point estimates will be accompanied with two-sided 95% CIs where applicable.

6.3 Stratification registration errors

All patients enrolled into this study were randomized into the IWRS system based on Bracket IRT Randomization List Requirements. [redacted] in the [redacted] system was not consistent with a vendor [redacted] report strata and actual baseline TTP strata based on the e-Diary in some

patients. Therefore, it is planned to summarize the status of randomization factor registration error in the section of stratification registration errors and perform the sensitivity analysis for the primary efficacy endpoint to investigate the impact by the errors for study outcome.

6.4 Dosing suspension

One case (Subject ID: [redacted]) with 3 serious adverse events (SAEs; cholestasis, ALT increased, and AST increased) was reported in this study. The SAE of cholestasis led to drug discontinuation and was fatal in this subject with a significant history of hepatic disease (i.e., cholestasis). The Investigator assessed the fatal SAE as probably related to study drug and the Sponsor assessed the fatal SAE as unlikely/unrelated to study drug. The principal investigator at the site 108 contacted their IRB in early July 2021 with their SAE assessment. As a result, the central IRB in the US requested a suspension of dosing for this study to MTDA and PI for US sites on July 14th 2021. Subsequently, the IRB released the dosing suspension on July 20th 2021 and allowed the US sites to resume dosing on the 21st July 2021. This dosing suspension gave some impact on dosing status for all ongoing subjects at every US site. Therefore, it is planned to summarize the status of dosing suspension in the section of treatment duration and compliance and perform the subgroup analysis of study drug compliance for the primary efficacy endpoint to investigate the impact by this drug suspension for the study outcome.

7 DATA CONVENTIONS

Prior to the database lock, a blinded data review meeting for Primary Week 26 Analysis and a data review meeting for Final Analysis were conducted. Protocol deviations, protocol defined analysis populations and analysis visits were confirmed during these meetings (Blind Data Review Meeting minutes for Primary Week 26 analysis and Data Review Meeting minutes for Final analysis).

7.1 Treatment Group Definitions and The Corresponding Analyzed Period Data

Two treatment group definitions for DBT data analysis and for DBE data analysis will be used as follows:

For DBT period data analysis

All DBT period data in all Subject type and Follow up period data in Subject type A, B, C and D in Section 4.1 will be analyzed with the below definition.

Treatment Group	Definition
MT-7117 [redacted]	Allocated to MT-7117 [redacted] group in DBT period
MT-7117 [redacted]	Allocated to MT-7117 [redacted] group in DBT period

Treatment Group	Definition
Placebo	Allocated to Placebo group in DBT period

For DBE period data analysis

All DBE period data and all Follow up period data in Subject Type A and B in Section 4.1 will be analyzed with the below definition.

Treatment Group	Definition
MT-7117 [redacted]	Allocated to MT-7117 [redacted] group in DBT period and Enrolled in DBE period.
MT-7117 [redacted]	Allocated to MT-7117 [redacted] group in DBT period and Enrolled in DBE period.
MT-7117 [redacted] (switched from Placebo)	Allocated to Placebo group in DBT period and switched to MT-7117 [redacted] group in DBE period.
MT-7117 [redacted] (switched from Placebo)	Allocated to Placebo group in DBT period and switched to MT-7117 [redacted] group in DBE period.

7.2 Analysis Variable Definitions

7.2.1 Study Subjects

7.2.1.1 Protocol Deviation

Protocol deviations was be documented, reviewed, and determined in the blinded data review meeting for Primary Week 26 Analysis. The major protocol deviations that potentially influence the evaluation of the primary endpoint were selected in this meeting (Blind Data Review Meeting minutes for Primary Week 26 analysis).

7.2.1.2 Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1dp.

BMI (kg/m^2) = weight at screening (kg) / {height at screening (m)}^{2}.

(2) Disease Duration

Disease Duration (days) = the date of informed consent – the date of diagnosis+ 1.

Disease Duration (years) = Disease Duration (days) / 365.25.

7.2.1.3 Medical History

Medical history will be coded according to the MedDRA version 23.1.

7.2.1.4 Prior or Concomitant Medication

Medications will be coded according to the WHO Drug Dictionary (WHO-DD) B3 MAR 2019 version.

(1) Prior Medication

Prior medications are defined as any medication taken within 1 month before the start date of study drug.

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. It should be noted if subjects have ever used afamelanotide.

(2) Concomitant Medication

Concomitant medication is defined as any medication, other than study medication, which is taken during the study after the start date of study drug , 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. Concomitant medication will be given only if deemed necessary by the Investigator or the subject's personal physician.

Rules to determine prior medications and concomitant medications:

Medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing or ongoing at study will be considered concomitant medications.

Rule to determine concomitant medication for pain:

If indication in the eCRF for the concomitant medications includes "Pain" or "pain", the drug was regarded as comitant use for pain.

7.2.1.5 Treatment Duration and Compliance

(1) Treatment Duration

For DBT period, treatment duration (days) = end of treatment date in DBT period – first treatment date + 1

For DBE period, treatment duration (days) = end of treatment date in DBE period – first treatment date in DBE period + 1

The time period of treatment duration is as below;

- 1 <= - =<29 (days)
- 29 < - =<85 (days)
- 85< - =<183 (days)
- >183 (days)

For subjects lost to follow up, the treatment end date is taken to be the date of their last visit in the treatment periods. Interruptions and dose changes are not taken into account for treatment duration.

(2) Treatment Compliance

Treatment compliance will be calculated using the formula below and reported to 1dp by treatment periods. Interruptions and dose changes are not taken into account for treatment duration.

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

7.2.2 Efficacy assessments

7.2.2.1 The Sunrise and Sunset Time to Use

The primary and some secondary efficacy endpoints are derived from the diary data. The sunlight exposure time between 1 hour post sunrise and 1 hour pre-sunset will be used. For the subjects exposed to sunlight, the sunrise and sunset times will be calculated for the corresponding country or geographical area. If the subjects exposed themselves while based in the US, the sunrise and sunset times for the corresponding US state, federal district, islands, or territory will be used.

To calculate sunrise and sunset times anywhere in the world, we will use the algorithms published by the National Oceanic and Atmospheric Administration (https://www.esrl.noaa.gov/gmd/grad/solcalc/calcdetails.htm).

During the ongoing study, the subjects' geographical locations for sunlight exposure will be reviewed from time to time. The sunrise and sunset time for the US locations, other countries, cities, and geographical 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 a subject had sun exposure while being in the location for which no sunrise and sunset time is readily available, 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.

7.2.2.2 Data Handling of eDiary records

(1) If there is inconsistency between start date and end date of a record for sunlight exposure, the following handling rule will be adapted.
- If recorded end date is later than start date, end datatime will be changed to 23:59 on the same day of the start date.
- If recorded start date is later than end date/time, the record will not be used for analysis.

(2) If there is inconsistency between start date/time and end date/time of a record for prodromal symptom or phototoxic reaction, the following handling rule will be adapted.
- If recorded end date/time is later than start date/time, keep as it is.
- If recorded start date/time is later than end date/time, the record will not be used for calculation each time duration but used for counting the number of each event or summarizing the intensity of each event.

(3) How to handle missing data for prodromal symptom and phototoxic reaction start/end time:
For prodromal symptom and phototoxic reaction start/end date missing, complete with the following handling rule after sorting by subject, day, and the linked sunlight exposure start time.

For the end time of prodromal symptom and phototoxic reaction missing, the earliest datetime of following three datetime after the linked sunlight exposure end time will be used as the end datetime.

1. Start datetime of next sunlight exposure record
2. Start/end datetime of next prodrome symptom or phototoxic reaction record
3. 23:59 of the day of linked sunlight exposure record

For the start time of prodromal symptom and phototoxic reaction missing, the latest datetime of following three datetime will be used as the start datetime.

1. End datetime of prior sunlight exposure record.
2. Start/end datetime of prior prodrome symptom or phototoxic reaction record
3. 0:00 of the day of linked sunlight exposure record

For the start/end time of prodromal symptom and phototoxic reaction missing without a linked sunlight exposure record, complement with the same rules as above after sorting by subject, the entry date time.

(4) How to handle overlapping of eDiary start/end time:
For sunlight exposure records, complete with the following handling rule after sorting by subject, day, and the linked sunlight exposure start time to remove the overlapping among records by subjects and day.

1. Compare the record's end time with next record's start time.

2. Combine them into one record and use the latest end time if end time is after the next start time.

7.2.2.3 Derivation Rule for Efficacy Endpoints from eDiary records

7.2.2.3.1. The average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure

The following is the procedure to calculate the average daily time to first prodromal symptom associated with exposure to sunlight after removing overlapping among records. The analysis windows are defined in the Table 2 Analysis Visit Window for diary data.

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. A diary day is qualified if the subject had non-zero duration of sunlight exposure in the day.
3. 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 occurring the first prodromal symptom or phototoxic reaction associated with sunlight exposure (which means to occur after 1st sunlight exposure in a day) 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.
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, ..., 24, 26, 39, 52 and Follow-up for each period) 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. 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.

7.2.2.3.2. The average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms

The following is the procedure to calculate the average daily mean intensity on an 11-point Likert scale of the subject's sunlight-induced (equal to associated with sunlight exposure)

prodromal symptoms . The analysis windows are defined in the Table 2 Analysis Visit Window for diary data.

1. A day without any prodromal symptoms is not qualified.
2. The mean intensity on an 11-point Likert scale of the subject's prodromal symptoms in a day is calculated. It is the average of all the intensity on an 11-point Likert scale of the subject's sunlight-induced prodromal symptoms in the day. The average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms at a time point (Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, ..., 24, 26, 39, 52 and Follow-up for each period) is the average of the daily mean intensity 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.

