Study Protocol

Protocol Number: MT-7117-A01

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

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Date: 13 August 2019
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Mitsubishi Tanabe Pharma Development America, Inc.

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Pre-IND Number:	137573
Investigational Medicinal Product:	MT-7117
Indication:	Prevention of phototoxicity in subjects with erythropoietic protoporphyria
Development Phase:	Phase 2
Sponsor:	Mitsubishi Tanabe Pharma Development America (MTDA), Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310, USA
Protocol Version and Date:	Amendment 2 – Version 3.0 – 13-August-2019

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CONTACT LIST

Sponsor: Mitsubishi Tanabe Pharma Development America (MTDA), Inc. 525 Washington Boulevard, Suite 400; Jersey City, New Jersey 07310, USA [redacted]
Sponsor's Responsible Signatory: [redacted] Vice President and Head, Clinical Development

Mitsubishi Tanabe Pharma Development America, Inc.

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MT-7117-A01

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

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board approval of the necessary essential documents and study procedures will not be initiated until the subject signed the approved Subject Information and Informed Consent Form(s).

Sponsor Signatory:

[redacted] [redacted]

Date

Vice President and Head, Clinical Development

Mitsubishi Tanabe Pharma Development America, Inc.

525 Washington Boulevard, Suite 400

Jersey City, New Jersey 07310, USA

Mitsubishi Tanabe Pharma Development America, Inc.

SIGNATURE PAGE (STATISTICIAN)

Protocol Number: MT-7117-A01

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

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and has undergone statistical review.

Statistician:

[redacted] _____ [redacted]

Date

Associate Director, Biostatistics

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525 Washington Boulevard, Suite 400

Jersey City, New Jersey 07310, USA

SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

Protocol Number: MT-7117-A01

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

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and the principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Federal Medication Administration and Institutional Review Board approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
α-MSH	α-melanocyte-stimulating hormone
AE	Adverse event
AESI	AE of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Autoregressive
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
cAMP	Cyclic adenosine 3',5'-monophosphate
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical Study Report
[redacted]	[redacted]
EC	Ethics committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
EPP	Erythropoietic protoporphyria
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
hERG	Human ether-a-go-go-related gene
hMC1R	Human melanocortin-1 receptor
hMC4R	Human melanocortin-4 receptor
IC_{50}	Concentration associated with 50% inhibition
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web-based Response System
LFT	Liver function test

Abbreviation	Definition
LS	Least squares
MC1R	Melanocortin-1 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MTDA	Mitsubishi Tanabe Pharma Development America
MTPC	Mitsubishi Tanabe Pharma Corporation
MV	Minute volume
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
[redacted]	[redacted]
PGx	Pharmacogenetic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient-reported Outcom
[redacted]	[redacted]
PT	Preferred Term
QP	Qualified Person
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
QTcF	Corrected QT interval using Frederica's formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SNP	Single-nucleotide polymorphism
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
ULN	Upper limit of normal
WHO	World Health Organization
WMA	World Medical Association

PROTOCOL SYNOPSIS

Protocol Number:	MT-7117-A01
Protocol Title:	A Phase II, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy, safety, and tolerability of MT-7117 in subjects with erythropoietic protoporphyria (EPP)
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310, USA
Development Phase:	Phase 2
Indication:	Prevention of phototoxicity in subjects with EPP
Investigational Medicinal Product:	MT-7117 [redacted] Placebo to match MT-7117 [redacted]
Treatment Regimen:	**Dose:** MT-7117 [redacted] or placebo **Route:** Oral **Frequency:** once daily in the morning with food
Treatment Duration:	16 weeks
Objectives:	**Primary Objective:** To investigate the efficacy and safety of MT-7117 on time to onset and severity of prodromal symptoms associated with sunlight exposure in subjects with EPP. **Secondary Objectives:** 1. To investigate the effect on sunlight exposure duration and tolerance in subjects with EPP. 2. To investigate the effect on melanin density in subjects with EPP. 3. To assess the effect of on quality of life in subjects with EPP. 4. To investigate the pharmacokinetics (PK) in subjects with EPP. **Exploratory Objectives:** 1. To evaluate skin biopsy samples from EPP subjects for exploratory biomarkers related to pathogenesis of EPP, inflammatory response, and the mode of action of MT-7117. 2. To evaluate pharmacogenetics (PGx) including melanocortin-1 receptor (MC1R) with single-nucleotide polymorphisms (SNPs), if applicable, as this could lead to pigmentation. 3. To evaluate porphyrin and protoporphyrin levels.
Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in subjects with EPP. The study consists of a 2-week screening period, a 16-week double-blind treatment period, and a 6-week follow-up period at Week 22. The total participation period is approximately 24 weeks. This study is being conducted without regard to

	seasonality. Subjects will attend the screening visit (Visit 1) up to 2 weeks before Randomization (Visit 2), in order to confirm eligibility and obtain pre-study safety assessments including nevi evaluation. Subjects will also be instructed how to use a sunlight exposure diary. At Visit 2, subjects meeting eligibility criteria will be randomized in a 1:1:1 ratio to receive MT-7117 [redacted], [redacted] or placebo in a double-blind manner. Baseline average daily sunlight exposure time without prodromal symptoms (≤30 min and >30 min) will be used as stratum for the randomization. The first dose will be administered at Visit 2 following baseline assessments including in-clinic sunlight exposure test. Active or placebo [redacted] will be administered once daily in the morning with food. Subjects will subsequently attend in-clinic visits at Weeks 4, 8, and 12 (Visits 5, 6, and 7, respectively) during which assessments will be performed. In addition, subjects undergo local laboratory sample collection at Weeks 1 and 2 (Visits 3 and 4, respectively) to measure liver function markers (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], direct and total bilirubin). Subjects will attend the end of treatment visit at Week 16 or early termination (Visit 8). Following the last treatment visit, subjects will attend a follow-up visit at Week 22 or 6 weeks after early termination.
Planned Number of Subjects:	A total of approximately 102 subjects are planned to be randomized in this study (34 subjects in each treatment group).
Subject Population:	Subjects with EPP, aged ≥18 to ≤75 years.
Main Inclusion Criteria:	1. Subjects provided written informed consent to participate. 2. Male and female subjects with a confirmed diagnosis of EPP based on medical history, aged 18 years to 75 years, inclusive, at Screening. 3. Subjects are willing and able to travel to the study sites for all scheduled visits. 4. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the protocol restrictions and requirements (including travel).
Main Exclusion Criteria:	1. History or presence of photodermatoses other than EPP. 2. Subjects who are unwilling or unable to go outside during daylight hours (e.g., between 1 hour post sunrise and 1 hour pre-sunset) during the study. 3. Presence of clinically significant hepatobiliary disease based on LFT values at Screening. 4. Subjects with AST, ALT, ALP ≥3.0 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN at Screening. 5. Subjects with or having a history (in the last 2 years) of excessive alcohol intake in the opinion of the Investigator.

	6. History or presence of melanoma and/or atypical nevus at Screening. 7. History of familial melanoma (defined as having 2 or more first-degree relatives, such as parents, sibling and/or child). 8. History or presence of pre-malignant skin lesion, squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions. 9. History or presence of psychiatric disease judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subjects. 10. Presence of clinically significant acute or chronic renal disease based upon the subject's medical records including hemodialysis; and a serum creatinine level of greater than 1.2 mg/dL or a glomerular filtration rate (GFR) <60 ml/min. 11. Presence of any clinically significant disease or laboratory abnormality which, in the opinion of the Investigator, can interfere with the study objectives and/or safety of the subjects. 12. Pregnancy or lactation. 13. Females of child-bearing potential and male subjects with partners of child-bearing potential unwilling to use adequate contraception measures as described in the protocol. 14. Treatment with phototherapy within 3 months before Randomization (Visit 2). 15. Treatment with afamelanotide within 3 months before Randomization (Visit 2). 16. Treatment with cimetidine within 4 weeks before Randomization (Visit 2). 17. Treatment with antioxidant agents at doses which, in the opinion of the Investigator, may affect study endpoints (including but not limited to beta-carotene, cysteine, pyridoxine) within 4 weeks before Randomization (Visit 2). 18. Chronic treatment with prescription-based analgesic agents including but not limited to opioids and opioid derivatives such as morphine, hydrocodone, oxycodone or their combination with other analgesics or non-steroidal anti-inflammatory drug (NSAID, as Percocet and Vicodin-like prescription drugs) within 4 weeks before Randomization (Visit 2). 19. Treatment with any drugs or supplements which, in the opinion of the Investigator, can interfere with the objectives of the study or safety of the subjects. 20. Previous exposure to MT-7117. 21. Previous treatment with any investigational agent within 12 weeks before Screening OR 5 half-lives of the investigational product (whichever is longer). 22. [redacted]

	[redacted]
Study Restrictions **Life Style Change and Restricted Medication**	1. Female subjects of child-bearing potential or male subjects with partners of child-bearing potential must use appropriate birth control from the Screening visit (for female subjects) or the first dose of study medication (for male subjects) until 3 months after the last dose of study medication. 2. [redacted] 3. Subjects must not take any prescribed or non-prescribed systemic or topical treatment (including sunscreen containing zinc oxide, herbal remedies, or supplements) with known potential to have an effect on phototoxity, photosensitivity in EPP, and/or increased pigmentation during the study. Such treatments include, but not limited to afamelanotide, cimetidine, beta-carotene, cysteine, pyridoxine, cholestyramine, and chronic treatment with centrally acting analgesic agents (including opioids and opioid derivatives).
Endpoints:	**Primary Efficacy Endpoint:** 1. Change from baseline in average daily time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 16 (Visit 8). To calculate the average daily duration, a 14-day window on or before a visit/time-point (Week 2, 4, 6, 8, 10, 12, 14, and 16) will be used. For baseline, a 14-day window before Day one will be used. A 14-day window will be applied to similar situations for other efficacy endpoints. **Secondary Efficacy Endpoints:** 1. Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms at Week 16. 2. Change from baseline in average daily mean duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. The daily mean duration is considered as multiple periods of sunlight exposure in each day and measurable by sum of duration of each period divided by number of periods. 3. Total number of sunlight exposure episodes with prodromal symptoms

	during 16-week double-blind treatment period. 4. The average daily mean intensity of the subject's prodromal symptoms during 16-week double-blind treatment period. 5. Change from baseline in average daily duration (minutes) of prodromal symptoms during 16-week double-blind treatment period. 6. Change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments. Average of 6 skin segments for the change from Baseline and % change from baseline in melanin density at Week 8, 16, and 22. 7. Total number of pain events during 16-week double-blind treatment period.
Endpoints (Continued):	**Other Efficacy Endpoints:** 1. Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms. 2. Total time (hours) during 16-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. 3. Total number of days subject is exposed to sunlight for any duration between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms during 16-week double-blind treatment period. 4. Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset on Saturday without prodromal symptoms at Week 16. 5. Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 16. 6. The average daily mean intensity of the subject's pain events during 16-week double-blind treatment period. 7. Change from baseline in average daily duration (minutes) of pain events during 16-week double-blind treatment period. 8. Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity in PROMIS 57. 9. Patient Global Impression of Change (PGIC) and Patient Global Impression of Change_2 (PGIC_2). 10. Quality of life and meaningful clinical benefit of MT-7117 using the exit interview questionnaire. **Safety Endpoints**: 1. Treatment-emergent adverse events (AEs) (including serious adverse events and adverse events of special interest [AESIs]). 2. Physical examination. 3. Vital signs (blood pressure, pulse rate, and body temperature). 4. Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin). 5. 12-lead ECG at Baseline and EOT.

	6. 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. **Pharmacokinetic Endpoints:** Assessment of plasma PK: Plasma concentrations of MT-7117 will be measured at protocol scheduled visits. **Exploratory Endpoints:** 1. Biomarker assessments using skin biopsy samples. 2. PGx analysis including MC1R, with SNPs. 3. Porphyrin and protoporphyrin levels.
Statistical Methods:	**Sample Size Consideration:** The sample size for this study is not based on a formal statistical calculation since this is a clinical study for a rare disease. However, a sample size of 34 subjects per treatment group is considered to be adequate to meet the objectives of the study. **Analysis Populations:** 1. Safety population: includes all randomized subjects who received at least 1 dose of study medication. 2. Intent-to-treat (ITT) population: includes all randomized subjects who received at least 1 dose of study medication and who have at least 1 post-baseline efficacy assessment. 3. Per-protocol (PP) population: includes all ITT subjects who do not have any major protocol violations and complete Week 16 (the end of double-blinded treatment period). 4. PK population: includes all randomized subjects who receive at least 1 dose of study medication and who have at least 1 post-dose value of plasma concentration time point to be included in the PK analysis without important protocol deviations which may affect the PK of study medication. **Statistical Methods:** A Statistical Analysis Plan (SAP) containing details of all the analyses and outputs will be prepared and approved before the study database lock. The ITT population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population and PK assessments will be performed on the PK population. Unless otherwise specified, the baseline values will be the last non-missing value before receiving the first dose of study medication. Baseline for an efficacy endpoint based on sunlight exposure time will be the mean of the daily value of the endpoint in a 14-day window before Day 1. Similarly, for this endpoint, their values at each post baseline visits (Week 2, 4, 6, 8, 10, 12, 14, 16, and 22) are the mean of the daily value of the endpoint in a 14-

	day window on or before the visit. To calculate the average daily duration, a 14-day window on or before visit/time points (Week 2, 4, 6, 8, 10, 12, 14, and 16) will be used. Continuous endpoints will be summarized with the descriptive statistics (the number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages. All statistical tests will be 2-sided with 5% significance level. Point estimates of treatment differences will be provided with 2-sided 95% confidence intervals (CIs) where applicable. As this trial is exploratory in nature, no adjustments for multiplicity will be made. The primary treatment comparisons of interest are 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 16 (Visit 8). To assess the treatment effect at Week 16, 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 and 16 will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed categorical terms for treatment, randomization strata (the baseline average daily sunlight exposure time without prodromal symptoms (≤30 min or >30 min)), visit, and treatment by visit interaction together with continuous covariate terms for 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 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), other variance covariance matrices such as autoregressive [AR(1)] correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, adjusted (least squares [LS]) means and standard errors will be produced by treatment and visit. Difference in adjusted means at each visit (each MT-7117 dose vs. placebo) with standard errors, 95% CIs and associated P values will also be produced. All available data from all subjects will be used in the primary analysis without any imputation. A supportive analysis will be performed at the same way for the primary endpoints using the per-protocol set (PPS). Analyses for other endpoints/details including secondary efficacy endpoints, safety assessments, pharmacokinetic

	assessments and exploratory endpoints will be included into the protocol body text and SAP.

1. INTRODUCTION

MT-7117 is a novel synthetic, orally-administered, non-peptide small molecule, which acts as an agonist of melanocortin-1 receptor (MC1R) with a potential for being effective in the prevention of phototoxicity in erythropoietic protoporphyria (EPP) patients.

MC1R is a member of the G-protein-coupled receptors superfamily expressed in cutaneous and hair follicle melanocytes. MC1R is activated by α-melanocyte-stimulating hormone (α-MSH) when under sunlight exposure. Activation of MC1R is positively coupled to the cyclic adenosine monophosphate signalling pathway and leads to a stimulation of melanogenesis and a switch from the synthesis of pheomelanins to the production of eumelanic pigments. MC1R regulates the amount and type of pigment production and is a major determinant of skin phototype and sensitivity to ultraviolet light induced damage[1)]. In addition, activation of MC1R enhances DNA repair, upregulates antioxidant enzymes, reduces production of pro-inflammatory cytokines, and minimises the protoporphyrin-mediated damage and resulting pain in EPP patients[2)]. The results of pharmacological and pharmacokinetic (PK) studies *in vitro* and *in vivo*, suggested that MT-7117 has melanogenic and anti-inflammatory effects.

Mitsubishi Tanabe Pharma Corporation (MTPC) is developing MT-7117 for the treatment of EPP. Since MT-7117 is an investigational medication, and its safety profile in humans has not yet been fully investigated, all subjects receiving MT-7117 will be closely monitored. Further information can be found in the MT-7117 Investigator's Brochure[3)].