The following endpoint is derived when applying the similar rule as above.

- The average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) on an 11-point Likert scale

7.2.2.3.3. **The average daily duration of sunlight exposure regardless of time of day without prodromal symptoms**

The following is the procedure to calculate the average daily mean duration of sunlight exposure regardless of time of day without prodromal symptoms. The analysis windows are defined in the Table 2

1. Step 1 in section 7.2.2.3.1 will not be applied.
2. A diary day is qualified if the subject had non-zero duration of sunlight exposure in the day.
3. The duration of sunlight exposure without prodromal symptoms in a day is calculated. It is the sum of the duration of sunlight exposure time deducting the prodromal symptom or phototoxic reaction presenting time covered in each period.
4. Step 4 to 5 in section 7.2.2.3.1 will be applied.

7.2.2.3.4. **Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale**

The following is the procedure to calculate this endpoint.

1. If a subject had sunlight exposure with any prodromal symptom with pain rating of 1-10 on the Likert scale in a day, the sum of the number of events for the day is used as the number of sunlight-induced pain events in the day.
2. The sum of the number of the above events in each day during the 26-week DBT or DBE period (from Baseline date to Week 26 or from Week 26 to Week 52) is calculated as this endpoint.

The following endpoint is derived when applying the similar rule as above.
- Total number of sunlight-induced non-prodrome, phototoxic reactions
- Total number of sunlight-induced pain events defined as phototoxic events

7.2.2.3.5. **Total time (hours) in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.**

The following is the procedure to calculate this endpoint.

1. Step 1 in section 7.2.2.3.1 will be applied.
2. The duration of sunlight exposure without prodromal symptoms and without phototoxic reactions in a day is calculated.
3. The sum of the above duration in each day during the 26-week DBT or DBE period (from Baseline date to Week 26 or from Week 26 to Week 52) is calculated as this endpoint.

The following endpoint is derived when applying the similar rule as above. Total time (hours) in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours)

The following endpoint is derived as pain-free days when applying the similar rule as above.
- 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
- Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days)

7.2.2.4 PGIC

The following score will be assigned and used for each outcome.
1: Very Much Improved

2: Much Improved
3: Minimally Improved
4: No Change
5: Minimally Worse
6: Much Worse
7: Very Much Worse

7.2.2.5 PGIS

The following score will be assigned and used for each outcome.
1: None
2: Mild
3: Moderate
4: Severe
5: Very Severe

7.2.2.6 PROMIS-57

Raw score for each PROMIS domain will be calculated as follows:

- Physical function raw score= total of Question 1 (PRO001) – Question 8 (PRO008)
- Anxiety raw score = 48 (=6x8) – total of [Question 9 (PRO009) – Question 16 (PRO016)]
- Depression raw score = 48 (=6x8) – total of [Question 17 (PRO017) – Question 24 (PRO024)]
- Fatigue raw score = 48 (=6x8) – total of [Question 25 (PRO025) – Question 32 (PRO032)]
- Sleep Disturbance raw score = 48(=6x8) – total of [Question 33 (PRO033) – Question 40 (PRO040)]
- Ability to Paricipate in Social Roles and Activities raw score = total of Question 41 (PRO041) – Question 48 (PRO048)
- Pain Interference = Pain Intensity = 0 (No pain) to 10 (Worst pain imaginable) numeric rating scale (Categorical)

Total raw score for PROMIS all domain will be calculated as follows:

- The mean of physical function raw score, anxiety raw score, depression raw score, fatigue raw score, sleep disturbance raw score, ability to participate raw score, pain interference rawscore.

If there is missing score data in an domain or total, the corresponding domain or total score will be missing.

7.2.3 Safety Assessments

7.2.3.1 Adverse Events

Adverse events will be coded according to the MedDRA version 23.1.

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

AEs will be classified as 'treatment-emergent' if they arise following the first administration of study medication in the treatment period (after randomization) or if a pre-dose AE increases in severity following dosing in the treatment period (after randomization).

Rule to determine TEAE using onset date of AEs:

An AE is classified as treatment emergent if it newly occurred on or after the first dose of study drug. According to this data handling, for the severity part in the above TEAE definition, the AE with upgraded severity and with the new onset date during the treatment period will be automatically included as TEAE.

(2) Adverse Event Related to Study Drug

A TEAE is considered "adverse event related to study drug" if it has been assessed as having a "reasonable possibility" in relationship to the study drug.

(3) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1.

(4) Time to AE onset

For DBT period, time to AE onset (days) = AE start date – the first treatment date in DBT period + 1.

For DBE period, time to AE onset (days) = AE start date – the first treatment date in DBE period + 1.

7.2.3.2 Physical examiniation

If "Abnormal, Unchanged from previous assessment" is selected and there is no available data of "Clinically Significant" or "Not Clinically Significant" in the previous assessment, the analysis value will be regarded as "Abnormal, Clinically Significant".

7.2.3.3 Laboratory Tests

(1) Criteria for pre-defined limit

Liver function:

- ALT >= 10 × ULN
- 8×ULN <= ALT < 10×ULN
- 5×ULN <= ALT < 8×ULN
- 3×ULN <= ALT < 5×ULN
- 1×ULN <= ALT < 3×ULN

The above same criteria will be applied to AST.

- Total Bilirubin >= 2×ULN
- 1×ULN <= Total Bilirubin <2×ULN

7.2.3.4 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- Baseline QTc <450 msec and >500 msec at any post baseline
- Baseline QTc <450 msec and 500 msec ≥ QTc > 480 msec at any post baseline
- Baseline QTc <450 msec and 480 msec ≥ QTc > 450 msec at any post baseline
- Increase from baseline in QTc > 30 msec, 60msec at any post baseline

The above same criteria will be applied to QTcF and QTcB.

7.2.4 Data Handling of PK data and melanin density data

The PK data and melanin density (MD) data handling will be confirmed during blinded data review (BDR). PK data and MD data that are considered "invalid" will be flagged in the listing and will be excluded from the calculation of summary statistics. Due to the nature of PK data and MD data, some issues may only be discovered after PK data and MD data are unblinded. Should new issues be identified post unblinding, and new data handling rules would have to be applied, a separate PK data and MD data handling document will be produced to provide detailed rationale and decision making. If there is clear evidence that PK sample handling errors, MD 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 and MD data handling document.

7.3 Analysis Visit Definitions

(1) eDiary data excluding in-clinic sunlight exposure test

The subjects will, in their diaries, record 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 analysis windows are defined in the table below. The nominal day for each week relative to the first dose day will be used. Day 1 is the first dose day.

Table 2 Analysis Visit Window for diary data

Analysis Visit	Nominal day	Analysis Visit Window for DBT analysis
Baseline*	Day 1	Day -14 to -1
Week 2	Day 15	Day 1 to 14
Week 4	Day 29	Day 15 to 28
Week 6	Day 43	Day 29 to 42
Week 8	Day 57	Day 43 to 56
Week 10	Day 71	Day 57 to 70
Week 12	Day 85	Day 71 to 84
Week 14	Day 99	Day 85 to 98
Week 16	Day 113	Day 99 to 112
Week 18	Day 127	Day 113 to 126
Week 20	Day 141	Day 127 to 140
Week 22	Day 155	Day 141 to 154
Week 24	Day 169	Day 155 to 168
Week 26 (DBT EOT)	Day 183	Day 169 to 182
Week 26 (DBE Baseline)	Day 183	Day 169 to 182
Week 28	Day 197	Day 183 to 196
Week 32	Day 225	Day 211 to 224
Week 39	Day 274	Day 260 to 273
Week 52 (DBE EOT)	Day 365	Day 351 to 364
EOT for DBT	Day 182 or discontinued during DBT	14 days before EOT for DBT
EOT for DBE	Day 365 or discontinued during DBE	14 days before EOT for DBE
Follow-up until Week 32 (DBT EOS)	6 weeks after EOT for DBT	the latest 1 to 14 days before Follow-up date not overlapping with treatment duration in DBT period
Follow-up until Week 58 (DBE EOS)	6 weeks after EOT for DBE	the latest 1 to 14 days before Follow-up date not overlapping with treatement duration in DBE period

During 26 weeks (DBT)	1 to 182	Day 1 to EOT for DBT period
During 26 weeks (DBE)	183 to 364	DBE Baseline to EOT for DBE period

* If subjects have at least 1 day between Day -1 and Day -14, the baseline value will be calculated from the data between Day -1 and Day -14. If subjects have no data of sunlight exposure between Day -1 and Day -14, then the Analysis Visit window will be expanded to Day -28 and the baseline value will be calculated from the data between Day -1 and Day -28.

(2) Non-diary data including in-clinic sunlight exposure test

Table 3 Analysis Visit Window for non-diary efficacy data

Analysis Visit	Nominal day	Analysis Visit Window
Baseline	First dose day	NA
Week 4	Day 29	Day 16 to 64
Week 12	Day 85	Day 72 to 119
Week 26 (DBT EOT)	Day 183	Day 134 to 202
Week 26 (DBE Baseline)	Day 183	Day 134 to 202
Week 39	Day 274	Day 250 to 320
Week 52 (DBE EOT)	Day 365	Day 321 to 396
Follow-up until Week 32 (DBT EOS)	6 weeks after EOT for DBT	NA
Follow-up until Week 58 (DBE EOS)	6 weeks after EOT for DBE	NA

(3) Safety data

Table 4 Analysis Visit Window for safety data

Analysis Visit	Nominal day	Analysis Visit Window
Screening*	Day -42*	-
Baseline*	First dose day*	NA*
Week 2	Day 15	Day 2 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 119
Week 16 (Only for Norway site)	Day 113	-
Week 18(Only for Japan and Canada site)	Day 127	-
Week 20 (Only for Norway site)	Day 141	-
Week 26 (DBT EOT)	Day 183	Day 134 to 190

Week 26 (DBE Baseline)	Day 183	Day 134 to 190
Week 28	Day 197	Day 191 to 211
Week 30 (Only for Germany site)	Day 211	-
Week 32	Day 225	Day 212 to 249
Week 36 (Only for Norway, Germany and Canada site)	Day 253	-
Week 39	Day 274	Day 250 to 320
Week 43 (Only for Norway site)	Day 302	-
Week 47 (Only for Norway site)	Day 330	-
Week 52 (DBE EOT)	Day 365	Day 321 to 396
EOT for DBT (LOCF)	Day 182 or discontinued during DBT	The latest visit during DBT period
EOT for DBE (LOCF)	Day 365 or discontinued during DBE	The latest visit during DBE period
Follow-up until Week 32 (DBT EOS)	6 weeks after EOT for DBT	NA
Follow-up until Week 58 (DBE EOS)	6 weeks after EOT for DBE	NA

* For liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin), the mean value of two numerical values at screening visit and at randomization visit (the first dose day) will be treated as a baseline value.

The date of the first dose of study drug is defined as Day 1.
Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (for DBT) or will be the available value of parameter of Week 26 (for DBE).
For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

According to country specific protocol for Japan, Norway, Germany and Canada, liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin) will be measured at each country specific visit in each country.

7.4 Data Handling Convention for Missing Data

For missing of the onset time of the first prodromal symptom in in-clinic sunlight exposure test, impute from the formula of "end test time - start test time" as sensoring time.

For the purpose of determining TEAE and AE duration, if the AE start date is incomplete, it will be imputed as follows:

- If the start date is completely missing, the start date will be equal to the date of the first dose date of study treatment. However, if the stop date is not missing and is before the date of the first dose of study treatment, then the stop date will be used instead and the AE will not be considered as TEAE.
- If the start day is missing, but the month and year are not missing and are equal to the month and year of the first study dose, then this event will be considered as TEAE.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If an AE stop date is incomplete, it will be imputed as follows for the purpose of determining AE duration:

- If the AE stop date is completely missing, then the stop date will be equal to the subject's last observed date.
- If the Stop day is missing, but the month and year are not missing and are equal to the month and year of the last observed date, then stop date will be equal to last observed date.
- If the start day and month are missing, then the first day of the first month (January) will be used.

For the purpose of determining prior and concomitant use, if the medication start date is incomplete, then it will be imputed as follows:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining prior and concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

8 STATISTICAL METHODOLOGY

Listings will be presented in treatment, subject, visit (where applicable), and date (where applicable) order.

8.1 Study Subjects

8.1.1 Subject Disposition

Subject disposition will be summarized on the RAND population.

The number of subjects who completed all treatment period (DBT and DBE), prematurely discontinued either DBT period or DBE period, completed DBT period, DBE period, and the safety follow-up period with the reasons for discontinuation in each period will be summarized. In addition, the number and percentage of the subjects that received placebo treatment in MT-7117-A01 study will be summarized.

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.

8.1.2 Analysis Populations

Analysis populations will be summarized on the RAND population. Analysis populations will be listed on the RAND population.

8.1.3 Protocol Deviations

Protocol deviations including major deviations specified in the blinded blinded data review meeting will be listed on the RAND population.

8.1.4 Stratification Registration Errors

In addition, the number of subjects with unmatched stratification registration will be summarized by comparing between IWRS strata data and actual strata from e-Diary data derivation and between IWRS strata data and vendor [redacted] report strata on the RAND population.

8.1.5 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	Descriptive
Sex	Male, Female	
Age (years)	Adolescent(<18) Adult(18 – 65, >65)	Yes
Height (cm) at screening visit		Yes
Weight (kg) at screening visit	<45 >=45	Yes
BMI (kg/m2)	[redacted]	Yes
Race	White, Black or African American, Asian(Japanese), American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other	
Country	US, Australia, Canada, Germany, Italy, Japan, Norway, Spain, Sweden, United Kingdam (from IWRS data)	
Region (Randomization stratification factor)	North America, Rest of world (Europe, Japan, Australia) (from IWRS data)	
Ethnicity	Hispanic or Latino, Non-Hispanic or Latino	
EPP/XLP	EPP, XLP	
Protoporphyrin (PPIX level) (mcg/dL)		Yes
Disease duration (years)		Yes
Baseline average daily time to first prodromal symptom (Randomization stratification factor)	[redacted]	
Actual baseline average daily time to first prodromal symptom	[redacted]	Yes
Seasonality 1	Randomized in Spring and Summer inclusive, Other	

	(Spring and Summer: between September 1st to February 29 in Australia or between March 1st and August 31th in the other countries)	
Seasonality 2	Week 26 visit in Spring and Summer inclusive, Other (Spring and Summer: the date of Week 26 analysis visit is between September 1st and February 29th in Australia or the date of Week 26 analysis visit is between Mar 1st and August 31th in the other countries)	
Melanin density		Yes
Fitzpatrick skin type	I, II, III, IV, V-VI	
[redacted]	[redacted]	

Demographic and other baseline characteristics will be summarized on the ITT1, ITT2 , SAF1, and SAF2 populations. Demographic and other baseline characteristics will be summarized on the ITT1, ITT2 , SAF1, and SAF2 populations by region (North America, Europe, Japan, Australia).

Demographic and other baseline characteristics will be listed on the RAND population.

8.1.6 Medical History

Medical history will be summarized on the SAF1 and the SAF2 populations. In this summary, SOC is sorted by International order; then within SOC, PT is sorted by descending counts under MT-7117 [redacted], MT-7117 [redacted] or Placebo (switched to [redacted], switched to [redacted]) column, then alphabetic order for PTs with the same count. Medical history will be listed on the RAND population.

8.1.7 Prior or Concomitant Medications

The prior will be summarized in table separately by ATC level 2, preferred name and treatment group for the SAF1 and presented in data listing for the RAND population. The concomitant medications that were used based on the start date of use during each period of DBT and DBE will be summarized by ATC level 2, preferred name and treatment group for the SAF1 and SAF2 populations respectively and presented in data listing for the RAND population.

8.1.8 Prohibited medication

The prohibited medications coded by the protocol Appendix 1 Table 18-1 will be summarized on the SAF1 and SAF2 populations and listed on the RAND population. The summary will be presented by ATC level 2 and preferred name and treatment.

8.1.9 Treatment Duration and Compliance

Treatment duration will be summarized on the ITT1 and ITT2 populations.
Treatment duration and compliance will be listed on the RAND population. Study drug interruptions will be listed on the RAND population.
Compliance to Double-Blind study medication will be presented for the ITT1 and ITT2 population in table by treatment group. The range 80% <= compliance <= 120% will be used to define a subject being treatment compliant.
The number and percentage of subjects with no study drug suspension, any study drug suspension and permanent study drug discontinuation will be summarized by the DBT period on the ITT1 population and by the DBE period on the ITT2 population.
All study medication administration and accountability data will be listed by subject.

8.1.10 Fitzpatrick skin scale test

The Fitzpatrick skin type will be summarized with number and percentage and the Fitzpatrick total score will be summarized by treatment group and analysis visit for the ITT1 and ITT2

populations.

8.1.11 Subject Questionnaire for Study Medication

Subject questionnaire for study medication will be summarized and listed.

8.2 Efficacy Assessments

All efficacy endpoints will be analysed under primary estimand unless otherwise stated.
All data will be listed.

For DBT data analysis

All efficacy endpoints in Section 2.3.1, 2.3.2, and 2.3.3 will be summarized using descriptive statistics or using the number with percentage in the ITT1 population. All of the statitistcal model analyses stated in the below sections will be done in the ITT1 only for DBT data analysis only.

8.2.1 Primary Efficacy Endpoint

Primary Analysis

For the ITT1 population, the primary estimand will be tested including retrieved dropout data (after treatment discontinuation), using treatment comparisons of interest in change from baseline in average daily time to first prodromal symptoms associated with exposure to sunlight between 1 hour post sunrise and 1 hour pre-sunset for the two MT-7117 doses ([redacted] and [redacted]) compared with placebo at Week 26 (Visit 7).

To assess the treatment effect at Week 26, 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 Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed categorical terms for treatment, [redacted] visit, and treatment by visit interaction together with continuous covariate terms for baseline average daily duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset to first prodromal symptom and baseline average daily duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset to first prodromal symptom by visit interaction. An unstructured (UN) 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), the heterogeneous compound symmetry (CSH) and the heterogeneous Toeplitz structure (TOEPH), autoregressive [AR(1)] and compound symmetry (CS) correlation matrix will be used in that order instead of UN. 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 group 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 subjects will be used in the primary analysis without any imputation.

Sensitivity Analysis

(1) Use of actual strata of baseline average daily sunlight exposure time to first prodromal symptom for randomization registration errors

In the above primary analysis model, [redacted] directly derived from e-Diary raw dataset.

(2) Controlled multiple imputation method

The primary analysis model is using likelihood based approach to handle missing data under Missing At Random (MAR) missingness pattern in the primary estimand. In order to assess the robustness of the primary analysis also under Missing Not At Random (MNAR) pattern, a control group-based multiple imputation (MI) of the Pattern Mixture Model (PMM) method will be used. This model assumes MNAR for missing data mechanism in MT-7117 [redacted] and [redacted] and MAR for missing data mechanism in placbo on the ITT population.