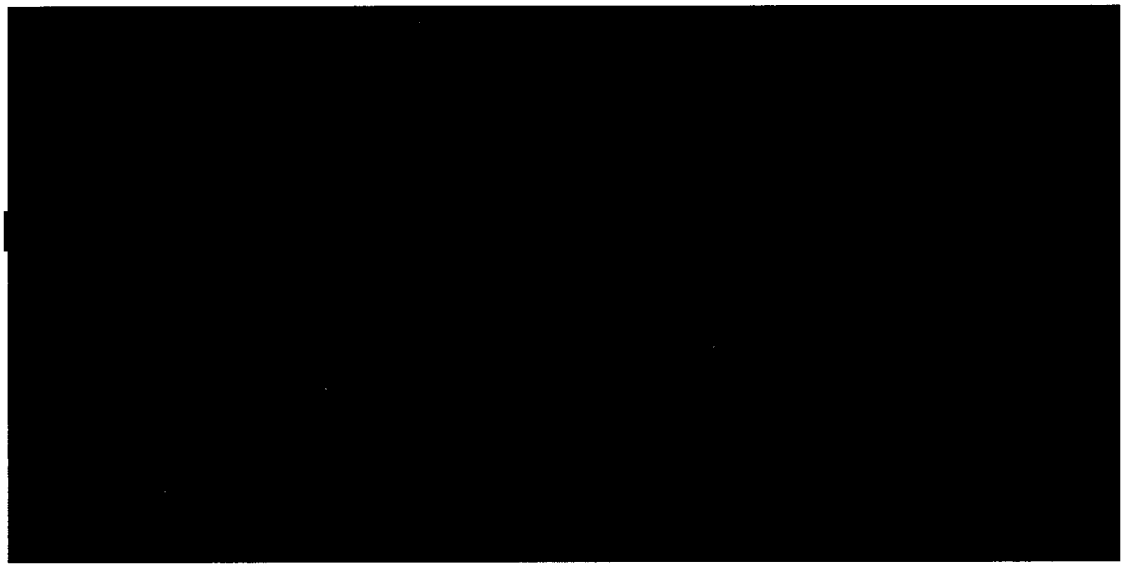
EPP is an inherited disorder of the heme metabolic pathway characterised by accumulation of protoporphyrin in blood, erythrocytes, and tissues and cutaneous manifestations of photosensitivity. EPP can result either from mutations of the ferrochelatase gene, or less commonly the aminolevulinic acid synthase-2 gene. It usually manifests in early infancy on first exposure to sunlight. The protoporphyrin molecule absorbs light radiation in a range of wavelengths from 320 to 595 nm. The absorption of these wavelengths increases the energy content of the protoporphyrin molecule and enables the excess energy to be transferred to oxygen, resulting in a reactive oxygen species. Oxygen species generation may injure tissues by complement activation and mast cell degranulation phenomena that explain the vasodilatation and edema components of the skin photosensitivity reactions in EPP patients. Photosensitivity is the main symptom of EPP and it is manifested, upon exposure of uncovered skin areas to sunlight, by acute cutaneous symptoms such as stinging, burning and severe pain. With prolonged exposure to sunlight, patients may also develop erythema, cutaneous edema, and petechiae. Photosensitivity has a significant impact on the quality of life of EPP patients, as it leads to chronic avoidance of both long-wave radiation and visible light resulting in profound decrease of social activity[4)]. Approximately 3% of patients with EPP develop liver manifestations[5)]. EPP is a lifelong disorder whose prognosis depends on the evolution of the hepatic disease[6)].

Few epidemiological studies of EPP exist. EPP is a rare disease characterised by a worldwide geographical distribution with varying prevalence (prevalence ranging between

1:75,000 [The Netherlands] and 1:200,000 [Wales]). According to existing data EPP starts from birth and males and females are equally affected[4].

There is no recognized standard of care for EPP in the USA. EPP is primarily managed by a preventative approach, which consists of avoidance of sun exposure (long-wave radiation and visible light). The use of adequate clothing (hats, glasses, gloves) and sunscreens is also advisable. Oral antioxidants such as beta-carotene and cysteine are also used, however their efficacy remains questionable. EPP patients with severe liver complications may require liver transplantation[5].

1.1 Non-clinical Pharmacology



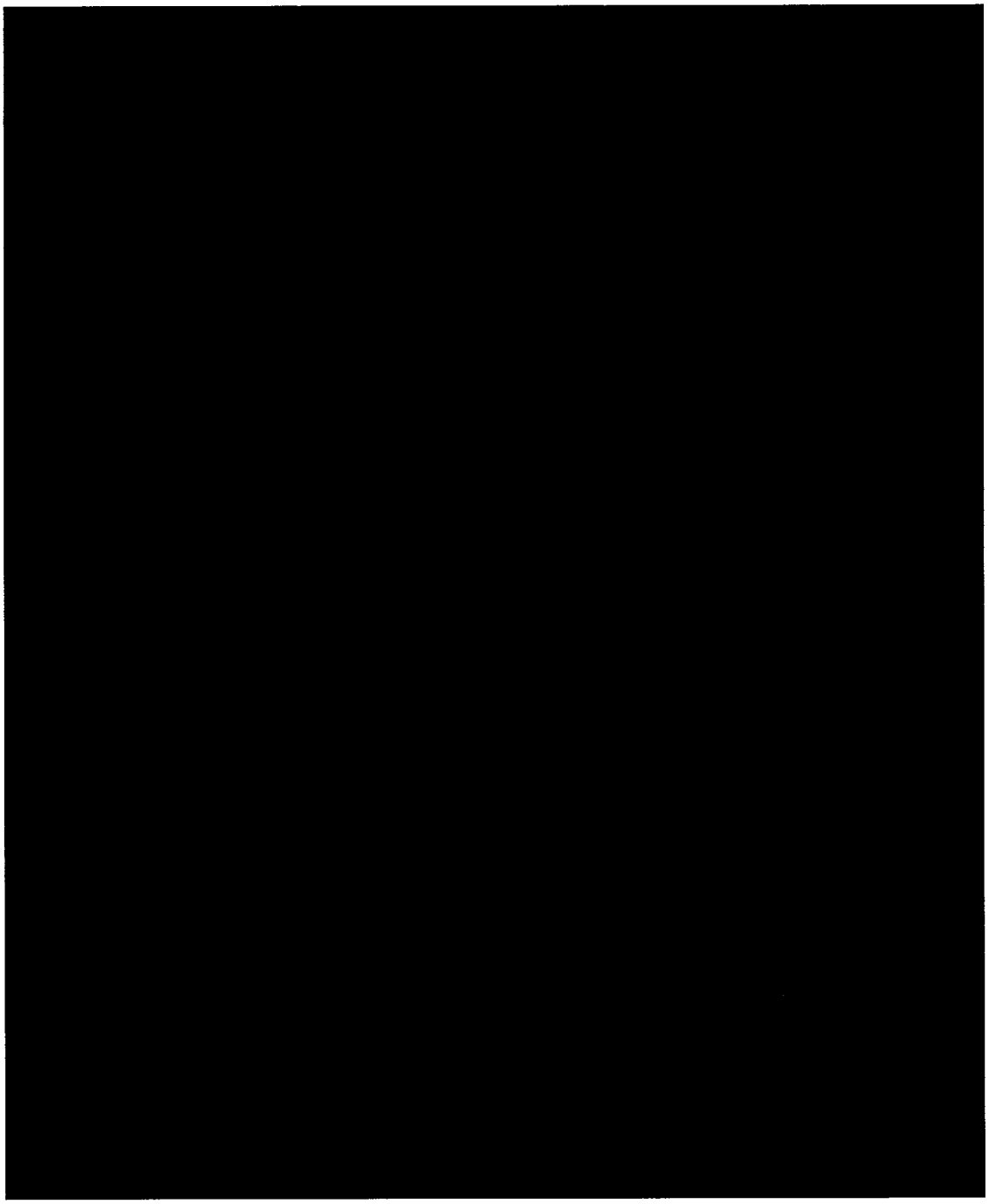
1.2 Non-clinical Safety Pharmacology

1.3 Non-clinical Pharmacokinetics

[redacted]

1.4 Non-clinical Toxicology

[redacted]



1.5 Clinical Studies

A first in human Phase I study (MT-7117-E01), evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of

MT-7117 in healthy subjects, has completed dosing and data are available. The study was divided into eight parts; Part A: single ascending doses, Part B: suspension food effect, Part C: tablet food effect, Part D: gender effect, Part E: multiple ascending doses, Part F: ethnicity effect (Black/Afro-Caribbean subjects), Part G: ethnicity effect (Japanese subjects) and Part H: age effect. A total of 96 healthy volunteers received single oral doses of MT-7117 or placebo in 12 cohorts (dose range [redacted] to [redacted] and 48 healthy volunteers received multiple oral doses (dose range [redacted] to [redacted] for 14 days) of MT-7117 or placebo in 4 cohorts. All volunteers were male except for Part D in which a cohort of 8 female subjects were administered a single dose of [redacted] MT-7117 or placebo.

Single oral doses of MT-7117 did not cause any safety concerns in healthy Caucasian male subjects at dose levels of [redacted] to [redacted] in the fasted state, and at a dose level of [redacted] in the fed state. In addition, single doses of [redacted] MT-7117 were well tolerated in healthy Caucasian female, Black/Afro-Caribbean, Japanese and elderly Caucasian male subjects. Following multiple oral doses of MT-7117 up to [redacted] for 14 days, the most frequently reported treatment-emergent adverse events (TEAEs) were skin-related; including formation of new freckles, formation of new lentigines, formation of new nevi, darkening and increase in size of pre-existing nevi, increased skin tan, darkening of facial hair and increased color of tattoos. Lips and glans penis skin were involved in these reports in addition to the body skin. There were signs of reversibility of these skin events during the follow-up period. These skin events were considered to be related to the pharmacological effects of the study medication.

Dose-proportional increases in systemic exposure based on AUC and C_{max} were observed over the single dose range of [redacted] to [redacted] Following multiple doses at [redacted], [redacted], [redacted], and [redacted] MT-7117 was rapidly absorbed with median t_{max} values ranging from 4 to 5 hours post-dose on both Day 1 and Day 14. Mean $t_{1/2}$ values ranged from 6.28 to 15.55 hours on Day 1 and 10.56 to 18.97 hours on Day 14. Systemic exposure to MT-7117 in plasma, based on calculation of AUC and C_{max}, appeared to increase in a slightly more than dose-proportional manner over the [redacted] to [redacted] dose range. Steady-state was generally reached by 5 days of multiple dosing.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

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

2.1.3 Exploratory Objectives

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

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoint

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

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

2.2.2 Secondary Efficacy Endpoints

- Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms at Week 16.
- Change from baseline in average daily mean duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. The daily mean duration is considered as multiple periods of sunlight exposure in each day and measurable by sum of duration of each period divided by number of periods.

- Total number of sunlight exposure episodes with prodromal symptoms during 16-week double-blind treatment period.
- The average daily mean intensity of the subject's prodromal symptoms during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during 16-week double-blind treatment period.
- The change from baseline and % change from baseline in melanin density at Week 8, 16, and 22 by skin segments. Average of 6 skin segments for the change from Baseline and % change from baseline in melanin density at Week 8, 16, and 22.
- Total number of pain events during 16-week double-blind treatment period.

2.2.3 Other Efficacy Endpoints

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms.
- Total time (hours) during 16-week double-blind treatment period in duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total number of days subject is exposed to sunlight for any duration between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset on Saturday without prodromal symptoms at Week 16.
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 16.
- The average daily mean intensity of the subject's pain events during 16-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of pain events during 16-week double-blind treatment period.
- Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity in PROMIS 57.
- Patient Global Impression of Change (PGIC) and Patient Global Impression of Change_2 (PGIC_2).
- Quality of life and meaningful clinical benefit of MT-7117 using the exit interview questionnaire.

2.2.4 Safety Assessments

- Treatment-emergent adverse events (AEs) (including serious adverse events [SAEs] and adverse events of special interest [AESIs]).
- Physical examination.
- Vital signs (blood pressure, pulse rate, and body temperature).

- 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.

2.2.5 Pharmacokinetic Assessments

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

2.2.6 Exploratory Endpoints:

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

3. STUDY DESIGN

3.1 Overall Study Design

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

This study is being conducted without regard to seasonality.

The study design is illustrated in Figure 3.1-1.

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

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

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

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

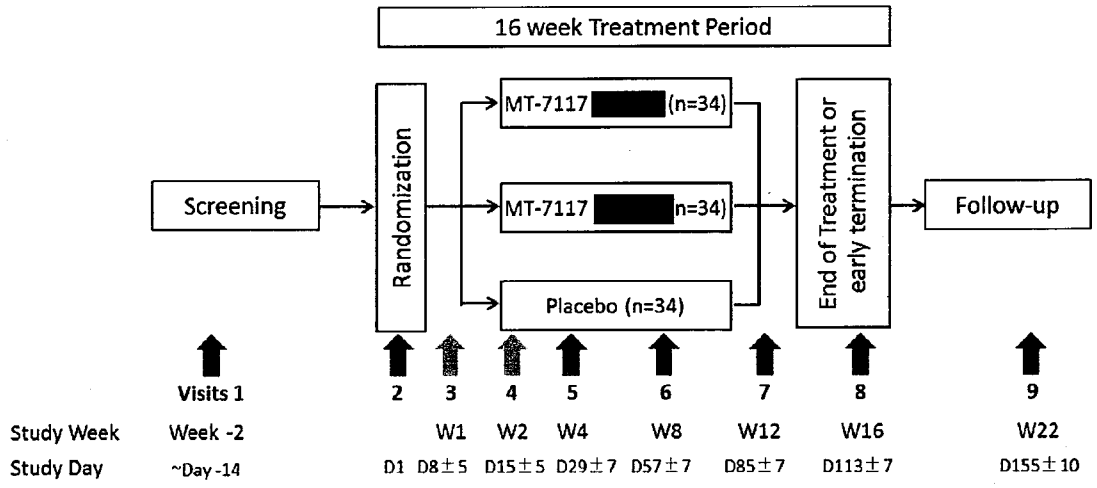


Figure 3.1-1 Study Design Schematic

3.2 Rationale for Study Design and Treatment Regimens

The objectives of this study are to obtain efficacy, tolerability, and safety data for the selected two doses [redacted] and [redacted] day) of MT-7117 and placebo when administered to subjects with EPP over a 16-week treatment period. A standard randomized, placebo controlled, double-blind treatment allocation is considered appropriate in order to obtain unbiased results in this study. Safety and PK/pharmacodynamic effects will be evaluated based upon these comparable data from the Phase I, MT-7117-E01 study.

Abnormal biochemical parameters related to the hepatic function were observed in rats and monkeys. In MT-7117-E01 human study, in subjects receiving 14 days of study drug, treatment emergent transaminase elevations were reported in 6/36 (17%) subjects receiving MT-7117 and 2/12 (17%) subjects receiving placebo. Of the six subjects receiving MT-7117 for 14 days reporting treatment emergent transaminase elevations, 4 had elevated baseline transaminase values. Therefore, frequent assessments of liver function markers are performed in this study.

The 16-week treatment period is considered a sufficient duration for evaluation of the efficacy and tolerability of MT-7117 for this study. Subjects will attend a follow-up visit 6 weeks after the end of treatment (or early termination) which is considered a sufficient duration to evaluate pigmentation recovery and safety of subjects. For the primary and secondary endpoints, the effect of MT-7117 on the duration of sunlight exposure will be measured using a sunlight exposure diary. Melanin density assessments are safe and routinely used in clinical studies of skin disorders and will be used in this study to assess the effect of MT-7117 on pigmentation. The effect of MT-7117 on quality of life will be assessed using questionnaires. The exit interview questionnaire will measure the clinical

benefit of MT-7117 and perspectives of quality of life.

3.3 Risk:Benefit Statement

MT-7117 is an investigational drug, and its safety profile in humans has not yet been fully investigated. Therefore, all subjects will be closely monitored.

In embryo-fetal development study in mice, the total incidence of fetuses with skeletal anomalies was increased at [redacted], the lethal dose for adult female mice, with increased incidence of fused rib and fused sternebrae. Female subjects of child-bearing potential and male subjects with partners of child-bearing potential participating in the study will be required to use adequate contraception as defined in Section 4.7.1.

The Sponsor will undertake all reasonable measures, including thorough screening and safety monitoring procedures, to minimize the risk to subjects. Due to the potential of MT-7117 to increase liver function markers, liver function markers will be monitored at all planned study visits and assessment of AEs related to elevation of liver function markers and liver injury will be conducted. Additionally, subjects will be instructed to immediately stop study treatment if they meet any of the withdrawal criteria listed in Section 4.5.

3.4 Rationale for Dose Selection

The current study will investigate the efficacy and safety, of MT-7117 in subjects with EPP. In the MT-7117-E01 human healthy volunteer study, single doses up to [redacted] and multiple doses of up to [redacted] over 14 days in healthy male subjects, and single doses of [redacted] in healthy female subjects have been shown to be safe. Some reversible increases in skin pigmentation, consistent with the expected pharmacology, were noted following repeat dosing and appeared to show a dose-related trend. No SAEs occurred during Study MT-7117-E01. In summary, the proposed dose levels of [redacted] and [redacted] of MT-7117 once daily pose no appreciable safety concerns and are supported by previous human and animal experience.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a protocol waiver system for eligibility criteria.

4.1 Number of Subjects

A total of approximately 102 subjects are planned to be randomized in this study (34 subjects in each treatment group).

4.2 Recruitment Methods

A sufficient number of subjects will be screened to ensure the planned sample size will be achieved. Each subject will be screened according to the criteria described in Sections 4.3 and 4.4. Only subjects who are eligible for the study will be randomized.

4.3 Inclusion Criteria

A subject will be eligible for enrolment in the study if ALL of the following criteria apply:

1. Subjects provided written informed consent to participate.
2. Male and female subjects with a confirmed diagnosis of EPP based on medical history, aged 18 years to 75 years, inclusive, at Screening.
3. Subjects are willing and able to travel to the study sites for all scheduled visits.
4. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the protocol restrictions and requirements (including travel).

4.4 Exclusion Criteria

A subject will NOT be eligible for this study if ANY of the following criteria apply:

1. History or presence of photodermatoses other than EPP.
2. Subjects who are unwilling or unable to go outside during daylight hours (e.g., between 1 hour post sunrise and 1 hour pre-sunset) during the study.
3. Presence of clinically significant hepatobiliary disease based on LFT values at Screening.
4. Subjects with AST, ALT, ALP $\geq$3.0 $\times$ upper limit of normal (ULN) or total bilirubin >1.5 $\times$ ULN at Screening.
5. Subjects with or having a history (in the last 2 years) of excessive alcohol intake in the opinion of the Investigator.
6. History or presence of melanoma and/or atypical nevus at Screening.
7. History of familial melanoma (defined as having 2 or more first-degree relatives, such as parents, sibling and/or child).
8. History or presence of pre-malignant skin lesion, squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions.

9. History or presence of psychiatric disease judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subjects.
10. Presence of clinically significant acute or chronic renal disease based upon the subject's medical records including hemodialysis; and a serum creatinine level of greater than 1.2 mg/dL or a glomerular filtration rate (GFR) <60 ml/min.
11. Presence of any clinically significant disease or laboratory abnormality which, in the opinion of the Investigator, can interfere with the study objectives and/or safety of the subjects.
12. Pregnancy or lactation.
13. Females of child-bearing potential and male subjects with partners of child-bearing potential unwilling to use adequate contraception measures as described in the protocol.
14. Treatment with phototherapy within 3 months before Randomization (Visit 2).
15. Treatment with afamelanotide within 3 months before Randomization (Visit 2).
16. Treatment with cimetidine within 4 weeks before Randomization (Visit 2).
17. Treatment with antioxidant agents at doses which, in the opinion of the Investigator, may affect study endpoints (including but not limited to beta-carotene, cysteine, pyridoxine) within 4 weeks before Randomization (Visit 2).
18. Chronic treatment with prescription-based analgesic agents including but not limited to opioids and opioid derivatives such as morphine, hydrocodone, oxycodone or their combination with other analgesics or non-steroidal anti-inflammatory drug (NSAID, as Percocet and Vicodin-like prescription drugs) within 4 weeks before Randomization (Visit 2).
19. Treatment with any drugs or supplements which, in the opinion of the Investigator, can interfere with the objectives of the study or safety of the subjects.
20. Previous exposure to MT-7117.
21. Previous treatment with any investigational agent within 12 weeks before Screening OR 5 half-lives of the investigational product (whichever is longer).
22. [redacted]

    a. [redacted]

    b. [redacted]

    d. [redacted]

4.5 Withdrawal of Individual Subjects

A subject will be withdrawn from study if ANY of the following criteria are met:

1. The subject requests to voluntarily withdraw from further participation in study.
2. The subject is significantly noncompliant with the protocol.
3. Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, e.g.,

    a. The subject experiences intolerable AEs or SAEs.
    b. The subject has clinically significant changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result.
    c. If there are any clinically significant adverse findings from post-baseline nevi evaluation, subjects will not be allowed to continue taking study medication (see Section 6.9.4). If biopsy findings are benign, subject may reinitiate study treatment based on investigators discretion.
    d. Development of any clinically significant liver dysfunction, as follows:

        i. ALT or AST >6 x ULN.
        ii. ALT or AST >4 x ULN for more than 2 weeks.

            a) Elevated total bilirubin >2 × ULN and ALT or AST >2 x ULN or
            b) Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia >5%) with concomitant ALT or AST values >3 × ULN.

Subjects (meeting above criteria) do not require withdrawal if alternative etiology is identified on discussion with the Study Medical Monitor.

Subjects meeting above criteria (with or without alternative etiology) should be reported as hepatic AE of special interest (AESI) (see Section 8.3).

These subjects will be discontinued from treatment but may be managed on study per the Investigator's discretion and followed per protocol (see Section 8.6). In addition, a subject may be withdrawn from treatment at any time for reason(s) other than those listed here.

If a subject is discontinued prematurely from the treatment or the study, the date the subject is withdrawn and the reason for withdrawal will be recorded on the site source documents and in the electronic Case Report Form (eCRF). Subjects who withdraw or are withdrawn from study treatment should be encouraged to complete all study visits and study procedures as outlined in the protocol.

In case of permanent discontinuation from study, the end of treatment and follow-up visit assessments should be performed, as completely as possible (Sections 5.3.2.7 and 5.3.3, respectively). Unresolved AEs and SAEs will be followed up on according to Section 8.10.

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). Return of unused medication and any other materials (e.g., diary) will be performed by courier where allowed.

In the event that a subject elects not to return to the study site for the end of treatment or Follow-up visit, the Investigator must make every effort to contact the subject to review/capture all AEs, assess dosing compliance, review concomitant medication and make every effort to complete all end of study assessments.

Subjects withdrawn from the study following randomization onto double-blind treatment may not re-enter the study. Subjects withdrawn from treatment may remain on study and continue with study procedures off treatment based on the Investigators clinical discretion.

4.6 Study-stopping Criteria

The study may be terminated by the Sponsor at any time upon becoming aware of data that could compromise the safety and/or well-being of subjects, or for any other reason it deems appropriate. Subjects may be withdrawn from treatment and remain on study.

4.7 Lifestyle Restrictions

Subjects must adhere to the following restrictions:

1. Follow study attendance guidelines.
2. Follow study physical activity and sun exposure guidelines.
3. Female subjects of child-bearing potential or male subjects with partners of child-bearing potential must use birth control from the screening visit (for female subjects) or the first dose of study medication (for male subjects) until 3 months after the last dose of study medication.
4. [redacted]
5. Subjects must not take any prescribed or non-prescribed systemic or topical treatment (including sunscreen containing zinc oxide, herbal remedies or supplements) with known potential to have an effect on phototoxicity, photosensitivity in EPP, and/or increased pigmentation during the study. Such treatment includes, but not limited to afamelanotide, cimetidine, beta-carotene, cysteine, pyridoxine, cholestyramine, and chronic treatment with centrally acting analgesic agents (including opioids and opioid derivatives).

These restrictions are described in more detail in the following sections, and in Section

14.1, a complete list of prohibited concomitant medications is provided.

4.7.1 Subject Contraception

Female subjects of child-bearing potential and male subjects with partners of child bearing potential must be willing and able to use a highly effective method of birth control (i.e., contraceptive measure with a failure rate of <1% per year), in conjunction with male barrier contraception (i.e., male condom with spermicide) for the duration of the study, from the Screening visit until 3 months after the last dose of study medication. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of study medication until 3 months after the last dose of study medication.

Highly effective methods of contraception include:

1. Placement of an intrauterine device or intrauterine system in women.
2. Established use of oral, injected, or implanted hormonal methods of contraception associated with inhibition of ovulation.
3. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.)
4. Bilateral tubal ligation.
5. True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
6. Male subjects with partners of child-bearing potential must use a barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable second methods of female partner contraception include:

    a. Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
    b. Cap, diaphragm, or sponge with spermicide.
    c. Male subjects must not donate sperm for the duration of the study, from the time of the first dose of study medication until 3 months after the last dose of study medication.

Women are considered to be of child-bearing potential unless they meet one or more of the following criteria as documented by the Investigator:

1. Post-menopausal for at least 1 year, confirmed by follicle stimulating hormone (FSH) assessment (>40 mIU/mL).
2. Documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
3. Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

4.7.2 Physical Activity and Subject Sun Exposure

Subjects will be encouraged to go outside during daylight hours (e.g., between 1 hour post sunrise and 1 hour pre-sunset) during the treatment period by the investigators or designated study site staff. Time outside should be correlated with or limited by the onset of prodromal symptoms. Subjects will be asked to make note of time period spent outside or until the onset of prodromal symptoms in the sunlight exposure diary. Outside exposure is considered locations outside of a building such as the time riding in a car or train. Time next to a window indoors is not considered outside exposure.

Patients will be informed by the investigator regarding the objectives of the study and the importance of the patient seeking some level of direct sun exposure on a daily basis. This discussion will include clarification that the goal is not to intentionally induce phototoxic reactions, but for the subject to spend enough time to generate some level of prodromal symptoms. The goal of the study is to determine whether the study drug has an effect on increasing the symptom-free time in the sun and/or reducing the duration or intensity of symptoms associated with sun exposure. Once randomized, no subject will be coerced into direct sun exposure that would induce phototoxicity, or discontinued for noncompliance if the subject expresses a concern for their own safety and well-being.

5. STUDY PLAN

5.1 Study Time and Events Schedule

Study assessments and corresponding event schedules are summarized in the time and events schedule (Table 5.1-1).

Table 5.1-1 Schedule of Assessments

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

Study Period	**Screening**	**Double-blind Treatment**							**Follow-up**
Visit Number	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3[f]**	**Visit 4[f]**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[n] (EOT)**	**Visit 9[o] (EOS)**
Study Week	**Week -2**		**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 22**
Study Day ± Window	**~Day –14[a]**	**Day 1**	**Day 8±5**	**Day 15±5**	**Day 29±7**	**Day 57±7**	**Day 85±7**	**Day 113±7**	**Day 155±10**
medication									
Medication accountability					X	X	X	X	
Subject Questionnaire for study medication[j]								X	
PROMIS-57		X				X		X	X
PGIC						X		X	X
PGIC_2									X
Sunlight exposure diaries[k]	←								→
Melanin density evaluation		X				X		X	X
In-clinic sunlight exposure test[l]		X						X	
Nevi evaluation[m]		X				X		X	(X)
Exit interview Questionnaire[p]									X
Concomitant medication	←								→
Adverse events	←								→

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.2 Subject Informed Consent

Before performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the Informed Consent Form (ICF), as described in Section 11.2.1.

5.3 Description of Study Phases

5.3.1 Screening (Visit 1)

Screening assessments will be performed in clinic during Screening period with all results reviewed prior to Randomization.

Written informed consent will be obtained before any screening procedures are performed. The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Written informed consent.
- Inclusion/exclusion criteria.
- Medical history.
- Demography.
- Complete physical examination (including height and body weight).
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Plasma porphyrin and erythrocyte protoporphyrin sample collection.
- Serum pregnancy test (for female subjects of child-bearing potential only).
- Fitzpatrick skin type assessment.
- In-clinic sunlight exposure test: Conduct a formalized baseline collection of the subject's time to onset of 1st prodromal symptom in sun-exposed setting (e.g. preferably outside or by window) using timer (as weather condition may vary this procedure may be conducted any time prior to first dose of study medication).
- Provide sunlight exposure diary and educate subjects in use.
- Nevi evaluation (baseline nevi evaluation will be performed at any time during the screening period before randomization).
- AE and prior medication recording.

5.3.2 Double-blind Treatment (Visits 2 - 8)

5.3.2.1 Visit 2 (Randomization Visit, Day 1)

Eligible subjects who continue to meet protocol eligibility will proceed to randomization and dosing. The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Verify inclusion/exclusion criteria.
- Medical history.
- Abbreviated physical examination (including body weight).
- 12-lead ECG.

- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test (for female subjects of child-bearing potential only).
- Blood sampling for PK analysis (pre-dose).
- Optional pharmacodynamics skin biopsy for exploratory analysis.
- PROMIS-57 questionnaire.
- Review sunlight exposure diary (re-educate subject if necessary).
- Melanin density evaluation as measured by spectrophotometer.
- Nevi evaluation (baseline nevi evaluation will be performed at any time during the screening period before randomization).
- Blood sample for PGx (if applicable).
- AE and concomitant medication recording.
- In-clinic sunlight exposure test: If not collected at Screening Visit 1, conduct a formalized baseline collection of the subject's time to onset of 1st prodromal symptom in sun-exposed setting (e.g. preferably outside or by window) using timer.
- Randomization and dispensing of MT-7117 or placebo.

5.3.2.2 Visit 3 (Week 1, Day 8±5)

Subjects will undergo mobile laboratory sample collection and blood samples will be taken and the following assessments will be performed by the central laboratory (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Liver function marker evaluations (ALT, AST, GGT, ALP, direct and total bilirubin).

5.3.2.3 Visit 4 (Week 2, Day 15±5)

Subjects will undergo mobile laboratory sample collection and blood samples will be taken and the following assessments will be performed by the central laboratory (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Liver function marker evaluations (ALT, AST, GGT, ALP, direct and total bilirubin).

5.3.2.4 Visit 5 (Week 4, Day 29±7)

The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Abbreviated physical examination (including body weight).
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test (for female subjects of child-bearing potential only).
- Blood sampling for PK analysis.
- Dispensing of MT-7117 or placebo.
- Medication accountability.
- Review sunlight exposure diary (re-educate subject if necessary).
- AE and concomitant medication recording.

5.3.2.5 Visit 6 (Week 8, Day 57±7)

The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Abbreviated physical examination (including body weight).
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Plasma porphyrin and erythrocyte protoporphyrin sample collection.
- Urine pregnancy test (for female subjects of child-bearing potential only).
- Blood sampling for PK analysis.
- Dispensing of MT-7117 or placebo.
- Medication accountability.
- PROMIS-57 questionnaire.
- PGIC.
- Review sunlight exposure diary (re-educate subject if necessary).
- Melanin density evaluation as measured by spectrophotometer.
- Nevi evaluation and biopsy (for any nevi of clinical concern to the dermatologist or other qualified site staff).
- AE and concomitant medication recording.
- Fitzpatrick skin type assessment.

5.3.2.6 Visit 7 (Week 12, Day 85±7)

The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Abbreviated physical examination (including body weight).
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test (for female subjects of child-bearing potential only).
- Blood sampling for PK analysis.
- Dispensing of MT-7117 or placebo.
- Medication accountability.
- Review sunlight exposure diary (re-educate subject if necessary).
- AE and concomitant medication recording.

5.3.2.7 Visit 8: End of Treatment Visit (Week 16, Day 113±7 or Early Termination)

Subjects will attend the end of treatment visit at Week 16 or early termination. The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Abbreviated physical examination (including body weight).
- 12-lead ECG.
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Plasma porphyrin and erythrocyte protoporphyrin sample collection.
- Urine pregnancy test (for female subjects of child-bearing potential only).

- Blood sampling for PK analysis (at the visit and 3 to 4 hours after the first PK sample collection [both post-dose]).
- Medication accountability.
- Subject Questionnaire for study medication.
- PROMIS-57 questionnaire.
- PGIC.
- Review sunlight exposure diary (re-educate subject if necessary).
- Melanin density evaluation as measured by spectrophotometer.
- Nevi evaluation and biopsy (for any nevi of clinical concern to the dermatologist or other qualified site staff).
- Optional skin biopsy for exploratory pharmacodynamics analysis.
- In-clinic sunlight exposure test: Perform a formalized collection of the subject's time to onset of 1st prodromal symptom in sun-exposed setting (e.g. preferably outside or by window) using timer.
- AE and concomitant medication recording.
- Fitzpatrick skin type assessment.

5.3.3 Follow-up (Visit 9, Week 22, Day 155±10)

Subjects will return to the study site for a follow-up visit at 6 weeks after end of treatment visit (Week 16 or early termination). The following assessments will be performed (please refer to Table 5.1-1 for details regarding the complete time and events schedule for this study):

- Abbreviated physical examination (including body weight).
- Vital signs (including sitting blood pressure, pulse rate, and oral body temperature).
- Routine laboratory evaluations (hematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test (for female subjects of child-bearing potential only).
- PROMIS-57 questionnaire.
- PGIC and PGIC_2.
- Review sunlight exposure diary.
- Melanin density evaluation as measured by spectrophotometer.
- Nevi evaluation (and biopsy for any nevi of clinical concern based on the opinion of the dermatologist or other qualified site staff).
- AE and concomitant medication recording.
- Exit interview questionnaire (The exit interview questionnaire can be assessed at Visit 9 or as a post study follow-up phone call or online survey.)

5.3.4 Post-study Access to Treatment

MT-7117 will not be available to subjects following completion or termination of the study, in accordance with the study information given to the subjects.

5.3.5 Unscheduled Visits

An unscheduled visit is defined as follows:

- Any visit to the Investigator site outside of the Protocol specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement

errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.
- Any visit to the mobile units outside of the Protocol specified time points when a repeated measurement of liver function markers is required (e.g., safety reasons, obvious measurement errors, measuring device failure, confirmation of out-of-range results).

Additional unscheduled samples for safety assessments may be performed at the discretion of the Investigator, if deemed necessary. All unscheduled visits and assessments performed during the visits will be recorded in the eCRF.

6. STUDY PROCEDURES

Procedures will be performed according to the time and events schedule (Table 5.1-1).

6.1 Informed Consent Form

The Investigator or designee will fully explain the nature of the study to subjects using the Institutional Review Board (IRB) approved ICF. When the subject agrees to participate in the study, the subject must voluntarily sign an ICF before the initiation of any study procedures. A copy of the signed and dated informed consent document will be given to the subject. The signed and dated original ICF will be retained by the Investigator. Informed consent will be obtained from all subjects. A subject cannot be entered the study until he or she has signed and dated the ICF.

The Investigator or designee is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information in a timely manner that may be relevant to the subject's willingness to continue his/her participation in the study.

Any information conveyed to the subject in advance of screening visit 1 used to recruit subject or enable travel arrangements require IRB/EC submission and approval per local requirement. Certain procedures outlined in this protocol are optional and are not required if subject opts out. These procedures include sample collection for PGx testing and skin biopsy assessment obtained for the noted exploratory endpoints (biopsy may be requested for safety if they arise via the post baseline Nevi assessments per the investigator judgement). For PGx testing, DNA and mRNA will be measured. These procedures will be performed only on subjects who specifically provided consent to undergo these optional procedures. Separate informed consent for PGx testing and skin biopsy will be required.