- Step 1: This methodology will structure data based on missing data patterns. The PMM method will be based on a missingness pattern having a monotone structure, i.e. if among the observations over time one data value is missing, all other values after this missing value will also be missing. For patients with intermittent missing values, before performing MI based on the PMM, it will be necessary to create a monotone missingness pattern. 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 100 times, creating different datasets with a monotone missing data structure. Seed value of 2022 will be used in the MI procedure. The imputation with the explanation variables of the baseline value and the post-baseline values is based on the MAR assumption, i.e. the missing data are assumed to follow the same model as the other patients. The minimum number

will be set as 0 because the imputed value for time to first prodromal symptom should be greater than or equal to 0.

The following SAS code will be used to generate the monotone missing data pattern:

[redacted]

- Step 2: After this, the remaining missing data will be imputed using a MI method for monotone missingness, with the assumption that the data on MT-7117 [redacted] and [redacted] once daily groups are MNAR and the data on placebo group are MAR. Control group-based assumption will be used for the missing data. Thus, for each of the created dataset with a monotone missing data pattern in step 1, the MI procedure in SAS will be used to impute missing values based on a sequential procedure reflecting the monotone missing data pattern. The MNAR statement of the following (see SAS code) will be used to generate the imputation.

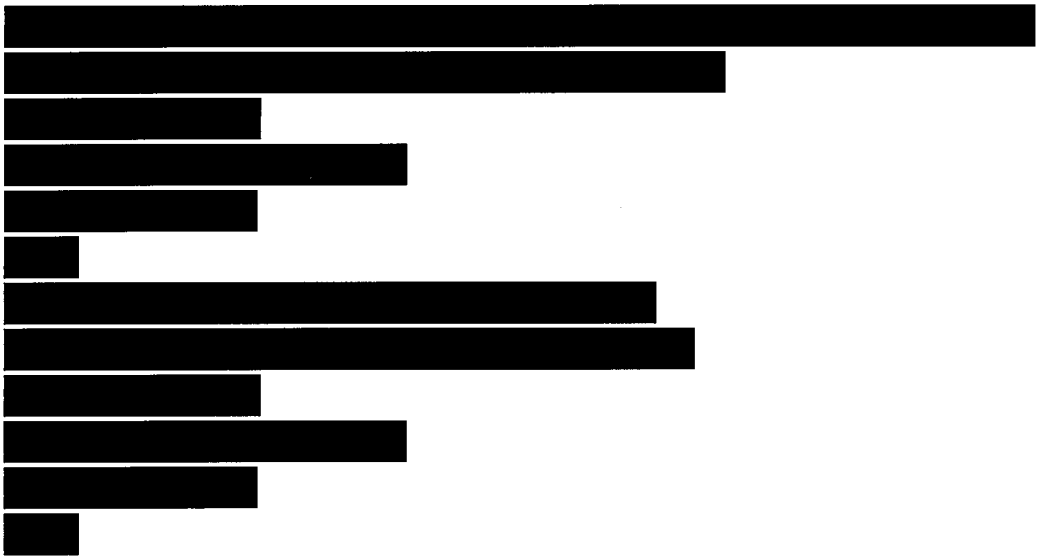
Patients with the first missing value occurring at Week 2 ("W2") will have their missing Week 2 value replaced by an imputed value from a regression model with [redacted] and the baseline value (BASE) as explanatory variables. In the next step, patients with their Week 4 ("W4") value missing will have their missing Week 4 value replaced by an imputed value from a regression model with baseline average daily first to prodromal symptoms and the Week 2 value as explanatory variables. Similar procedure will be used to replace the missing values at week 4, 6, 8 and 10 etc. [redacted] If the imputated value is less than 0 and then the valus will be replaced with 0.

The following SAS code for the missing data imputation at Week 26 will be used to make the imputation with the MNAR assumption:

[redacted]

- Step 3: The imputed dataset (IMPUTED) generated with the approach described above do contain only non-missing values. MMRM model similar to that described for the primary analysis will thus be run on each of the 100 generated imputed datasets and the differences between the treatment groups at Week 26 will be estimated (and export to data 'ESTIMATES'). 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 W26. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated.

The following example SAS code will be used:



(3) Non-parametric analysis

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,..., 24, and 26) 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 100 times, creating different datasets with a monotone missing data structure. Seed value of 2022 will be used in the MI procedure. The minimum number will be set as 0 because the imputed value for time to first prodromal symptom should be greater than or equal to 0.

The following SAS code will be used to generate the monotone missing data pattern:

[redacted]

- 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. Subjects 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 (trtp), [redacted] and the baseline value (base) as the explanatory variables. In the next step, subjects 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, the randomization strata, baseline value and Week 2 value as explanatory variables. Similar procedure will be used to replace the missing values at Week 4, 6, ..., 24, and 26. If the imputated value is less than 0 and then the valus will be replaced with 0.

The following example SAS code will be used to make the imputation with the MAR assumption:

[redacted]

- 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. For the difference between the treatment groups with paired comparison

(MT-7117 [redacted] vs. Placebo and MT-7117 [redacted] vs. Placebo) in Week 2, 4, ..., 24, and 26, the Hodges-Lehman estimator and asymptomtic standard error of this estimator will be calculated on each of the 100 generated imputed datasets, using the NPAR1WAY procedure in SAS. 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, ..., 24, 26 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:

[redacted]

(3) LOCF imputation analysis

For this primary endpoint, ANCOVA with treatment group (trtp), [redacted] and the baseline value as the explanatory variables will be also performed. For missing data for the primary endpoint, LOCF approach assuming MNAR will be used to impute this missing data.

(4) Impact of removing the 3 subjects (USUBJID: [redacted], [redacted] and [redacted], See the detail in the DRM minutes) with ICH E6 GCP violation (Lost of source document).

These three subjects data will be removed from the primary endpoint and the above primary analysis model will be performed.

Supportive Analysis

The secondary estimand will use similar estimator as for the primary analysis. The ITT1 population with the primary efficacy data without retrieved dropout data (after treatment discontinuation) will be used for this analysis. Likelihood based model method under Missing at Random assumption will be performed using the same MMRM as specified for the primary analysis. The only primary endpoint will be also analyzed in the secondary estimand and the other efficacy endpoints will not be analyzed in this estimand.

Multiplicity adjustment for treatment comparison on primary and secondary endpoints

The overall study-wise type I error will be 5%. Type I error will be globally strongly controlled by employing the fixed sequence approach, (i.e., each endpoint will be formally analyzed only in case the preceding endpoint will have a p-value less than or equal to 0.05).

To protect the study from type I error inflation, the lower ordered comparison will be interpreted inferentially only if a statistically significant treatment effect is detected in the higher ordered comparison (H1=>H2,..., H11=>H12). The following null hypothesis will be sequentially tested via the following order;

H1: There is no treatment difference between MT-7117 [redacted] and placebo in 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 Week 26.

H2: There is no treatment difference between MT-7117 [redacted] and placebo in 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 Week 26.

H3: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.

H4: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.

H5: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.

H6: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.

H7: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.

H8: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.

H9: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.

H10: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.

H11: There is no treatment difference between MT-7117 [redacted] and placebo in change from

baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.
H12: There is no treatment difference between MT-7117 and placebo in change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

Subgroup Analysis

The consistency of treatment effect on the primary endpoint across different subgroups will be explored based on the ITT1 population and the primary estimand for the following subgroups using the primary efficacy analysis.

- Gender (Male, Female)
- Age group (age <18, 18=< age)
-
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino, Others)
- Race (White, Black or African American, Asian(Japanese), Others)
- BMI (BMI <30, BMI ≥30 kg/m^2)
-
- Seasonality1 (Randomized in Spring and Summer inclusive, Other)
- Seasonality2 (Week 26 visit in Spring and Summer inclusive, Other)
- Average melanin density at BL (>=Median, <Median)
- Fitzpatrick scale test category (I-II or III-VI)
- Protoporphyrin (>=Median, <Median)
- Porphyrin (>=Median, <Median)
- EPP vs XLP
-
-
- Study Drug Compliance by Week 26 (no study drug suspension, any study drug suspension or permanent study drug discontinuation)

Bayesian analysis for adult and adolescent subgroups

Age group (age <18, 18=<age)

In order to estimate treatment effects for adult and adolescent for the primary endpoint, Bayesian subgroup hierarchical model and Commensurate prior model will be performed using both adolescent and adult subgroup data in order to get greater precision on treatment effect

and address random high and random low data values due to small sample estimates. This means these analysis does not estimate treatment effect within adolescent subgroup in isolation of adult subgroup. Details of the model and the framework can be found in Appendix 1. The posterior means, SE and 95% Credible Interval(CrI) for the primary endpoint will be presented for each treatment group. The posterior mean, SE and 95% CrI will be obtained for the difference of each of the active MT-7117 treatment groups versus placebo. In addition, the probability that the difference in the primary endpoint versus placebo > 0 will be presented for MT-7117 [redacted] and [redacted], respectively. If this probability is at least greater than 95%, then this will be considered as "a statistically significant difference" for the active dose and the subgroup. If the posterior mean for the difference in the primary endpoint versus placebo will be greater than 0 in both adult and adolescent subgroups in the MT-7117 active dose, then this will be considered as "a positive trend" for the active dose among the subgroups.

Funnel plot analysis

In order to confirm the relation between change from baseline for the average potential outliers of treatment effect by site and by country for the primary endpoint, funnel plot analysis by site and by country will be performed respectively. The curves on the graph delineate overall mean treatment difference (MT-7117 [redacted] – Placebo, MT-7117 [redacted] – Placebo) plus/minus 2*standard error limits [Z(0.05/2) x overall standard deviation (SD) x sqrt (2/n), Note: Z(0.05/2)= quantile("Normal",0.975)]. Overall SD will be SD for overall in the calculated two treatment groups and n will be determined (e.g. 1 to 15) based on average sample size per treatment group in the calculated two treatment groups in each site and each country.

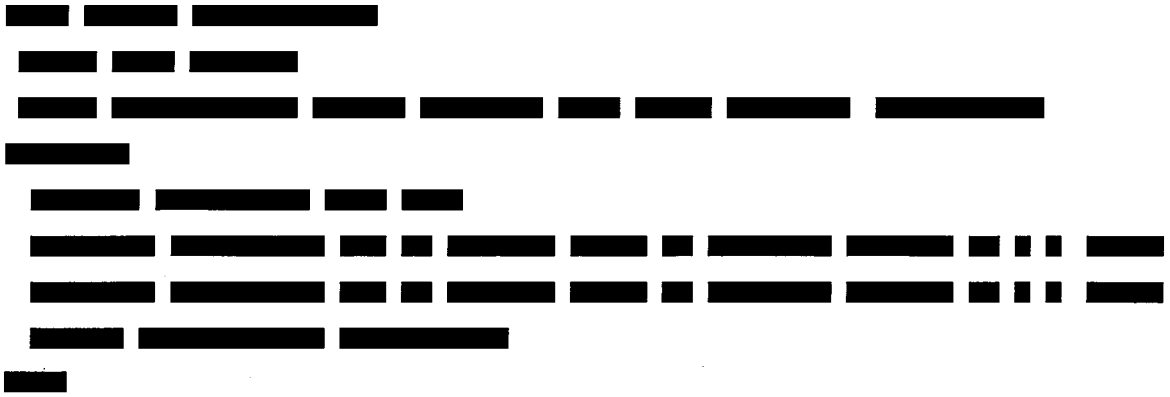
8.2.2 Secondary Efficacy Endpoints

The secondary endpoint PGIC at Week 26 will be analyzed using the similar model as specified for the primary analysis (MMRM) replacing the average daily sunlight exposure time to first prodromal symptom baseline covariate with PGIS covariates at baseline visit.
The change from baseline for total score in each domain of physical function and pain intensity in the PROMIS-57 at Week 26 will be analyzed in the same way.

For the total number of sunlight-induced pain events defined as prodromal symptoms with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period, the negative binomial regression model with log link will be used. The model will include treatment and the randomization stratification factors as fixed effect. 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.

The following example SAS code will be used;



The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26, will be analyzed using logistic regression analysis. The model will include the treatment group and the randomization stratification factors as fixed effect and the baseline average daily sunlight exposure time to first prodromal symptom as covariate. The treatment odds ratio at Week 26 will be estimated using a contrast. The missing data at Week 26 due to no available average daily sunlight exposure time to first prodromal symptom will be addressed as non-responder.

For each secondary efficacy endpoint, a subgroup analysis by region (North America, Europe, Japan, Australia) will be done.

8.2.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be analysed using the similar model as specified for the primary analysis (MMRM) replacing the baseline average daily sunlight exposure time to first prodromal symptom as covariate with the corresponding covariates at baseline visit in the below bullets.

- Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during 26-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during 26-week double-blind treatment period.

- Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during 26-week double-blind treatment period on an 11-point Likert scale.
- Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during 26-week double-blind treatment period.
- Change from baseline for all total score and total score in each domain of, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference in the PROMIS-57
- Change from baseline in PGIS at each visit.

The following endpoints will be analysed using the same negative binomial model with log link as specified for the secondary efficacy endpoint.

- Total number of sunlight-induced pain events defined as phototoxic events during 26-week double-blind treatment.
- Total number of sunlight-induced non-prodrome, phototoxic reactions during 26-week double-blind treatment.

The following endpoint will be analysed using the same logistic regression model as specified for the secondary efficacy endpoint.

- The percentage of subjects who are responders at Week 26 based on PGIC (Very Much Improved or Much Improved).

The following 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 each visit by skin segments and average of 6 skin segments will be plotted by treatment. The average of 6 skin segments for the melanin density and for the change from baseline in melanin density at each visit, will be analysed using MMRM model similar to the analyses for the primary endpoint. A subgroup analysis by region (North America, Europe, Japan, Australia) , by Fitzpatrick scale test category (I-II or III-VI), by Melanin density at BL (>=Median, <Median) and by the [redacted] will be done.

- Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.

The following endpoints will be analysed using either ANCOVA or ANOVA model. The ANCOVA model will include the treatment group, randomization strata as fixed factors together with continuous covariate terms for the corresponding baseline values except for the below total

time endpoints.

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours).
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 26.

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 without prodromal symptoms during 26-week double-blind treatment period.

- Total number of days subject is exposed to sunlight for any duration without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind treatment period.
- Total number of days subjects went outdoors during the 26-week double-blind treatment period.
- Total severity of phototoxic reaction on an 11-point Likert scale during the 26-week double-blind treatment period

Maximum severity of photoxic reaction on an 11-point likert scales will be summarized using frequency and percentage. Shift table of maximum phototoxic reaction on an 11-point Likert scale at Week 26 or EOT will be presented using frequnecye and perenctage.

For DBE data analysis

All efficacy endpoints in Section 2.3.4 will be simply and descriptively summarized in the ITT2 population in the above similar approach without statistical models.

8.3 Safety Assessments

Safety assessments of DBT period data and DBE period will be made on the SAF1 and SAF2 populations, resepectively. All data will be listed.

8.3.1 Adverse Events

The TEAEs are summarized for subjects with at least one TEAE, at least one treatment emergent adverse event related to study drug, at least one serious TEAE, at least one serious treatment emergent adverse event related to study drug, at least one TEAE leading to drug withdrawal, at least one treatment emergent adverse event related to study drug leading to drug withdrawal, at least one hepatic AE, at least one Adverse Events of Special Interest (AESI) and fatal TEAE. These TEAEs are summarized for subjects by region (North America, Europe, Japan, Australia) as well.

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 combined total group, then descending counts under MT-7117 [redacted] group, then descending counts under MT-7117 [redacted] 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
- TEAEs by SOC, PT and region (North America, Europe, Japan, Australia)
- Treatment emergent adverse event related to study drugs by SOC and PT
- Treatment emergent adverse event related to study drugs by SOC, PT and severity
- Serious TEAEs by SOC and PT
- Serious treatment emergent adverse event related to study drug s by SOC and PT
- TEAEs leading to drug withdrawn by SOC and PT
- TEAEs by SOC and PT for TEAEs with frequency >= 3% in MT-7117 any treatment groups
- Treatment Emergent Hepatic AEs by SOC and PT
  (Note: Hepatice AE will be defined by SMQ Hepatic List in the appendix)
- AESI by SOC and PT
- TEAEs by SOC, PT and treatment duration
- TEAEs by SOC, PT, treatment duration and region (North America, Europe, Japan, Australia)
- Serious TEAEs by SOC, PT and treatment duration
- TEAEs by SOC and PT (Removing USUBJID: [redacted], [redacted], [redacted])

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.

8.3.2 Laboratory Tests

Absolute values and changes from baseline will be summarized for the following laboratory tests parameters. For Haemoglobin, Haematocrit, Red Blood Cell, MCV, Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Gamma glutamyl transpeptidase and Bilirubin (direct and total), absolute values and changes from baseline will be summarized by region (North America, Europe, Japan, Australia). Standard Unit will be used for the summary.

Laboratory Test	Parameters
Hematology	Haemoglobin, Haematocrit, Red Blood Cell, Platelet count, MCV, MCH, MCHC, White blood cell count and differential
Biochemistry	Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Gamma glutamyl transpeptidase, Potassium Sodium, Chloride, Inorganic phosphate, Glucose, Bilirubin (direct and total), Blood urea nitrogen, Cholesterol, Triglycerides, High density lipoprotein cholesterol, Low density lipoprotein cholesterol, Protein (total), Albumin, Creatine kinase, Creatinine, Ferritin, Vitamin D
Coagulation	PT, INR, aPTT
Urinalysis	Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood Microscopic examination[a]

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

Shift table of clinically relevant categories will be presented for the following laboratory tests parameters. The categories will be Low, Normal and High for Hematology, Biochemistry, Urinalysis and Coagulation, and Normal and Abnormal for Urinalysis (Qualitative Value).
A shift table of the number and percentage will be provided for subjects who had any post baseline maximum value at any time during the treatment period and met the liver function tests (AST, ALT and Total bilirubin) criteria of the pre-defined limit for the maximum value.

8.3.3 Vital Signs

Absolute values and change from baseline will be summarized descriptively and shift table of clinically relevant categories (Normal, Abnormal(Not Clinically Significant, Clinically Significant)) from baseline to EOT will be also presented for the following parameters .

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate
- Respiratory Rate
- Body Temperature (°C)
- Body Weight (kg)

8.3.4 12-Lead ECGs

Absolute values and changes from baseline will be descriptively summarized and shift table of clinically relevant categories (Normal, Abnormal(Not Clinically Significant, Clinically Significant)) from baseline to EOT will be also presented for the following parameters.

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

A summary table of the number and percentage will be provided for subjects who met the 12-lead ECG criteria of QTcF and QTcB for pre-defined limit as numerator.

8.3.5 Physical Examinations

Physical examination will be summarized with the number and percentage of the subjects for clinically relevant categories (Normal, Abnormal(Not Clinically Significant, Clinically Significant)).