6.2 Demography

The following subject characteristics will be recorded at Screening: date of birth, sex, weight, height, ethnicity, and race.

6.3 Medical History

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

6.4 Prior and Concomitant Medication

Prior medications are defined as any medication taken before Screening.

Any prior medication, including prescription and over-the-counter medications, taken within 1 month before Screening will be recorded on the eCRF. Information recorded will

include: name of medication, dose, duration of and reason for use.

Concomitant medication is defined as any medication, other than study medication, which is taken during the study, 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.

6.5 Fitzpatrick Skin Type Assessment

A Fitzpatrick scale test[6)] will be completed at the times shown in the time and events schedule (Table 5.1-1). The results will be recorded in the source documents and the eCRF. The score for defining skin type will be recorded in the source documents. An example of the Fitzpatrick scale test is presented in Section 14.2 (Appendix 2).

6.6 Subject Questionnaire for Study Medication

Subject will be asked whether they receive active or placebo treatment at Week 16 or early termination (Visit 8). The results will be recorded in the source documents and the eCRF.

6.7 Efficacy Assessments

6.7.1 Primary Efficacy Endpoint

6.7.1.1 Sunlight Exposure Diary

The sunlight exposure diary will be completed on a daily basis from Screening to the follow-up visit by the subjects. An example of the sunlight exposure diary (extract) is presented in Section 14.3 (Appendix 3).

Subjects will record their sunlight exposure time in the sunlight exposure diary. For each sunlight exposure, they will record the presence, duration (onset time of the first symptom and recovery time) and severity of the prodromal symptoms. Pain, its severity and duration (onset time and recovery time) will also be recorded separately in the dedicated part of the diary. The severity of prodromal symptoms and pain will be measured using an 11-point Likert scale ranging from 0 to 10, with 0 indicating no symptom and 10 indicating greatest severity of symptom.

Subjects will be instructed to recognize the following photo-provoked symptoms as prodromal:

- Burning/hotness/heating up
- Tingling
- Itching/scratchy
- Stinging
- Others

Subject responses in the sunlight exposure diary will be used to investigate the primary

efficacy endpoint. The data from the diary will also be used for the secondary and other efficacy assessments.

Further details will be provided in a separate study reference manual, and statistical assessment methods for this study endpoint are described in Section 10.2.2.1.

6.7.2 Secondary and Other Endpoints

6.7.2.1 Melanin Density Evaluation

Sites will assign the unblinded personnel who will receive melanin density measurement training. Melanin density will be assessed at the times shown in the time and events schedule (Table 5.1-1) using a hand held spectrophotometer. The effect on pigmentation will be assessed in all subjects by measuring melanin density on 6 skin segments (forehead, left cheek, right inside upper arm, left medial forearm, right-hand side of abdomen, and left-hand side of buttock) as measured by spectrophotometer. The site will be required to successfully collect the data with specialized software and transfer to the designated data management entity.

Further details will be provided in a separate study reference manual.

6.7.2.2 Patient-reported Outcomes Measurement Information System Questionnaire

The PROMIS-57 questionnaire will be completed at the times shown in the assessment schedule (Table 5.1-1).

The PROMIS-57 assesses each of 7 domains with 8 questions per domain; physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference. The effect of treatment with MT-7117 on quality of life in subjects with EPP will be assessed by measuring the change in PROMIS-57 score (total and each domain).

An example of the PROMIS-57 questionnaire is presented in Section 14.4 (Appendix 4).

6.7.2.3 Patient Global Impression of Change and Patient Global Impression of Change_2

The PGIC is used to assess the subject's rating of overall improvement. Subjects rate their perceived change on a 7-point scale from 'a great deal better to 'no change'.

The PGIC will be completed at the times shown in the assessment schedule (Table 5.1-1). An example of the PGIC is presented in Section 14.5 (Appendix 5).

The PGIC_2 is also used to assess the subject's rating of overall improvement. Subjects rate their perceived change on a 7-point scale from 'very much improved' to 'very much worse'.[15)]

The PGIC_2 will be completed at the times shown in the assessment schedule (Table 5.1-1). An example of the PGIC_2 is presented in Section 14.5 (Appendix 5).

6.7.2.4 Exit Interview Questionnaire

The exit interview questionnaire is used to assess the subject's rating of quality of life and perspective on a clinically meaningful increased time in the sun without experiencing prodromal symptoms.

For some questions, subjects rate their perceived change on a 7 point scale from 'Very much better to 'Very much worse', or a simpler 3 point scale such as 'more XX', 'no change', or 'less XX', other questions will be drop-down choices. Questions about quality of life are evaluated using a 7 point scale from 'Not at all important (most negative is 1)' to 'Extremely important (most positive is 7)'.

The exit interview questionnaire will be completed at the time shown in the assessment schedule (Table 5.1-1). The exit interview can be assessed at Visit 9 or as a post study follow-up phone call or online survey. An example of the exit interview questionnaire is presented in Section 14.6 (Appendix 6).

6.7.2.5 In-Clinic Sunlight Exposure Test

In-clinic sunlight exposure test will be performed at the times shown in the assessment schedule (Table 5.1-1).

Site staff will lead subjects into a setting with sun-light exposure and subjects will be provided with a timer (e.g. preferably outdoors or near window) to collect the period of time it takes for the subject to experience the onset of the first prodromal symptom. Upon entry of the subject into the sunlight exposed setting, the timer will be started (as well as the time of day). Site staff will direct the subject to stop the timer upon the onset of the first sensation of prodromal symptoms. The time in minutes obtained from the time, as well as the time of day the assessment was performed, will be collected. This assessment should be performed in a manner that lends consistency to the amount of daylight exposure and/or intensity where feasible. Where weather conditions restrict the ability to capture this assessment, it will be so noted on the source and e-CRF. Further instructions will be outlined in the protocol procedures manual.

6.8 Pharmacokinetic Assessments

Blood samples will be collected by direct venipuncture in a suitable forearm vein. The actual date and time of each blood sample and the most recent dose date and time will be recorded in the source document and eCRF.

For each PK assessment, 1 blood sample of approximately 4 mL will be collected to ensure there is sufficient plasma for primary and contingency samples.

Sample handling details will be described fully in a separate document.

6.9 Safety Assessments

Please refer to Section 8 for details of AE management.

6.9.1 Physical Examination

The complete physical examination will consist of a routine assessment of major body systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, and 'other'.

The abbreviated physical examination will consist of a routine assessment of the following body systems: abdominal, cardiovascular, general appearance, and 'other'.

6.9.2 Vital Signs

The subject will undergo an assessment of blood pressure using a blood pressure recording device with an appropriate cuff size and with the subject in a sitting position. It is recommended that the subject rests for 5 minutes prior to this measurement. The same arm will be used for all measurements. Pulse and oral temperature will also be measured.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.9.3 Electrocardiogram

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in the supine position. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.9.4 Nevi Evaluation

Nevi will be assessed at the times shown in the time and events schedule (Table 5.1-1). Baseline nevi evaluation will be conducted at any time during the screening period before randomization. Nevi evaluation at Visit 9 will be performed based on the opinion of the Investigator or a dermatologist or other qualified site staff.

Nevi will be assessed locally by a visual full body examination performed by a dermatologist or other qualified site staff. Any subject with suspicious nevi of clinical concern will have treatment temporarily discontinued and be referred for further nevi evaluation (e.g., biopsy), as deemed necessary by the dermatologist or other qualified site staff. If there are any clinically significant adverse findings from the further nevi evaluation, subjects will not be allowed to continue taking study medication. The results will be recorded in the source documents and the eCRF.

Nevi assessment details will be fully described in a separate document.

6.9.5 Routine Laboratory Evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations according to the Schedule of Assessments (Table 5.1-1).

The specific laboratory parameters evaluated during the study are presented in Table 6.9-1.

6.9.5.1 Hepatic Markers

At Visits 3 and 4, subjects will undergo mobile laboratory collection to measure hematology (liver function) markers (ALT, AST, GGT, ALP, direct and total bilirubin). Blood samples for liver function markers will be shipped from mobile lab collection units to the central laboratory and the central laboratory will measure the liver markers.

6.9.5.2 Additional Laboratory Assessments

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with the Sponsor and documented in the Trial Master File.

The Investigator will perform a clinical assessment of all laboratory safety data. The Investigator will record the assessment as 'normal', 'abnormal CS', or 'abnormal NCS'. Lab test abnormalities of clinical significance will be reported as AEs. Repeat lab tests or measurements will be performed if needed.

If subjects will meet treatment withdrawal criteria for elevated liver function tests, the subjects should be treated using standard of care as directed by the Investigator and followed until resolution (Section 4.5).

Table 6.9-1 Routine Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell count	White blood cell count and differential
Biochemistry:	
Alkaline phosphatase	Cholesterol
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase	High density lipoprotein-cholesterol
Gamma-glutamyl transpeptidase	Low density lipoprotein-cholesterol
Potassium	Protein (total)
Sodium	Albumin
Chloride	Creatine kinase
Inorganic phosphate	Creatinine
Glucose	Ferritin

Urea Bilirubin (direct and total) Blood urea nitrogen	
Coagulation: Prothrombin time International normalized ratio	Activated partial thromboplastin time
Urinalysis: Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood Microscopic examination[a]	

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

Blood and urine samples will be analyzed by the central laboratory and/or specialized laboratory where applicable using standard methods. Procedures for the handling of samples will be described in full in a separate document.

6.9.6 Biomarker Assessments Using Pharmacodynamics Skin Biopsy Samples

Skin samples will be collected by subjects choosing to have a pharmacodynamics skin biopsy by using a 3 mm × 3 mm punch biopsy at Visits 2 and 8.

Exploratory biomarkers relating to the pathogenesis of EPP, inflammatory response, and the mode of action of MT-7117 will be assessed. Gene array analysis will be performed. In addition, EPP pathology or MC1R-pathway related genes including melanin synthesis, anti-oxidative, inflammatory, DNA repair, fibrosis, and vascular functions may be assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Sample handling details for the collection and processing of skin samples will be described fully in a separate document, and results from the biomarker assessment will be reported separately.

6.9.7 Pharmacogenetics

Blood samples will be collected for PGx analysis for those subjects who have given their consent for optional PGx analysis at Visit 2.

MC1R with SNPs will be assessed. Samples may be retained for future research use in genetic analysis for erythropoietic protoporphyria.

Sample handling processing of PGx samples will be described fully in a separate laboratory manual. Results from the PGx analysis will be reported separately.

6.9.8 Porphyrin and Protoporphyrin Levels

Plasma total porphyrins and erythrocyte protoporphyrin will be assessed at Visits 1, 6 and 8.

7. STUDY TREATMENT

7.1 Investigational Medicinal Product

7.1.1 Drug Product

MT-7117 and matching placebo [redacted] are light-orange, [redacted] with no identifying mark. MT-7117 [redacted] contain [redacted] of active drug product (its free-base form), the matching placebo [redacted] will be manufactured to be physically identical to the MT-7117 [redacted].

A bulk supply of MT-7117 [redacted] and matching placebo [redacted] will be packed into double-polyethylene bags with a desiccant, and placed into stainless steel drums with desiccant (silica gel) for bulk supply storage.

Individual subject doses will be packed in [redacted] using [redacted] then labeled and QP released from [redacted] according to good manufacturing practices (GMP). All labeling will comply with applicable regulatory requirements. The Sponsor will provide all required release documentation for the finished product before it is dispatched from [redacted].

All MT-7117 [redacted] and the matching placebo [redacted] will be manufactured, tested, and released according to GMPs.

7.1.2 Study Drug Supply

The Sponsor will provide MT-7117 and placebo [redacted] in [redacted] to each site, for each subject, for the duration of their participation in the study. The Investigator, a study nurse, or the hospital pharmacy will dispense a sufficient quantity of MT-7117 [redacted] consistent with each subject's daily dosage requirement and study visits according to the protocol. Specifically, MT-7117 or matching placebo [redacted] (each [redacted] of MT-7117 and matching placebo) will be dispensed in a manner consistent with each subject's daily dosage requirement (for blinded treatment equaling or mimicking MT-7117 at [redacted] or [redacted] day active medication or placebo, subjects will receive a total of 6 blinded [redacted] per day).

Subjects will be instructed to bring their study medication with them to each visit and the Investigator or designee will ensure the subject has a sufficient supply of medication according to their blinded, randomized treatment group to last until the next scheduled visit. Subjects will return all study medication that may remain in their possession to the study staff at the end of treatment visit. In cases where subject forget to return to the clinic with their [redacted], sites will be instructed to inquire as to the subjects daily dosing compliance, capturing total number of days missed. Subjects will be instructed to return medication packaging at the follow up visit.

7.1.3 Formulation, Packaging, Site Storage, and Labeling (MT-7117)

Study medication [redacted] will be provided in 2 strengths: 0-mg (placebo) and [redacted] (MT-7117) [redacted] Study medication will be provided to the study sites in labeled [redacted]

[redacted]. All study medication should be stored according to the investigational medicinal product (IMP) clinical label.

MT-7117 and placebo [redacted] must be dispensed in cold form[redacted]. Subjects will be instructed to store the medication per the IMP clinical label.

Required study site documentation for MT-7117 [redacted] will include, but may not be limited to, the following information:

- Receipt date.
- Description of medication package, and medication product.
- Lot number or code/Batch number or code.
- Expiration and manufacturing dates.
- Dispensing information.
- IND number.
- Certificate of compliance.

7.1.4 Shipping, Receipt, Handling and Storage

On receiving a shipment of finished study medication at the Investigator site, the Investigator or designee will conduct an inventory check and complete a supplies-receipt document, the original of which will be retained at the Investigator site. In addition, a copy must be returned to the Sponsor or designee. The Investigator or designee will maintain a record of all study medication received and returned.

Study medication at the Investigator site will be stored according to the conditions stated on the IMP clinical label in a locked, restricted-access area. A temperature log recording the daily continuous temperature of the storage area will be maintained (including weekends). Any study medication storage temperature deviations will be reported to the Sponsor.

7.1.5 Dispensing

At each visit, the Investigator or designee will provide the subject with the allocated dose. A record of the study medication dispensed to each subject will be maintained by the Investigator or designee in a Medication Accountability Log. Any opened [redacted] will not be re-dispensed.

In the cases where subject encounters a missed visit that renders a subject without sufficient medication to maintain daily dosing (e.g. a subject reside out of state relative to the investigator's location and experiences a travel conflict), site may ship resupply drug to the subject upon written sponsor approval. In these instances, the sponsor (and/or the CRO designee) will assist the site to ensure the process is documented appropriately. Shipments made in these rare instances will require that IMP be maintained within the required temperature range along with confirmation of receipt by the study subject. This process will not be allowed where site policies prohibit it.

7.1.6 Study Medication Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study medication in a Medication Accountability Log. Medication accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study medication and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

7.1.7 Disposal and Destruction

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study medication, packaging, medication labels, and a copy of the completed Medication Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study medication supply may be destroyed at the designated Sponsor facility or third party, as appropriate. Sites with documented drug destruction procedures and facilities may destroy drug on site with sponsor approval.

7.2 Dosing

Subjects are to self-administer study medication once daily in the morning with food.

MT-7117 and placebo [redacted] should be swallowed whole with approximately 8 oz. of water (subjects may drink an additional 8 oz. of water if they have difficulty swallowing the [redacted]). The [redacted] are not to be chewed, crushed, or divided.

7.3 Compliance

The prescribed dosage, timing, and mode of administration of study medication will not be changed. Subjects will be asked questions regarding the compliance, any departures from the intended regimen will be recorded in the eCRF.

Study medication accountability and subject compliance will be documented throughout the double-blind treatment period using study-specific study medication dispensing and return record forms. For subjects who do not return their [redacted], the site will question each to determine compliance (e.g. number of doses missed since the last visit).

Subjects will be asked to return all unused medication including empty and partially used [redacted]. Study medication dispensed at the previous visit will be retrieved by the Investigator and compliance assessed by returned medication count.

Non-compliance will be defined as taking ≤80% or ≥120% of study medication during any evaluation period (from any visit to the following visit).

7.4 Subject Identification

Each subject will be assigned a unique subject number at the screening visit. At Randomization, each subject will receive a unique randomization number. Both the subject number and the randomization number will be documented in the subject's source

documents. The subject number will be used to identify subjects in the study.

A list identifying the subjects by their subject number will be kept at the Investigator site. The randomization numbers will be stored in IWRS database until the database lock.

7.5 Procedures for Assigning Subjects to Treatment Groups

Randomization will take place after confirmation of inclusion/exclusion criteria before the first administration of study medication on Day 1. Subjects will be randomly allocated on a 1:1:1 basis to 1 of 3 treatments (Section 3.1). Subjects will be randomized with Interactive Web-based Response System (IWRS). Baseline average daily sunlight exposure time without prodromal symptoms (≤30 min and >30 min) will be used as stratum for the randomization.