- Abdominal
- Cardiovascular
- General Appearance
- Head
- Eyes
- Ears/nose/throat

- Lymph nodes
- Musculoskeletal
- Neck
- Neurological
- Dermatological
- Other

8.3.6 Nevi appearance

Nevi appearance will be summarized with the number and percentage of the subjects' suspicious nevi found:

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

8.4 Pharmacokinetics Evaluation

Pharmacokinetics evaluation of DBT period data and DBE period will be made on the PK population. All data will be listed.
Plasma concentrations of MT-7117 will be analyzed at randomization visit (pre-dose on Day 1 for not Japanese, 2, 4, 6, and 8 hours post-dose on Day 1 for Japanese), Week 4 (any time), Week 12 (any time), Week 26 (at the visit and 3 to 4 hours after the first PK sample collection), Week 39, (any time) and Week 52 (any time) visits for subjects who are ≥18 to ≤75. For subjects who are ≥12 to ≤17, plasma concentrations of MT-7117 will be analyzed at randomization visit (Day 1, at 2, 4, 6, and 8 hours post-dose), Week 12 (pre-dose and 3 hours post-dose), and Week 26 (pre-dose, 2, and 4 hours post-dose). For the calculation of the summary statistics of palsma concentrations at each sampling point, concentration values reported as below the limit of quantification (BLQ) will be set to 0.

Plasma MT-7117 concentrations 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. Moreover, individual concentrations will be plotted against actual sampling time for each treatment with different symbols for age (≥12 to ≤17 and ≥18 to ≤75) and ethnicity (Not Japanese and

Japanese) overlaid with visits.

8.5 Pharmacogenetics Evaluation

Pharmacogenetics assessments will be made on the ITT1 population.

[redacted]

8.6 Exploratory endpoint

Porphyrin and protoporphyrin levels will be listed and summarized using descriptive statistics for the following parameters on the SAF1 and the SAF2 population. Porphyrin and protoporphyrin levels will be summarized by region (North America, Europe, Japan, Australia) as well.

- Plasma total porphyrins(mcg/dL)
- Erythrocyte protoporphyrins(mcg/dL)
- Zinc protoporphyrins(%)
- Metal-Free protoporphyrins(%)

9 DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

(1) Non-PK related

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.1.2.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages[*1]	1 DP	All

Ratios	3 DPs	All
p-values*2	3 DPs	All

*1 Percentages: use 1 place beyond the decimal point, except for the following cases:

If the percentage is equal to 0, then leave blank, do not use (0)

If the percentage is equal to 100, then use "(100)" without a decimal

*2 p-values: use 3 places beyond the decimal point, except for the following cases:

If the p-value is less than 0.001, then use p<0.001

(2) PK Plasma Concentration

Statistic	Specification
Individual value	4 significant digits
Minimum, Maximum	Same number of DPs as the individual value
Mean, SD, Median	Number of DPs securing at least 2 significant digits for the minimum

9.2 Treatment Groups to Report

Treatment Group for DBT data analysis	For TFLs
MT-7117 [redacted]	MT-7117 [redacted]
MT-7117 [redacted]	MT-7117 [redacted]
Placebo	Placebo

Treatment Group for DBE data analysis		For TFLs
MT-7117 [redacted]		MT-7117 [redacted]
MT-7117 [redacted]		MT-7117 [redacted]
MT-7117 [redacted]	(switched from Placebo)	Placebo -> MT-7117 [redacted]
MT-7117 [redacted]	(switched from Placebo)	Placebo -> MT-7117 [redacted]

9.3 Analysis Visits to Report

eDiary:

Analysis Visit	Apply to					
	Analysis for DBT period data			Analysis for DBE period data		
	Change from baseline	Total time / number of days / severity of phototoxic reaction during 26 weeks	Maximum severity of phototoxic reaction	Change from baseline	Total time / number of days / severity of phototoxic reaction during 26 weeks	Maximum severity of phototoxic reaction

Baseline	X		X			
Week 2	X					
Week 4	X					
Week 6	X					
Week 8	X					
Week 10	X					
Week 12	X					
Week 14	X					
Week 16	X					
Week 18	X					
Week 20	X					
Week 22	X					
Week 24	X					
Week 26 (DBT EOT)	X					
During 26 weeks(DBT)		X	X			X
EOT for DBT			X			
Follow-up until Week 32(DBT EOS)	X					
Week 26 (DBE Baseline)				X		
Week 28				X		
Week 32				X		
Week 39				X		
Week 52 (DBE EOT)				X		X
During 26 weeks(DBE)					X	
EOT for DBE						
Follow-up until Week 58 (DBE EOS)				X		

Efficacy except for eDiary:

Analysis Visit	Apply to	
	Analysis for DBT period data	Analysis for DBE period data

	PROMIS-57	PGIC	PGIS	In-clinic sunlight exposure test	Melanin density evaluation	PROMIS-57	PGIC	PGIS	In-clinic sunlight exposure test	Melanin density evaluation
Baseline	X		X	X	X					
Week 4		X	X		X					
Week 12	X		X		X					
Week 26 (DBT EOT)	X	X	X	X	X					
Follow-up until Week 32(DBT EOS)	X		X		X					
Week 26 (DBE baseline)						X	X	X	X	X
Week 39						X		X		
Week 52 (DBE EOT)						X	X	X	X	X
Follow-up until Week 58(DBE EOS)						X		X		X

Safety:

Analysis Visit	Apply to							
	Analysis for DBT data				Analysis for DBE data			
	Laboratory Tests	Vital Signs	12-Lead ECGs	Nevi evaluation	Laboratory Tests	Vital Signs	12-Lead ECGs	Nevi evaluation
Screening	X***	X		X				
Baseline	X***	X	X					
Week 2	X (liver function)							
Week 4	X	X		X				
Week 8	X (liver function)							
Week 12	X	X		X				
Week 16	X**							

Week 18	X**							
Week 20	X**							
Week 26 (DBT EOT)	X	X	X	X				
EOT for DBT (LOCF)	X	X	X	X				
Follow-up until Week 32 (DBT EOS)	X	X		X				
Week 26 (DBE Baseline)					X	X	X	X
Week 28					X*			
Week 30					X**			
Week 32					X*			
Week 36					X**			
Week 39					X	X		X
Week 43					X**			
Week 47					X**			
Week 52 (DBE EOT)					X	X	X	X
EOT for DBE (LOCF)					X	X	X	X
Follow-up until Week 58(DBE EOS)					X	X		X

*At Visits 3, 5, 8, and 9, subjects may have mobile units or in-clinic visits to 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.

**For only specific country(See Table 4)

***For liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin), the mean value between a value at screening and at randomization will be treated as a baseline value.

10 CHANGE FROM THE PROTOCOL

There are currently no changes to analysis from protocol.