7.6 Maintenance of the Study Blind and Unblinding

All study treatment will be double-blinded; neither the subject nor the study site personnel will know which treatment is being taken. Each subject's treatment will be given a unique code number, traceable to the identity, dose, and batch number of the study medication. The IWRS will be used to hold treatment codes for each subject. The codes will only be accessible to authorized IWRS users.

The IWRS should not normally be accessed with a request to break the treatment code for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she are advised to consult the Sponsor (or designee) in advance where feasible. If this is not possible, the Investigator may access the IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. The Sponsor should be notified as soon as possible thereafter. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal will be performed (Section 4.5).

The sponsor and study team will remain blinded throughout the entire duration of the study.

Because PK analysis will only be performed on samples from subjects receiving active medication, unblinded randomization codes will be given to PK lab.

An electronic list of randomization codes will be retrieved from IWRS and transferred to the Sponsor at the end of the study.

MT-7117 and placebo [redacted] will be identical in appearance and will be packaged identically and suitably labeled to maintain the blind.

Since melanin density values could potentially be unblinding, adequate measures will be taken to protect the spectrophotometry data from disclosure to the sponsor and the study team until the end of the study. Melanin density component data will be measured by the dedicated unblinded site staff, securely uploaded to and processed by the dedicated unblinded data management team. The data handling procedure for melanin density will be described in the data management plan.

The handling of data that could potentially unblind the study will be defined in relevant study procedures documents (e.g. Unblinded Data Management plan or equivalent).

8. ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written informed consent is obtained until the end of the follow-up period (6 weeks after the last treatment visit, for safety monitoring) will be recorded in the eCRF.

ICF signing will occur weeks in advance of the first clinic visit (Visit 1), to account for subjects traveling long distances; these subjects will be required to sign the ICF before he or she travels to the clinic. In addition, there will be a provision for a pre-screening ICF in order to enable Visit 1 to align directly with the official study consent; however, the Sponsor safety team will determine when to officially collect AE.

Even if the AE is assessed by the Investigator as not related to study medication, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as occurring at 'Baseline' if they occur before the administration of study medication. AEs will be classified as 'treatment-emergent' if they arise following the first administration of study medication in the double-blind treatment period (after randomization) or if a pre-dose AE increases in severity following dosing in the double-blind treatment period (after randomization).

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator or designee should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading to avoid notifying either the subject or study site personnel of the actual treatment being administered.

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drugs, whether or not considered related to the study drugs.

8.2 Definition of a Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These

should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of medication dependency or medication abuse. These should also usually be considered serious.

The term 'life threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new subject is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalization (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 8.8.

8.3 Adverse Events of Special Interest

One AESI that will be considered during this study includes hepatic AESIs, defined as

- Clinically significant liver dysfunction, as follows:
    - ALT or AST >6 x ULN.
    - ALT or AST >4 x ULN for more than 2 weeks.
    - Elevated total bilirubin >2 × ULN and ALT or AST >2 x ULN, or
    - Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia >5%) with concomitant ALT or AST values >3 × ULN.
- Hepatic AEs or hepatic laboratory abnormalities that lead to study medication interruption or discontinuation (see Section 4.5).

8.3.1 Management and Evaluation of Hepatic Adverse Event of Special Interests

Hepatic AESIs should be treated per the Investigator's approved standard of care and assessed for possible alternative etiology(ies). Hepatic AESI will be followed clinically until resolution.

All hepatic AESIs (including event management and evaluation) will be recorded and reported similar to SAEs as described in Section 8.8.

8.4 Severity of Adverse Events

The severity of AEs will be classified according to the following criteria:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes discomfort and interferes with the subject's general condition.

Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This will not be not the same as 'serious', which will be based on subject/event outcome or action criteria usually associated with events that would pose a threat to a subject's life or functioning. Seriousness (not severity) will serve as a guide for defining regulatory reporting obligations.

8.5 Relationship of adverse events to Investigational Medicinal Product

The causal relationship of the AE to study medication will be determined as either 'a reasonable possibility' or 'no reasonable possibility,' and will be defined as having either one of the following:

- **A Reasonable Possibility** – The relationship of the clinical event to the study medication makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- **No Reasonable Possibility** – The relationship of the clinical event to the study medication makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

8.6 Clinical Laboratory Abnormalities, and Other Abnormal Assessments

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities which are clinically significant will be recorded as AEs or SAEs.

If an abnormal laboratory value or assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All 'abnormal, clinically significant' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant. Repeat laboratory tests or measurements will be performed if needed.

8.7 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to study medication, occurring from the time written informed consent is obtained from a subject until the end of the safety follow-up period or the withdrawal of the subject from the study, and any AEs or SAEs reported spontaneously through the end of the safety follow-up period, should be reported to the Sponsor or designee.

NOTE: elective hospitalization or procedure/surgery planned before subject enrollment for a preexisting medical condition does not constitute an AE unless the underlying disease or condition worsens after signing informed consent.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning will be open-ended and non-leading.

All AEs will be recorded in the source documents and AE eCRF. The AE eCRF will contain a description of the event, date of onset, date of resolution, severity, treatment required, relationship to study medication, action taken with the study medication, outcome, and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 8.3) and will assess the causality between the AEs and the study medication (as defined in Section 8.5).

Pre-existing illnesses, which started before entry and is still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information which appears to be either study or study medication related after the final follow-up period, then they must notify the Sponsor or the designee immediately.

8.8 Recording and Reporting of Serious Adverse Events or Hepatic Adverse Events of Special Interest

All SAEs and Hepatic AESI occurring from the time written informed consent is obtained from a subject until the end of the safety Follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor or the designee using the ***Serious Adverse Event/Adverse Event of Special Interest (SAE/AESI) in a Clinical Study Form*** within 24 hours of the Investigator becoming aware of the SAE/AESI. All SAE/AESIs must also be entered in the AE section of the eCRF within 24 hours.

The SAE/AESI report should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The reporting contact for SAE/AESIs by email is as follows:

Email: [redacted]

In case of any email problems, the SAE/AESI form will be sent to the Sponsor or the designee by fax to:

Fax: [redacted]

Reports of pregnancy, although not classified as an SAE, will be handled and reported as in Section 8.9.

The Sponsor will comply with the applicable regulatory requirements related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Regulatory Authorities and central IRB(s). The Investigator will be responsible for informing the local IRB(s) of SUSARs, as per local laws and requirements.

8.9 Pregnancy

If a female subject who has been exposed to the study medication becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the study medication becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

A pregnancy that occurs in a subject who has been exposed to the study medication must be reported using the same timelines and contact details as an SAE (Section 8.8) by a paper ***Pregnancy in a Clinical Study Notification Form***, although pregnancy alone will not be classified as an SAE. If the outcome of the pregnancy or an event occurs during the course of pregnancy that involves an SAE (e.g., a congenital anomaly), then the ***Serious Adverse Event (SAE) in a Clinical Study Form*** will also be completed.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 4.5.

8.10 Follow-up of Adverse Events

The Investigator should follow up subjects with AEs/SAEs, until the event has resolved or stabilized and any abnormal laboratory values have returned to baseline; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible a pathologist's full report should be supplied.

The reference safety information for this clinical study is the Investigator's Brochure[3)].

8.11 Overdose

There is no known antidote for MT-7117. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and supportive medical care will be given.

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this overdose is an AE and must be

reported to the Sponsor or the designee on the AE eCRF.

If the overdose results in AEs that meet serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness using the ***Serious Adverse Event (SAE) Form in Clinical Study*** according to SAE reporting procedures (see Section 8.8).

If the subject experiences any other associated symptoms as a result of the overdose, the Investigator will record this as a separate AE/SAE.

9. DATA COLLECTION AND PROCESSING

9.1 Data Collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records, or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF and the eCRF will be considered the source document.

Subjects will record sunlight exposure time, prodromal symptoms and pain, their severity and their duration on an ongoing basis using a sunlight exposure diary, which includes an electronic patient-reported outcome (PRO) instrument. The instrument will transmit data to a technology service provider database, where it will be stored as electronic source data for efficacy endpoints. To mitigate the potential risk of lost data collection, a printed equivalent of the electronic PRO instrument may be considered to provide emergency back-up in case of device malfunction or loss.

Before the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor or designee will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically, and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness, and consistency in accordance with the study monitoring plan and other relevant procedural documents. Any relevant discrepancies found during the eCRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data where required. The Investigator must sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

9.2 Case Report Form Completion

The eCRF will be presented in an electronic casebook comprising a series of electronic forms. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in timely manner so that this does not delay the ongoing data validation, review, and quality control. The final, completed eCRF for each subject must be signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times, and the credentials of the eCRF user who performed the operation will be maintained by the system.

9.3 Data Processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times, and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract, including sunlight exposure diary data, will be made available for statistical analysis according to the methods outlined in Section 10 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Medication Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

10. STATISTICAL METHODS AND PLANNED ANALYSES

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect planned analyses.

10.1 Sample Size Consideration:

The sample size for this study is not based on a formal statistical calculation since this is a clinical study for a rare disease. However, a sample size of 34 subjects per treatment group is considered to be adequate to meet the objectives of the study.

10.1.1 Analysis Populations

- Safety population: includes all randomized subjects who received at least 1 dose of study medication.
- Intent-to-treat (ITT) population: includes all randomized subjects who received at least 1 dose of study medication and who have at least 1 post-baseline efficacy assessment.
- Per-protocol (PP) population: includes all ITT subjects who do not have any major protocol violations and complete Week 16 (the end of double-blinded treatment period).
- PK population: includes all randomized subjects who receive at least 1 dose of study medication and who have at least 1 post-dose value of plasma concentration time point to be included in the PK analysis without important protocol deviations which may affect the PK of study medication.

10.2 Statistical Methods

A SAP containing details of all the analyses and outputs will be prepared and approved before the study database lock. The ITT population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population and PK assessments will be performed on the PK population.

Unless otherwise specified, the baseline values will be the last non-missing value before receiving the first dose of study medication.

Baseline for an efficacy endpoint based on sunlight exposure time will be the mean of the daily value of the endpoint in a 14-day window before Day 1. Similarly, for this endpoint, their values at each post baseline visits/time-points (Weeks 2, 4, 6, 8, 10, 12, 14, 16, and 22) are the mean of the daily value of the endpoint in a 14-day window on or before the visit.

Continuous endpoints will be summarized with the descriptive statistics (the number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages.

All statistical tests will be 2-sided with 5% significance level. Point estimates of treatment differences will be provided using 2-sided 95% confidence intervals (CIs), where

applicable.

10.2.1 Demographic and Other Baseline Characteristics

Baseline demographic such as age, sex, body weight, body mass index, ethnicity and race, and other baseline characteristics such as will be summarized by treatment group using descriptive statistics on the ITT population.

10.2.2 Efficacy Assessments

10.2.2.1 Analysis of Primary Efficacy Endpoints

The primary treatment comparisons of interest are the change from baseline in average daily time (**minutes**) to first prodromal symptom associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset for the two MT 7117 doses ([redacted], and [redacted] compared with placebo at Week 16 (Visit 8). As this trial is exploratory in nature, no adjustments for multiplicity will be made.

To assess the treatment effect at Week 16, 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 and 16 will be analyzed using mixed-effect model for a repeated measures (MMRM). The model will include fixed categorical terms for treatment, the baseline average daily sunlight exposure time without prodromal symptoms (≤30 min or >30 min), visit, and treatment by visit interaction together with continuous covariate terms for baseline average daily duration of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms 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 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), other variance-covariance matrices such as AR(1) correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, adjusted (least squares [LS]) means and standard errors will be produced by treatment and visit. Difference in adjusted means at each visit (each MT-7117 dose vs. placebo) with standard errors, 95% CIs and associated P-values will also be produced. All available data from all subjects will be used in the primary analysis without any imputation.

A supportive analysis will be performed in a similar manner for the primary endpoints using the PP set.

Non-parametric analysis will be performed in order to confirm the robustness for the above parametric model. The analysis will be carried out using Wilcoxon's rank sum test. The data of change from baseline in average daily duration (hours) of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms at each visit/timepoint (Weeks 2, 4, 6, 8, 10, 12, 14 and 16) from two treatments being compared will enter the corresponding analysis. In addition, the point estimates and two-sided 95% confidence intervals for the difference between the treatment groups will be obtained using the Hodges-Lehman estimator.

10.2.2.2 Analysis of Secondary and Other Efficacy Endpoints

The detail of analysis method for secondary and other efficacy endpoints will be described in the SAP. The detail model for each endpoint will be described in the SAP.

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

- Change from baseline in average daily duration **(minutes)** of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms.
- Change from baseline in average daily mean duration **(minutes)** of sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset without prodromal symptoms. The daily mean duration is considered as multiple periods of sunlight exposure in each day and measurable by sum of duration of each period divided by number of periods.
- Change from baseline in average daily duration **(minutes)** of prodromal symptoms during 16-week double-blind treatment period.
- Change from baseline in average daily duration **(minutes)** of pain events during 16-week double-blind treatment period.
- The average daily mean intensity of the subject's prodromal symptoms during 16-week double-blind treatment period.
- The average daily mean intensity of the subject's pain events during 16-week double-blind treatment period.
- Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity in PROMIS-57.
- PGIC.

The following endpoints will be analyzed; a negative binomial regression model with log link will be fitted. The model will include treatment as fixed effect, and baseline total number of sunlight exposure episodes with prodromal symptoms as the covariate. The estimated incidence rate (IR) and its 95% confidence interval for each treatment group, incidence rate ratio (IRR) of each active MT-7117 treatment group versus placebo, 95% confidence interval of the IRR together with relevant p-values will be reported.

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

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

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

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

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

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

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

10.2.3 Safety Assessments

Adverse Events

AEs are considered as treatment-emergent if they occur after the first dose administration of study drug or if a pre-dose event increases in severity following dosing.

AEs will be assumed to be treatment-emergent, unless there is clear evidence (if necessary through comparison of partial dates) to suggest that the AE started prior to the first dose of IMP.

The frequency and incidence of treatment-emergent AEs (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT) by treatment period and overall. Summaries will also be produced by relationship to study drug and by maximum severity. The summary will be sorted by International Agreed Order for SOC and alphabetical order for preferred term (or by frequency from the highest to the lowest).

The following summaries will be presented:

- Summary of TEAEs by SOC and PT.
- Summary of TEAEs by SOC, PT and severity.
- Summary of TEAEs by SOC, PT and relationship.
- Summary of Serious TEAE by SOC and PT.
- Summary of TEAE leading to drug withdrawn by SOC, PT.

For each of the summaries produced at the subject level, multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and preferred term; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum study drug

relationship category (reasonable possibility/no reasonable possibility). If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

Safety laboratory tests

Routine laboratory safety tests include hematology, coagulation, biochemistry and urinalysis.

Continuous laboratory parameters will be summarised by scheduled time point and treatment group. Observed values as well as changes from baseline (Day -1) will be summarized by treatment groups. Categorical parameters will be summarized by frequency counts and percentages of subjects within each category.

The laboratory data will be listed in full with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range or A=Abnormal if no reference range).

The number of subjects with post baseline assessments $\geq$ x3 ULN and $\geq$ x5 ULN and so on will be calculated for ALT, AST, GGT, ALP, direct and total bilirubin and summarized by treatment for each post baseline visit.

Vital signs and electrocardiogram data

Vital signs and 12-lead ECG variables and changes from baseline will be descriptively summarized at each visit by treatment.

The baseline for the vital sign parameters and 12-lead ECG measurements will be the last valid assessment obtained on Day 1 prior to the administration of double-blind treatment period.

Physical examination and Nevi evaluation

For physical examination, the frequency and percentage of subjects with abnormal physical examinations will be summarized at each time point by body system and treatment.

Nevi assessment will be summarized in table by treatment with frequency and percentage for subjects' suspicious nevi found.

10.2.4 Pharmacokinetic Assessments

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 decimal points. 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.

Population PK analysis will be performed using the plasma concentration of MT-7117 obtained in this study in combination with data obtained from other clinical studies.

Population PK analysis results will be reported separately from the Clinical Study Report (CSR).

10.2.5 Exploratory Endpoints

- Gene array analysis and qRT-PCR results will be reported separately from the CSR.
- PGx analysis will be reported separately from the CSR.
- Porphyrin and protoporphyrin levels will be listed and summarized by treatment using descriptive statistics.

11. STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

11.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Council on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

11.2 Investigator Responsibilities

11.2.1 Informed Consent

Before undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An IRB/EC approved ICF will be given to each subject.

The process of obtaining the informed consent will be in compliance with all regulatory regulations, ICH requirements, and local laws.

11.2.2 Ethical and Regulatory Approval

The study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

- Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
- ICH Harmonized Tripartite Guidelines for GCP 1996.
- Code of Federal Regulations (21 CFR)

The Investigator and Sponsor will sign this protocol to confirm agreement to abide by it.

Before any study-related procedure is performed on a subject, all IRB, FDA, and local approvals of this protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs.

- Periodic reports on the progress of the study.
- Notification of the end of study or early termination.
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this study medication are reported promptly to the regulatory authorities.

If it is necessary to amend the protocol during the study, proper notification will be made to the regulatory authorities and IRBs in the form of a Protocol Modification. Protocol Modification requiring IRB approval may be implemented only after a copy of the IRB's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented before receiving Sponsor, FDA and/or IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any protocol or other deviations that occur during the study will be documented and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the FDA and the IRB.

11.2.3 Source Document Requirements and Document Access during the Study

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of protocols, eCRFs, source data such as original reports of test results, study medication dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IRB reviews, and regulatory inspections providing direct access to source data/documents.

11.2.4 Study Records Retention

Study-related documentation must be kept for at least 25 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.2.5 Protocol Deviations

The Sponsor does not allow prospective deviations from the protocol. Any significant deviations affecting subject eligibility and/or safety must be reviewed or approved by the IEC/IRB and regulatory authority, as per applicable requirements. The Investigator is responsible for complying with all protocol requirements, and applicable to laws pertaining

to protocol deviations. If a protocol deviation occurs (or is retrospectively identified) after a subject has been enrolled, the Investigator is responsible for notifying their IEC/IRB, regulatory authorities (as applicable), and assigned Clinical Monitor or Sponsor.

Protocol deviations considered to be clinically significant will be escalated to the Sponsor and may include corrective measures.

11.3 Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrolment rate, and data quality at the Investigator site. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the investigation is conducted according to protocol, regulatory, and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel before the start of the study to discuss the protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 11.5.

11.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB, and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data, and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

11.5 End of Study and Site Closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor.
- Completion of data clarifications and/or resolutions.
- Accounting, reconciliation, and final disposition of used and unused study medication.
- Review of Investigator site study records for completeness.

Any unresolved AEs of SAEs will be followed according to Section 8.10.

11.6 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues, or serious and/or persistent non-compliance with the protocol.

If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the End of Treatment and Follow-up visit assessments should be performed, as far as possible (Sections 5.3.2.7 and 5.3.3, respectively).

Any unresolved AE or SAE will be followed up according to Section 8.10.

In the event that a subject elects not to return to the study site for the Follow-up visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general Investigator site activities required for the scheduled end of study and site closure should be completed, as described in Section 11.5.

11.7 Premature Discontinuation of Individual Investigator Sites

The Sponsor may at any time, at its sole discretion, discontinue the Investigator site for various reasons, including, without limitation, the following:

- Failure of the Investigator to enroll subjects into the study at a reasonable rate.
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations.
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities.
- Insufficient adherence to Protocol requirements.

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for noncompliance, appropriate regulatory authorities will also be notified by the Sponsor.

For all subjects, the End of Treatment and Follow-up visit assessments should be performed, as far as possible (Sections 5.3.2.7 and 5.3.3, respectively).

Any unresolved AE or SAE will be followed up according to Section 8.10.

In the event that a subject elects not to return to the study site for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make

every effort to complete all required end of study assessments.

In addition, all general Investigator site activities required for the scheduled end of study and site closure should be completed, as described in Section 11.5.

11.8 Liability and Insurance

Please refer to the written study information given to the subject.

12.DISCLOSURE OF DATA

12.1 Confidentiality

All information concerning MT-7117 is the sole property of the Sponsor. For the avoidance of doubt, the Sponsor has full ownership of the eCRFs completed as part of the study. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Subjects will be informed that all personal information made available for inspection will be handled in confidence and in accordance with applicable laws and regulations. All personnel involved in the study will observe and work within the confines of applicable data protection regulations.

12.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The Sponsor or designee will prepare a final report on the study. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

13.REFERENCES

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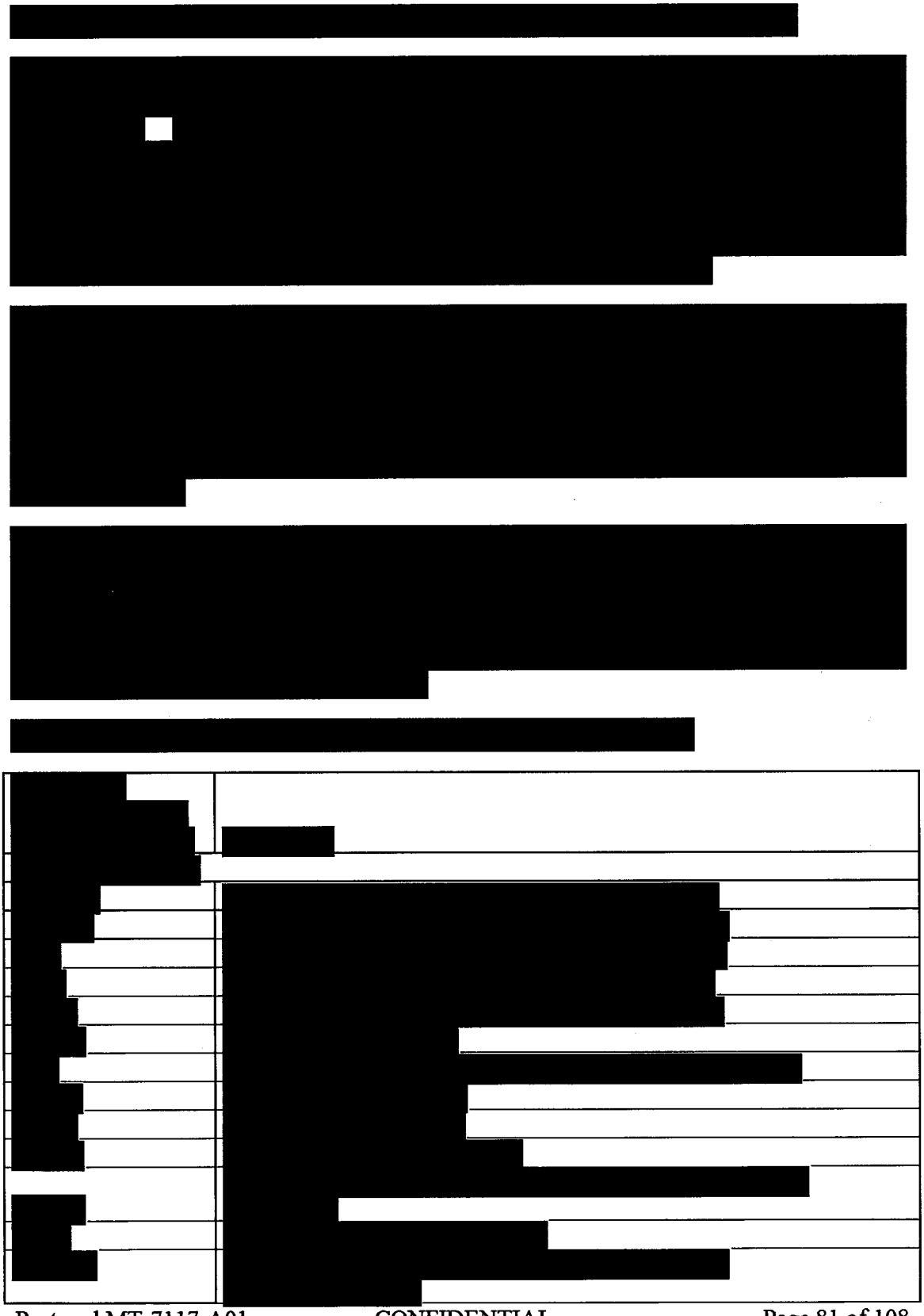
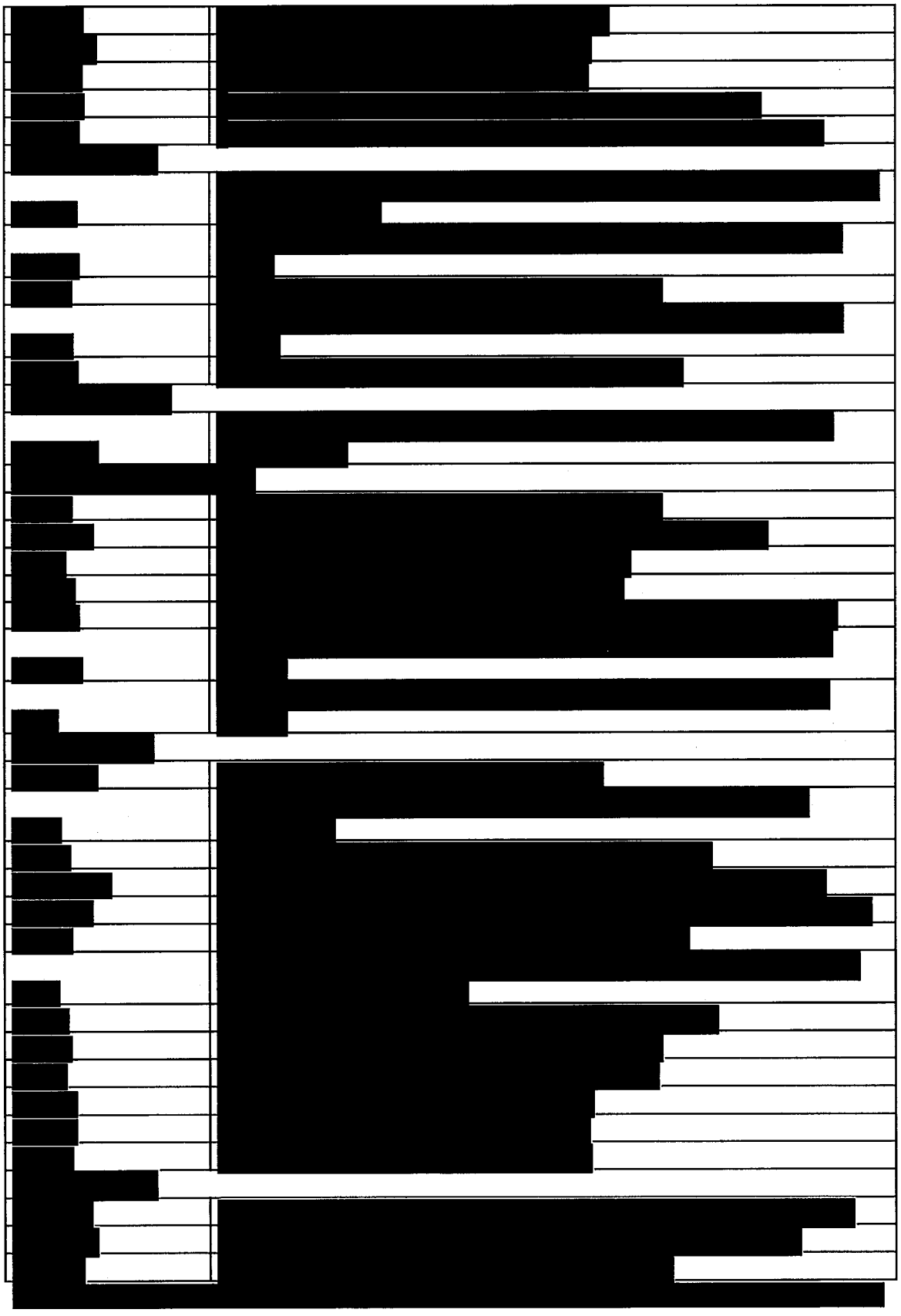
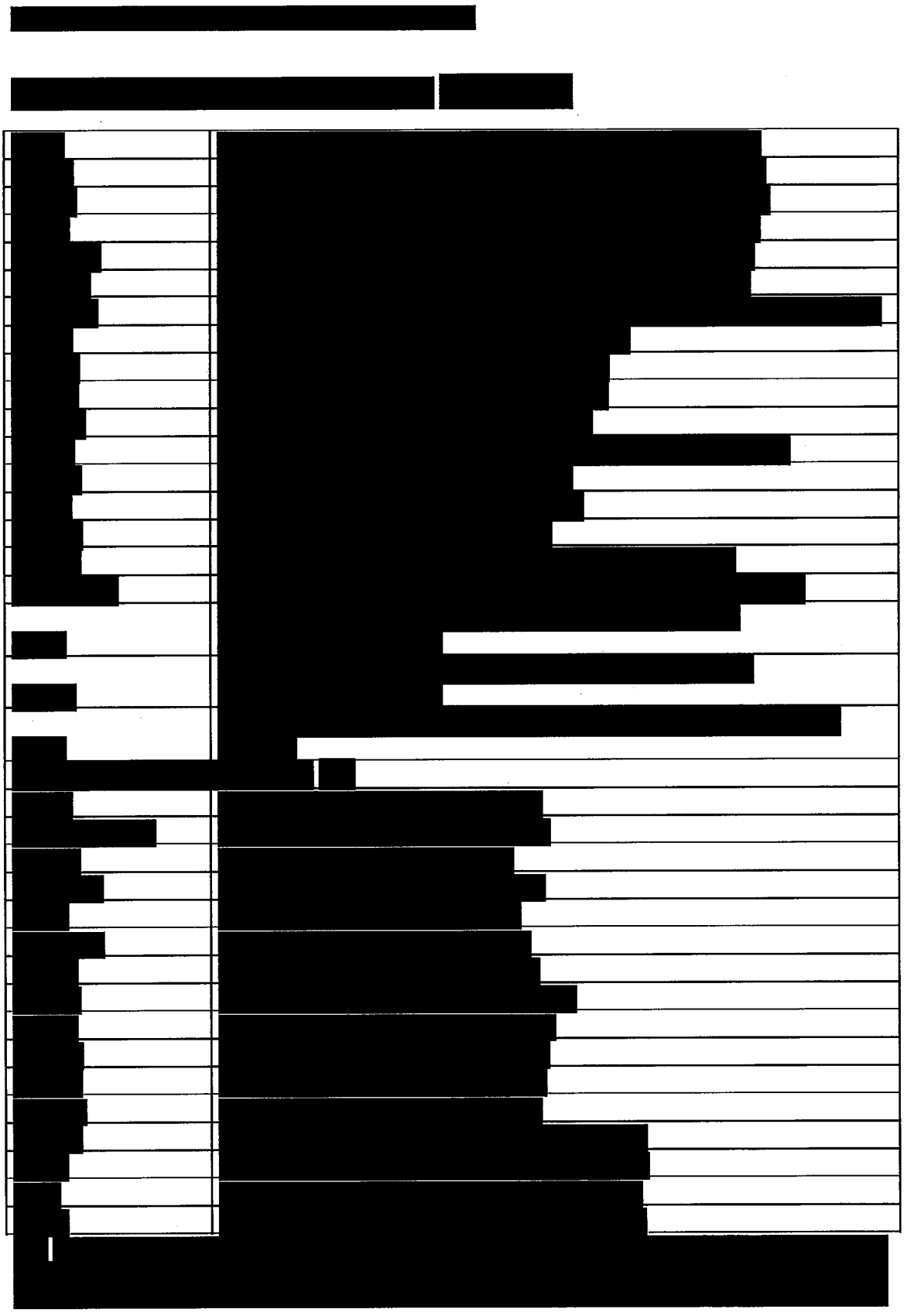
14.APPENDICES







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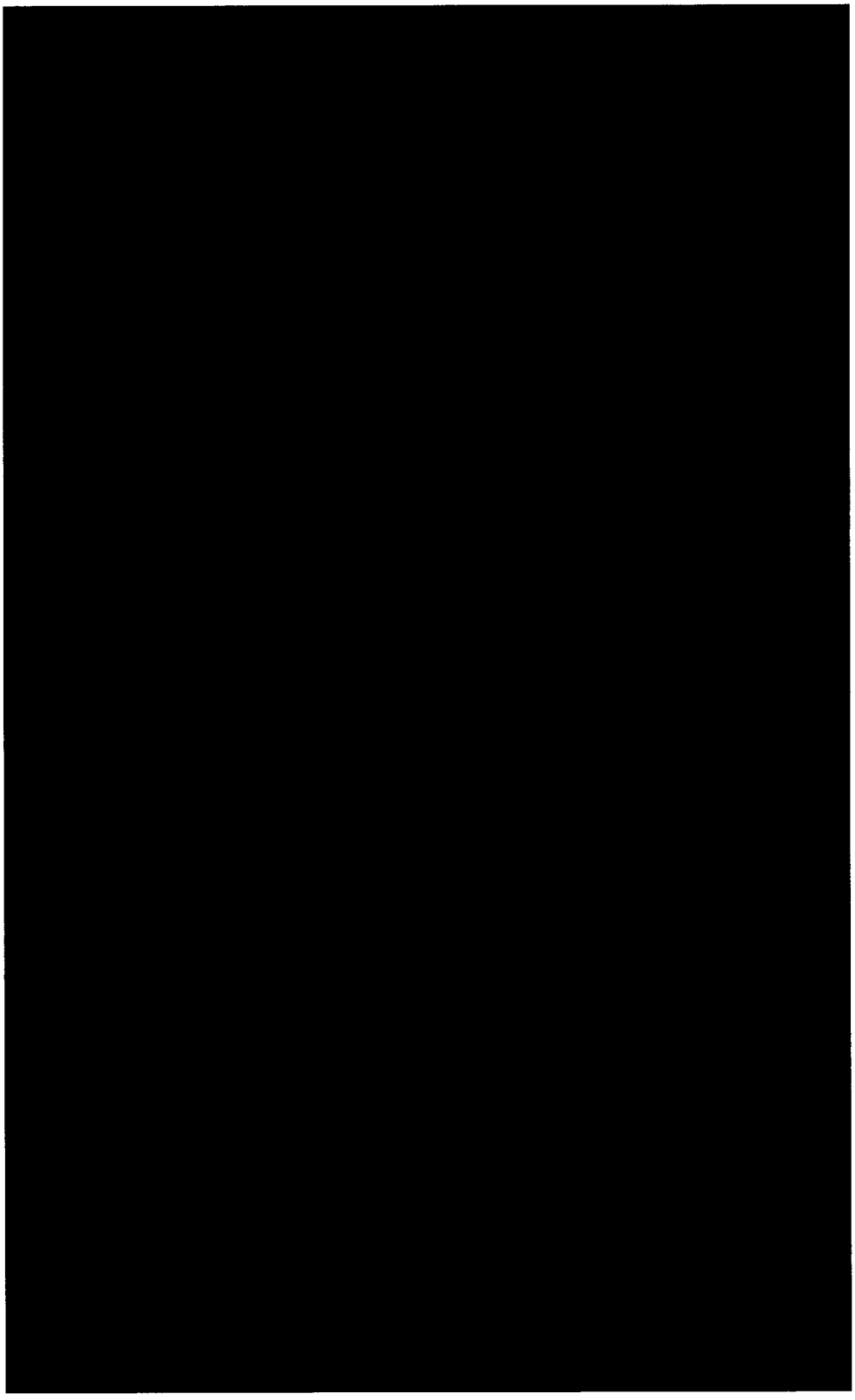