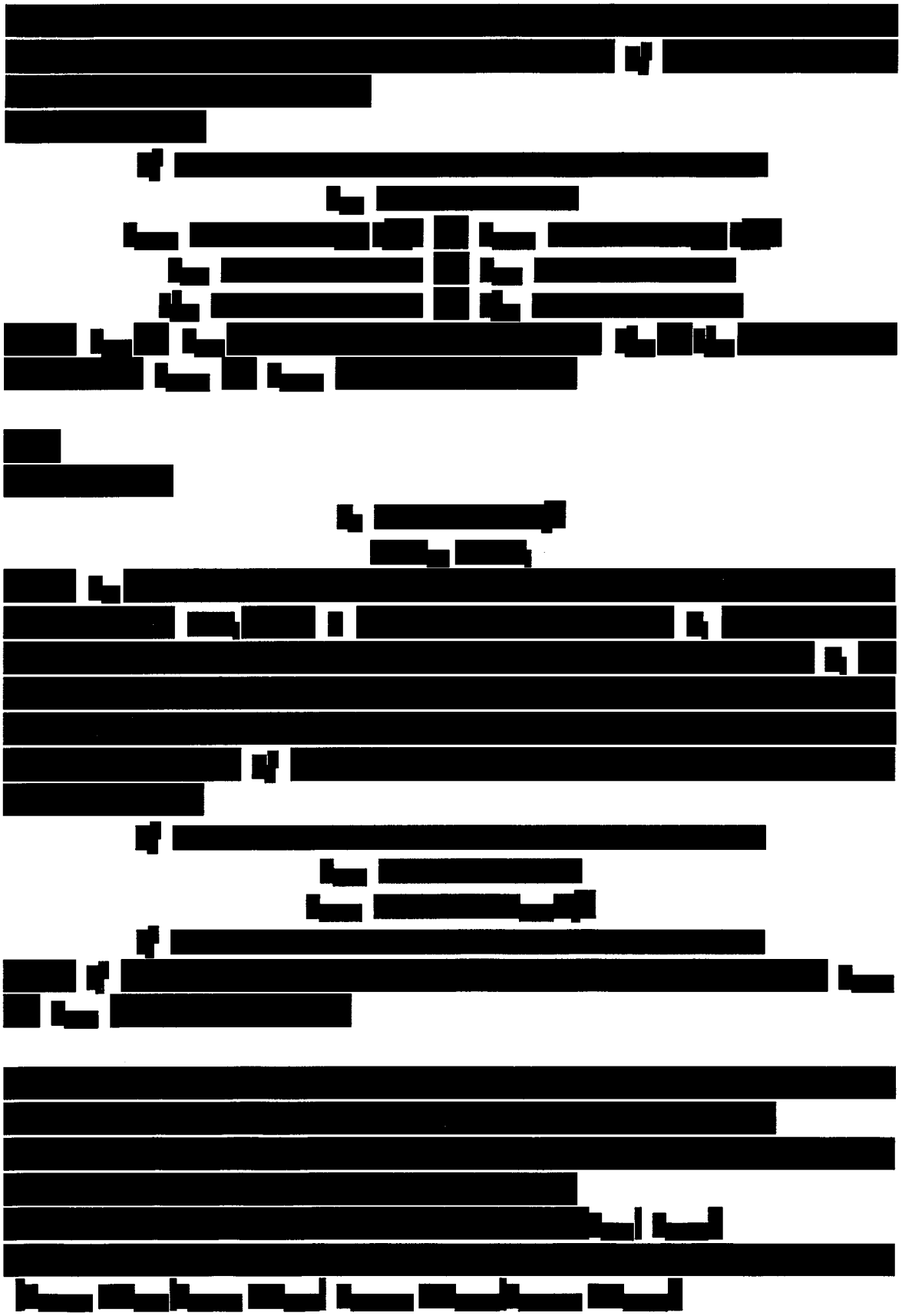
11 SOFTWARE

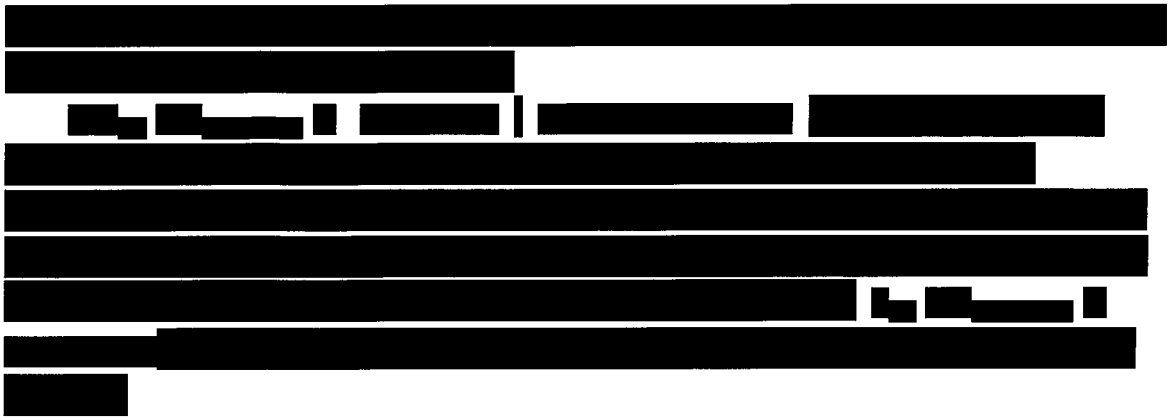
All statistical analyses will be performed using SAS version 9.4 or higher.

12 REFERENCES

N/A

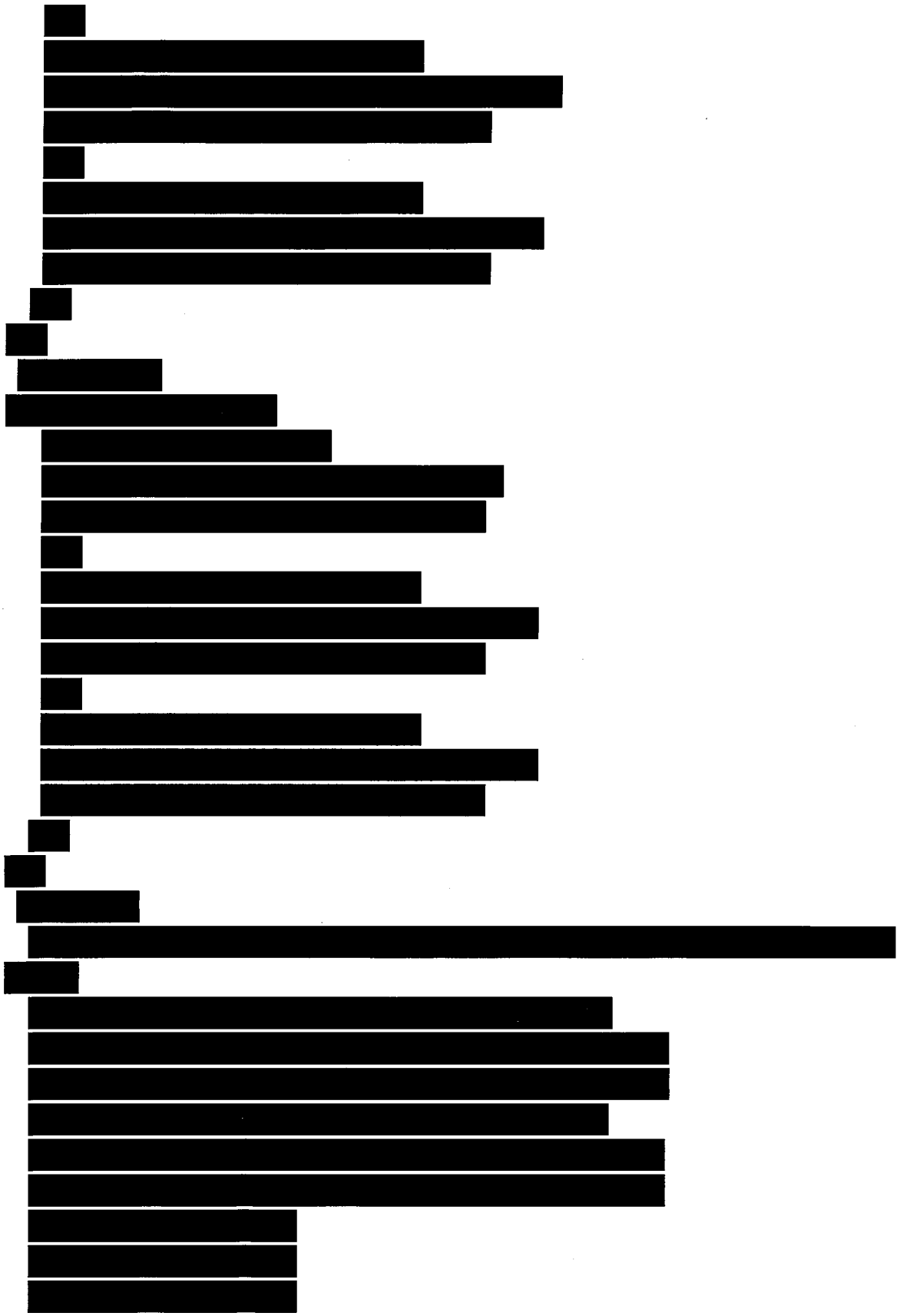
13





14 APPENDIX

14.1



[redacted]

14.2 SMQ List of Hepatic TEAE in MedDRA version 23.1

Bilirubin excretion disorder	10061009
Cholaemia	10048611
Cholestasis	10008635
Cholestatic liver injury	10067969
Cholestatic pruritus	10064190
Drug-induced liver injury	10072268
Hepatitis cholestatic	10019754
Hyperbilirubinaemia	10020578
Icterus index increased	10021209
Jaundice	10023126
Jaundice cholestatic	10023129
Jaundice hepatocellular	10023136
Mixed liver injury	10066758
Ocular icterus	10058117
Parenteral nutrition associated liver disease	10074151
Deficiency of bile secretion	10071634
Yellow skin	10048245
Acquired hepatocerebral degeneration	10080860
Acute hepatic failure	10000804
Acute on chronic liver failure	10077305
Acute yellow liver atrophy	10070815
Ascites	10003445
Asterixis	10003547
Bacterascites	10068547
Biliary cirrhosis	10004659
Biliary fibrosis	10004664
Cardiohepatic syndrome	10082480
Cholestatic liver injury	10067969
Chronic hepatic failure	10057573
Coma hepatic	10010075
Cryptogenic cirrhosis	10063075
Diabetic hepatopathy	10071265
Drug-induced liver injury	10072268

Duodenal varices	10051010
Flood syndrome	10084797
Gallbladder varices	10072319
Gastric variceal injection	10076237
Gastric variceal ligation	10076238
Gastric varices	10051012
Gastric varices haemorrhage	10057572
Gastrooesophageal variceal haemorrhage prophylaxis	10066597
Hepatectomy	10061997
Hepatic atrophy	10019637
Hepatic calcification	10065274
Hepatic cirrhosis	10019641
Hepatic encephalopathy	10019660
Hepatic encephalopathy prophylaxis	10066599
Hepatic failure	10019663
Hepatic fibrosis	10019668
Hepatic hydrothorax	10067365
Hepatic infiltration eosinophilic	10064668
Hepatic lesion	10061998
Hepatic necrosis	10019692
Hepatic steato-fibrosis	10077215
Hepatic steatosis	10019708
Hepatitis fulminant	10019772
Hepatobiliary disease	10062000
Hepatocellular foamy cell syndrome	10053244
Hepatocellular injury	10019837
Hepatopulmonary syndrome	10052274
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Hepatotoxicity	10019851
Immune-mediated cholangitis	10083406
Immune-mediated hepatic disorder	10083521
Intestinal varices	10071502
Intestinal varices haemorrhage	10078058
Liver dialysis	10076640
Liver disorder	10024670