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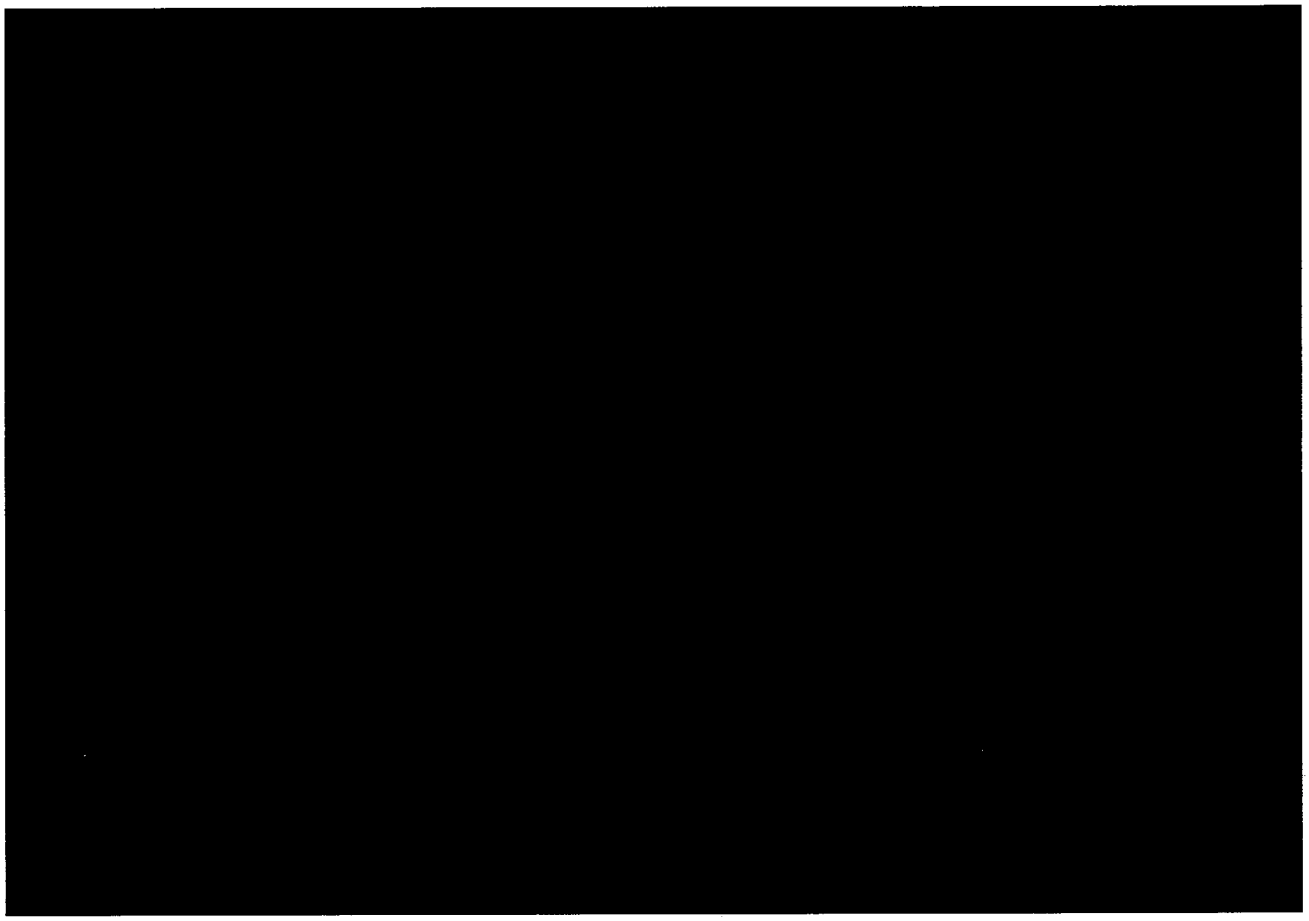

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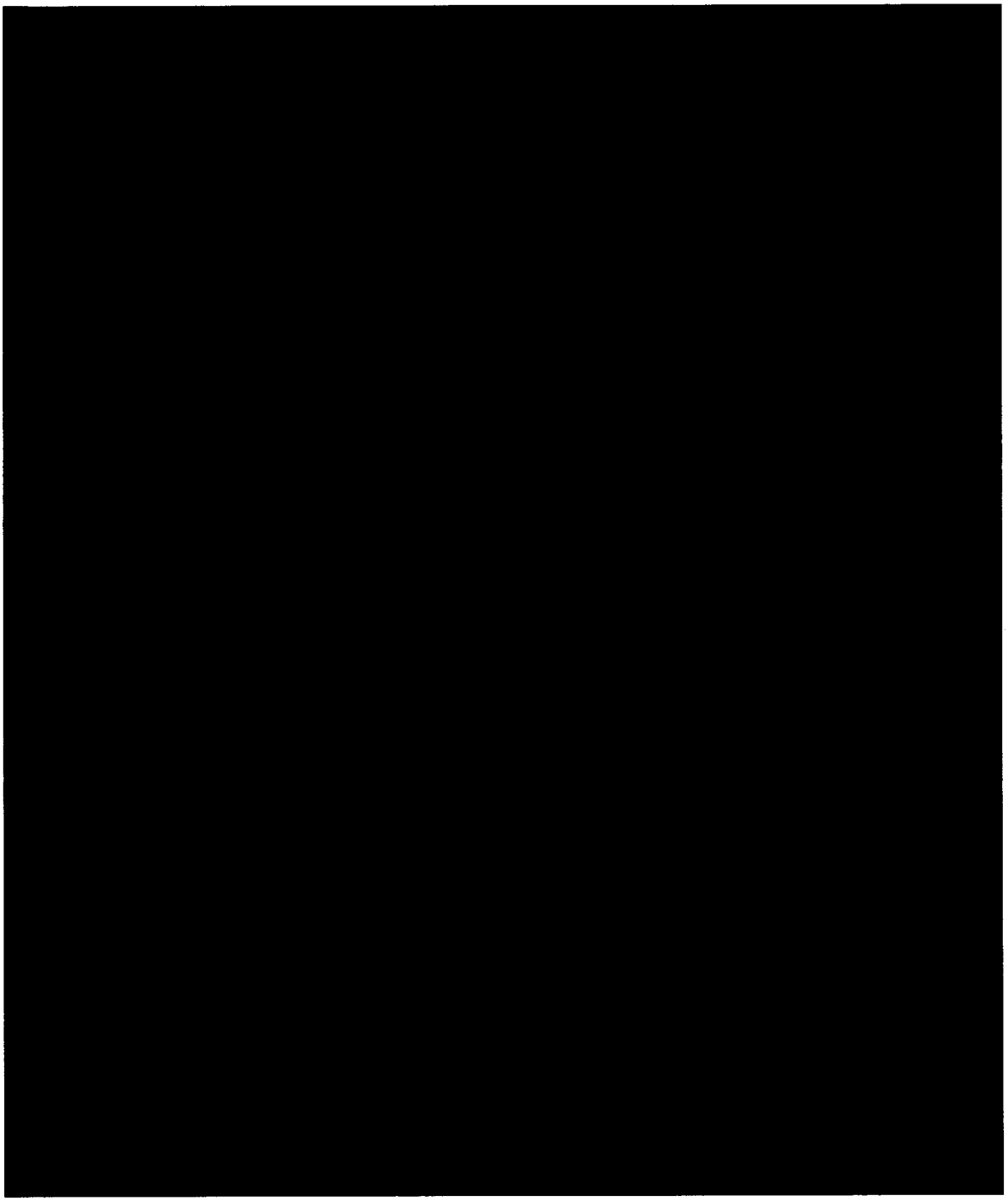

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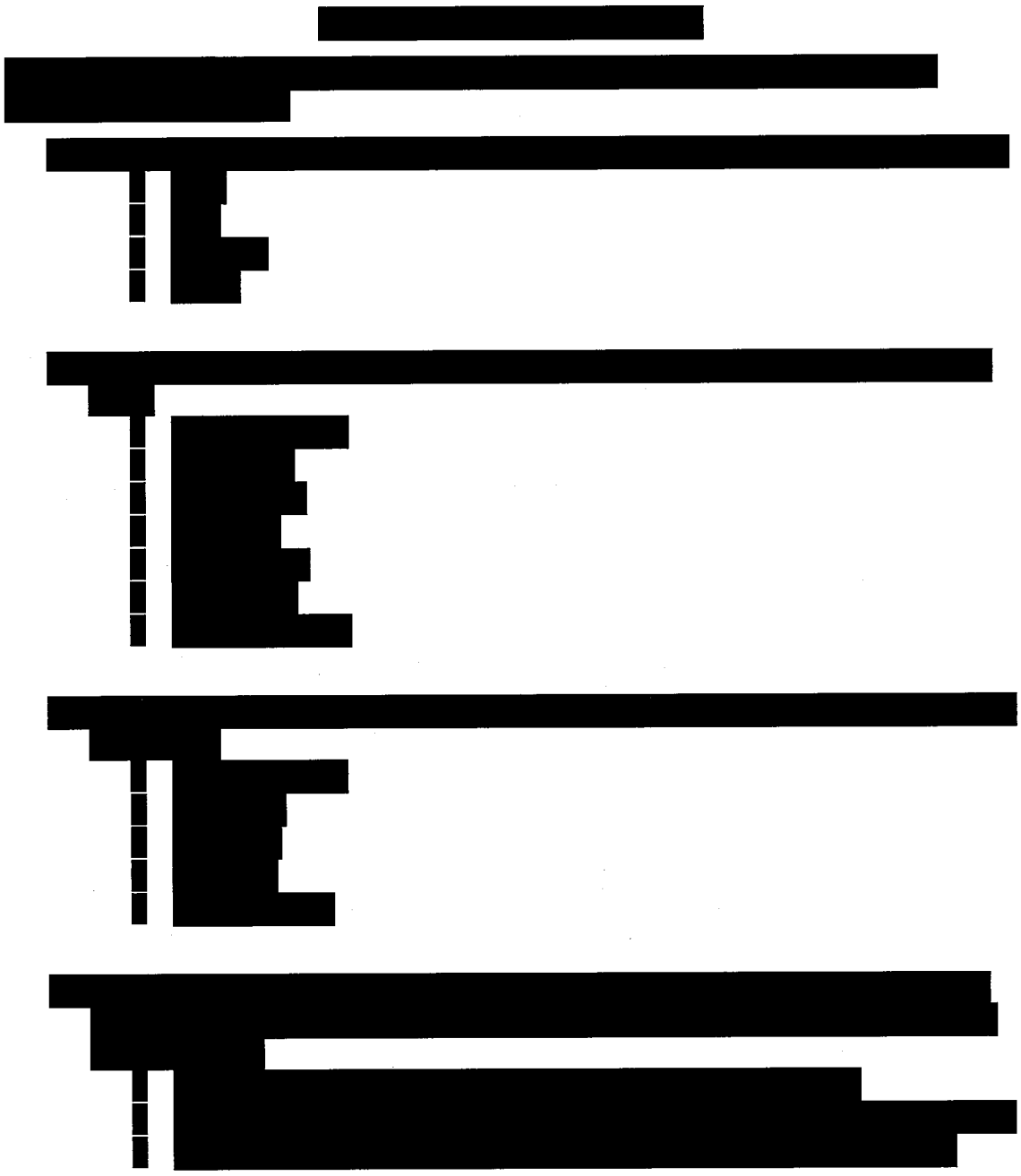

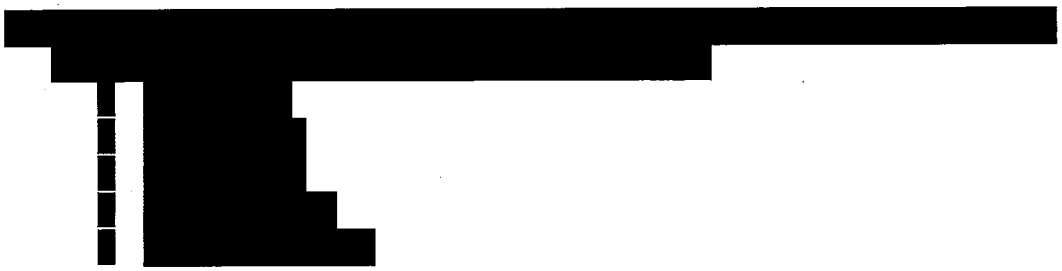

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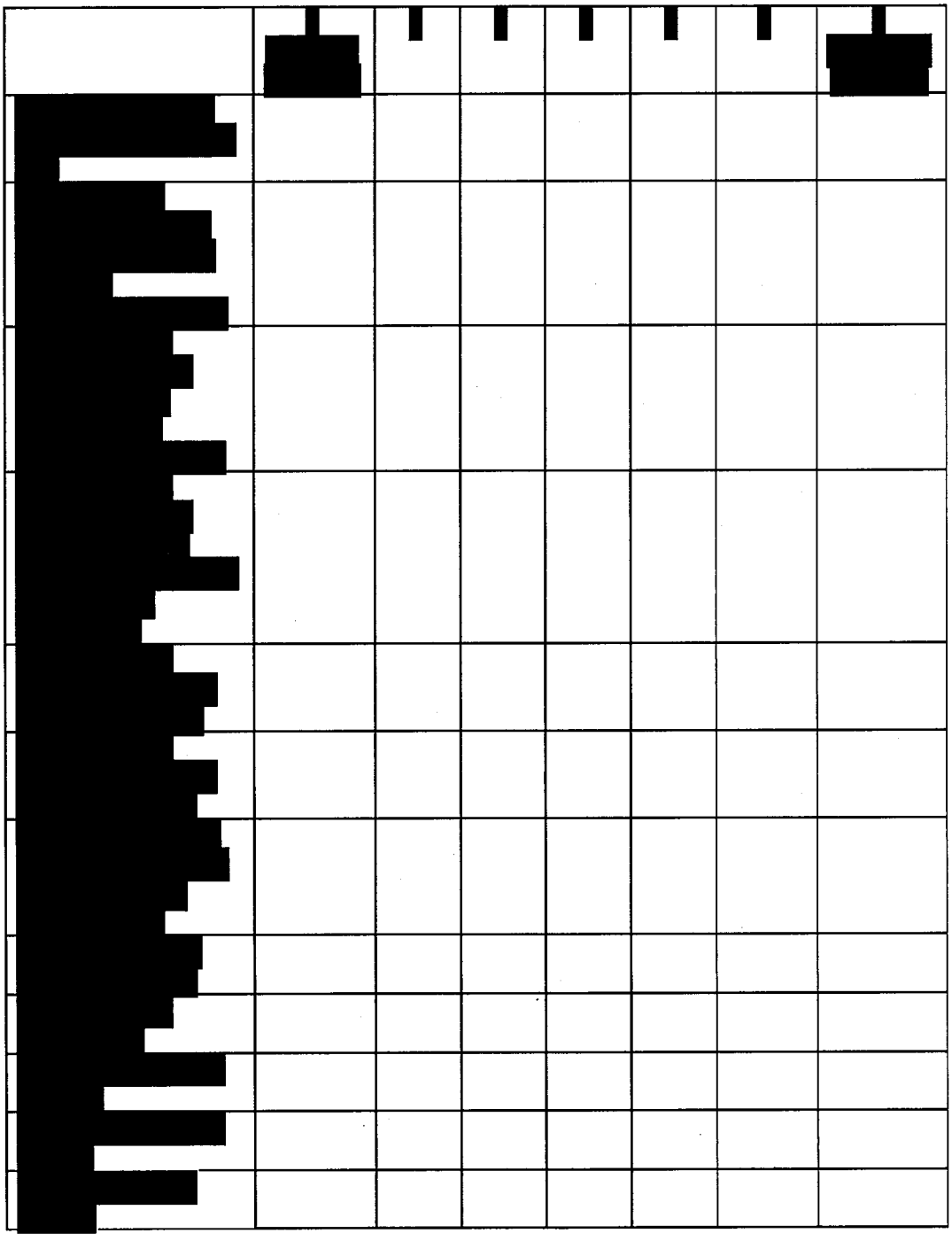