Liver injury	10067125
Liver operation	10062040
Liver transplant	10024714
Lupoid hepatic cirrhosis	10025129
Minimal hepatic encephalopathy	10076204
Mixed liver injury	10066758
Nodular regenerative hyperplasia	10051081
Nonalcoholic fatty liver disease	10082249
Non-alcoholic steatohepatitis	10053219
Non-cirrhotic portal hypertension	10077259
Oedema due to hepatic disease	10049631
Oesophageal varices haemorrhage	10030210
Peripancreatic varices	10073215
Portal fibrosis	10074726
Portal hypertension	10036200
Portal hypertensive colopathy	10079446
Portal hypertensive enteropathy	10068923
Portal hypertensive gastropathy	10050897
Portal vein cavernous transformation	10073979
Portal vein dilatation	10073209
Portopulmonary hypertension	10067281
Primary biliary cholangitis	10080429
Regenerative siderotic hepatic nodule	10080679
Renal and liver transplant	10052279
Retrograde portal vein flow	10067338
Reye's syndrome	10039012
Reynold's syndrome	10070953
Splenic varices	10067823
Splenic varices haemorrhage	10068662
Steatohepatitis	10076331
Subacute hepatic failure	10056956
Sugiura procedure	10083010
Varices oesophageal	10056091
Varicose veins of abdominal wall	10072284
White nipple sign	10078438
Anorectal varices	10068924

Anorectal varices haemorrhage	10068925
Complications of transplanted liver	10010186
Hepatic perfusion disorder	10083840
Increased liver stiffness	10082444
Intrahepatic portal hepatic venous fistula	10072629
Liver and pancreas transplant rejection	10051603
Liver transplant failure	10083175
Liver transplant rejection	10024715
Multivisceral transplantation	10082450
Peritoneovenous shunt	10052716
Portal shunt	10036204
Portal shunt procedure	10077479
Small-for-size liver syndrome	10069380
Spider naevus	10041519
Splenic artery embolisation	10083795
Splenorenal shunt	10041661
Splenorenal shunt procedure	10077281
Spontaneous intrahepatic portosystemic venous shunt	10076239
Stomal varices	10075186
Acute graft versus host disease in liver	10066263
Allergic hepatitis	10071198
Alloimmune hepatitis	10080576
Autoimmune hepatitis	10003827
Chronic graft versus host disease in liver	10072160
Chronic hepatitis	10008909
Graft versus host disease in liver	10064676
Hepatitis	10019717
Hepatitis acute	10019727
Hepatitis cholestatic	10019754
Hepatitis chronic active	10019755
Hepatitis chronic persistent	10019759
Hepatitis fulminant	10019772
Hepatitis toxic	10019795
Immune-mediated hepatitis	10078962
Ischaemic hepatitis	10023025
Lupus hepatitis	10067737

Non-alcoholic steatohepatitis	10053219
Radiation hepatitis	10051015
Steatohepatitis	10076331
Granulomatous liver disease	10018704
Liver sarcoidosis	10068664
Portal tract inflammation	10075331
Benign hepatic neoplasm	10004269
Benign hepatobiliary neoplasm	10077922
Focal nodular hyperplasia	10052285
Haemangioma of liver	10018821
Haemorrhagic hepatic cyst	10067796
Hepatic adenoma	10019629
Hepatic cyst	10019646
Hepatic cyst ruptured	10053973
Hepatic haemangioma rupture	10054885
Hepatic hamartoma	10079685
Hepatobiliary cyst	10079889
Cholangiosarcoma	10077861
Hepatic angiosarcoma	10067388
Hepatic cancer	10073069
Hepatic cancer metastatic	10055110
Hepatic cancer recurrent	10073070
Hepatic cancer stage I	10059318
Hepatic cancer stage II	10059319
Hepatic cancer stage III	10059324
Hepatic cancer stage IV	10059325
Hepatobiliary cancer	10073073
Hepatobiliary cancer in situ	10073074
Hepatoblastoma	10062001
Hepatoblastoma recurrent	10019823
Hepatocellular carcinoma	10073071
Liver carcinoma ruptured	10050842
Mixed hepatocellular cholangiocarcinoma	10027761
Hepatic neoplasm	10019695
Hepatobiliary neoplasm	10061203
Alanine aminotransferase abnormal	10001547

Alanine aminotransferase increased	10001551
Ammonia abnormal	10001942
Ammonia increased	10001946
Ascites	10003445
Aspartate aminotransferase abnormal	10003477
Aspartate aminotransferase increased	10003481
AST/ALT ratio abnormal	10082832
Bacterascites	10068547
Bile output abnormal	10051344
Bile output decreased	10051343
Biliary ascites	10074150
Bilirubin conjugated abnormal	10067718
Bilirubin conjugated increased	10004685
Bilirubin urine present	10077356
Biopsy liver abnormal	10004792
Blood bilirubin abnormal	10058477
Blood bilirubin increased	10005364
Blood bilirubin unconjugated increased	10005370
Bromosulphthalein test abnormal	10006408
Child-Pugh-Turcotte score abnormal	10077020
Child-Pugh-Turcotte score increased	10068287
Computerised tomogram liver abnormal	10078360
Congestive hepatopathy	10084058
Foetor hepaticus	10052554
Galactose elimination capacity test abnormal	10059710
Galactose elimination capacity test decreased	10059712
Gamma-glutamyltransferase abnormal	10017688
Gamma-glutamyltransferase increased	10017693
Guanase increased	10051333
Hepaplastin abnormal	10019621
Hepaplastin decreased	10019622
Hepatic artery flow decreased	10068997
Hepatic enzyme abnormal	10062685
Hepatic enzyme decreased	10060794
Hepatic enzyme increased	10060795
Hepatic function abnormal	10019670

Hepatic hydrothorax	10067365
Hepatic hypertrophy	10076254
Hepatic hypoperfusion	10084751
Hepatic mass	10057110
Hepatic pain	10019705
Hepatic sequestration	10066244
Hepatic vascular resistance increased	10068358
Hepatic venous pressure gradient abnormal	10083172
Hepatic venous pressure gradient increased	10083171
Hepatobiliary scan abnormal	10066195
Hepatomegaly	10019842
Hepatosplenomegaly	10019847
Hyperammonaemia	10020575
Hyperbilirubinaemia	10020578
Hypercholia	10051924
Hypertransaminasaemia	10068237
Kayser-Fleischer ring	10023321
Liver function test abnormal	10024690
Liver function test decreased	10077677
Liver function test increased	10077692
Liver induration	10052550
Liver palpable	10075895
Liver scan abnormal	10061947
Liver tenderness	10024712
Magnetic resonance imaging liver abnormal	10083123
Magnetic resonance proton density fat fraction measurement	10082443
Mitochondrial aspartate aminotransferase increased	10064712
Molar ratio of total branched-chain amino acid to tyrosine	10066869
Oedema due to hepatic disease	10049631
Perihepatic discomfort	10054125
Retrograde portal vein flow	10067338
Total bile acids increased	10064558
Transaminases abnormal	10062688
Transaminases increased	10054889
Ultrasound liver abnormal	10045428
Urine bilirubin increased	10050792

White nipple sign	10078438
X-ray hepatobiliary abnormal	10056536
5'nucleotidase increased	10000028
AST to platelet ratio index increased	10084175
Blood alkaline phosphatase abnormal	10059571
Blood alkaline phosphatase increased	10059570
Blood cholinesterase abnormal	10005429
Blood cholinesterase decreased	10005430
Deficiency of bile secretion	10071634
Glutamate dehydrogenase increased	10049483
Glycocholic acid increased	10080824
Haemorrhagic ascites	10059766
Hepatic fibrosis marker abnormal	10074084
Hepatic fibrosis marker increased	10074413
Hepatic lymphocytic infiltration	10079686
Hypoalbuminaemia	10020942
Leucine aminopeptidase increased	10024275
Liver iron concentration abnormal	10074352
Liver iron concentration increased	10074354
Liver opacity	10084071
Model for end stage liver disease score abnormal	10077291
Model for end stage liver disease score increased	10077292
Periportal oedema	10068821
Peritoneal fluid protein abnormal	10069000
Peritoneal fluid protein decreased	10068999
Peritoneal fluid protein increased	10068998
Pneumobilia	10066004
Portal vein flow decreased	10067337
Portal vein pressure increased	10064936
Retinol binding protein decreased	10048473
Urobilinogen urine decreased	10070480
Urobilinogen urine increased	10070479
Acquired antithrombin III deficiency	10074561
Acquired factor IX deficiency	10082747
Acquired factor VIII deficiency	10082745
Acquired factor XI deficiency	10082746

Acquired protein S deficiency	10068370
Anti factor X activity abnormal	10077670
Anti factor X activity decreased	10077674
Anti factor X activity increased	10077671
Antithrombin III decreased	10049547
Blood fibrinogen abnormal	10005518
Blood fibrinogen decreased	10005520
Blood thrombin abnormal	10005818
Blood thrombin decreased	10005820
Blood thromboplastin abnormal	10005824
Blood thromboplastin decreased	10005826
Coagulation factor decreased	10009736
Coagulation factor IX level abnormal	10061770
Coagulation factor IX level decreased	10009746
Coagulation factor V level abnormal	10061771
Coagulation factor V level decreased	10009754
Coagulation factor VII level abnormal	10061772
Coagulation factor VII level decreased	10009761
Coagulation factor X level abnormal	10061774
Coagulation factor X level decreased	10009775
Hyperfibrinolysis	10074737
Hypocoagulable state	10020973
Hypofibrinogenaemia	10051125
Hypoprothrombinaemia	10021085
Hypothrombinaemia	10058517
Hypothromboplastinaemia	10058518
International normalised ratio abnormal	10022592
International normalised ratio increased	10022595
Protein C decreased	10037005
Protein S abnormal	10051736
Protein S decreased	10051120
Prothrombin level abnormal	10037048
Prothrombin level decreased	10037050
Prothrombin time abnormal	10037057
Prothrombin time prolonged	10037063
Prothrombin time ratio abnormal	10061918

Prothrombin time ratio increased	10037068
Thrombin time abnormal	10051319
Thrombin time prolonged	10051390