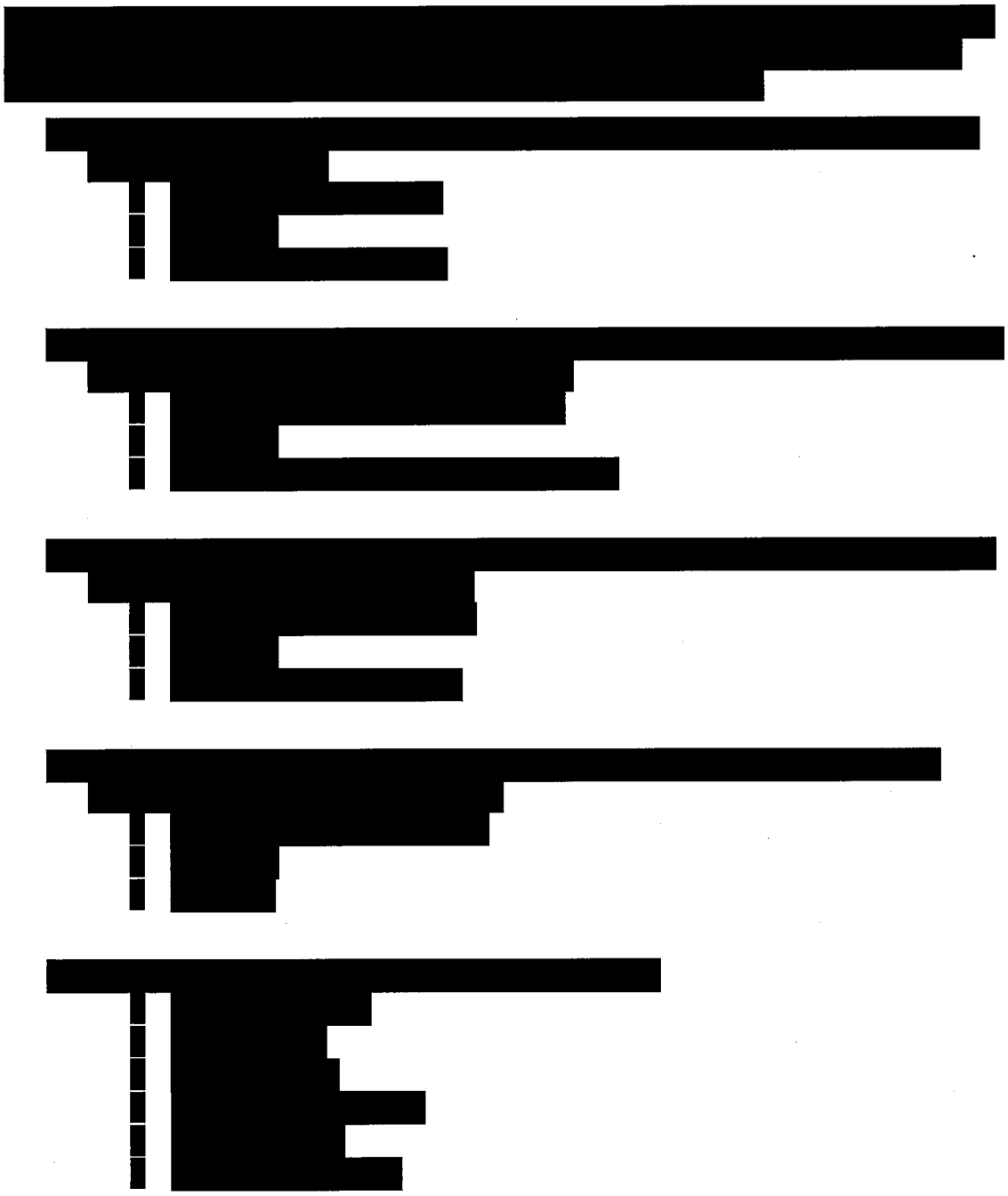

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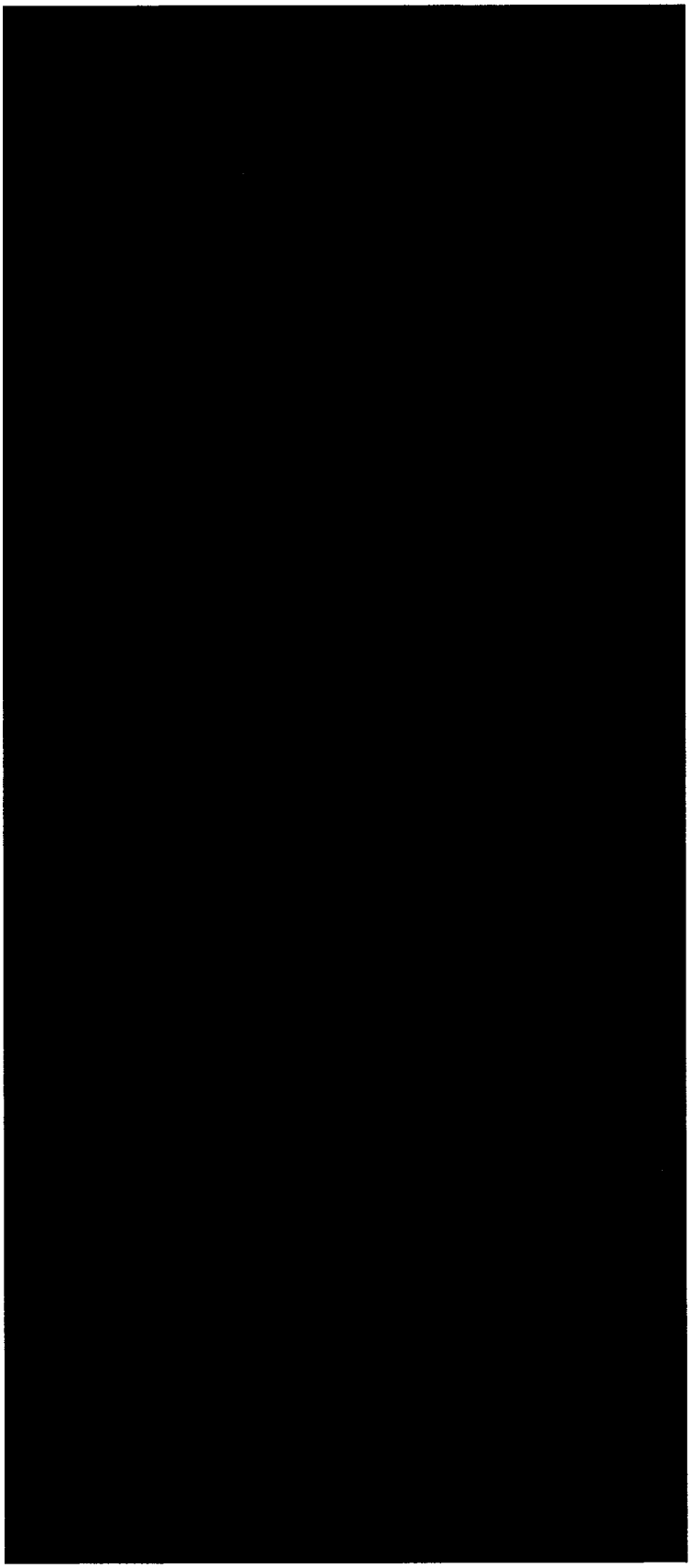

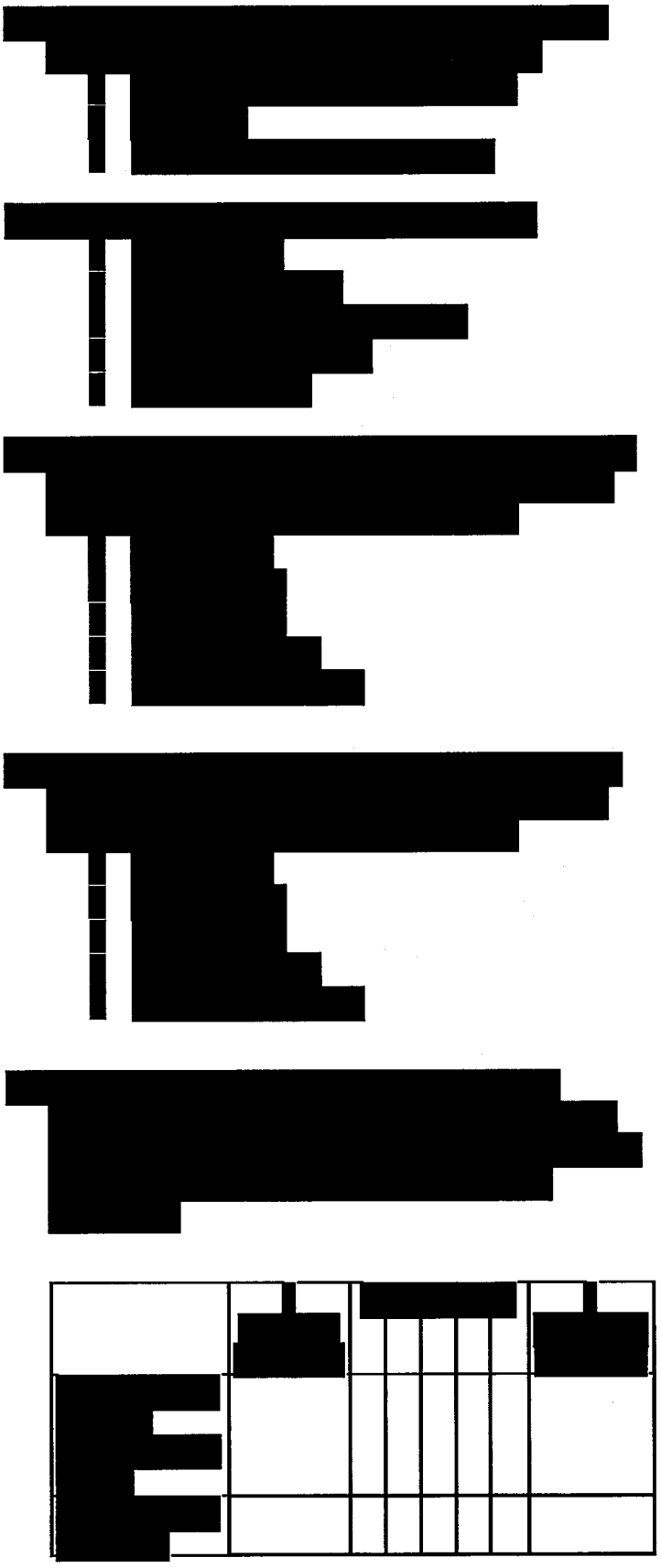

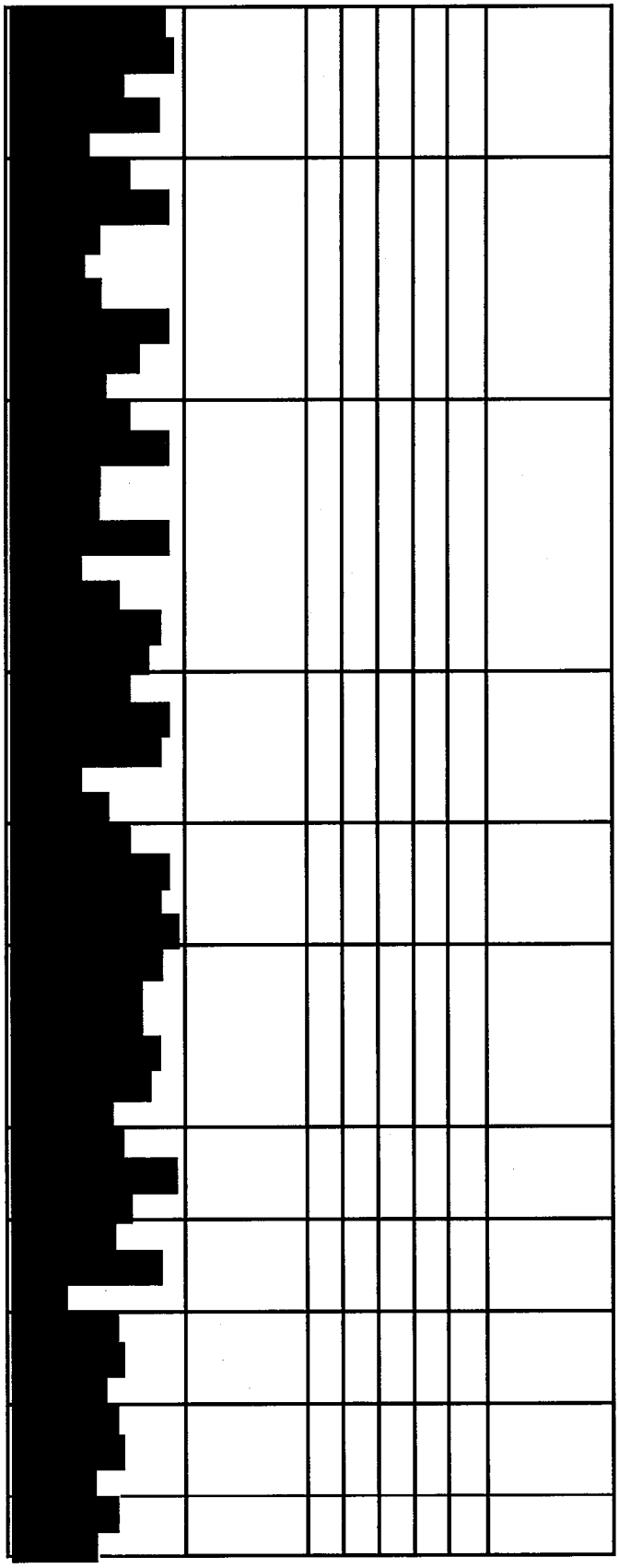

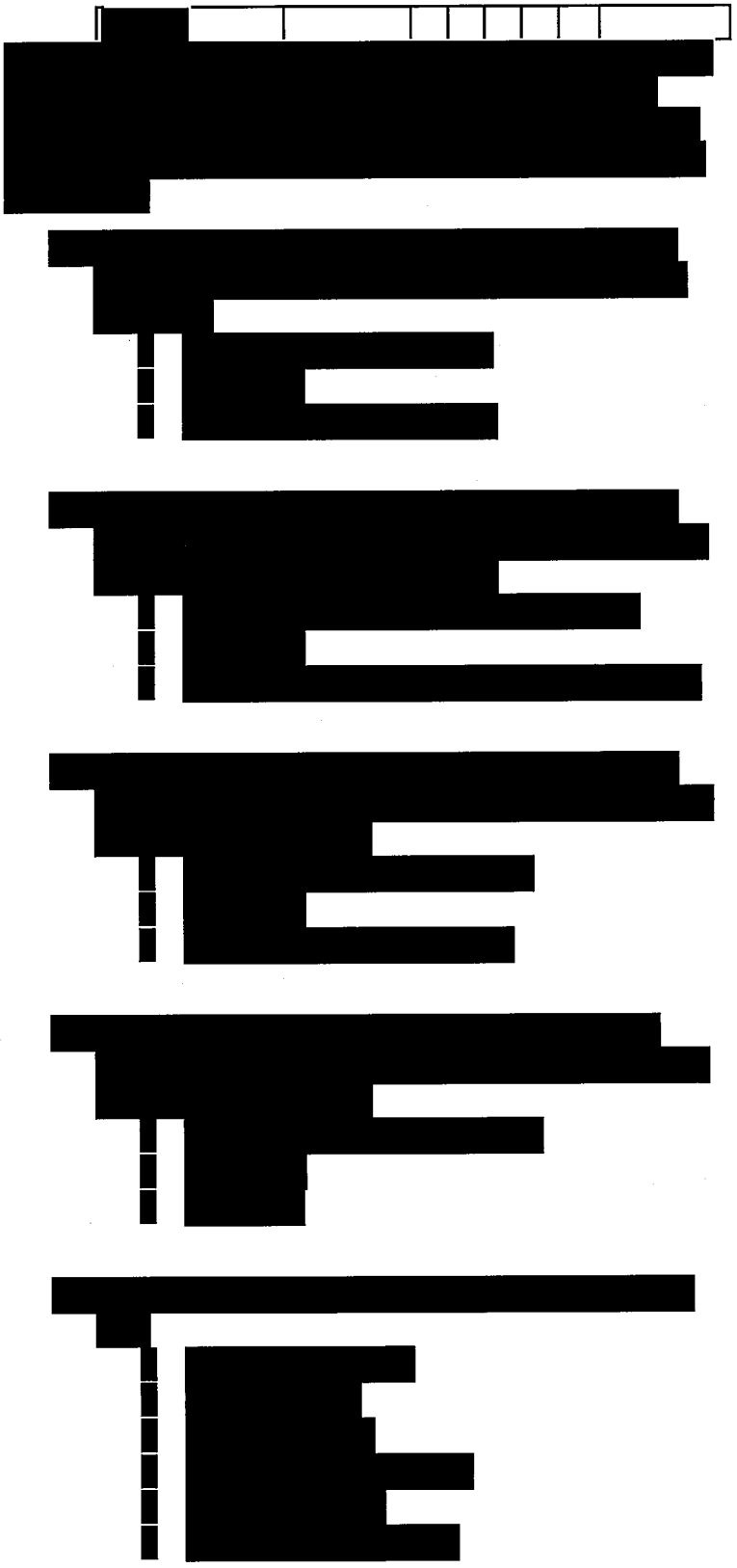

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