Protocol Number: TS121-US201

A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of TS-121 as an Adjunctive Treatment for Patients with Major Depressive Disorder with an Inadequate Response to Current Antidepressant Treatment

Investigational Product: TS-121

Sponsor: Taisho Pharmaceutical R&D Inc.
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Version: Amendment 4

Document Dates: Apr 23 2018

Original Protocol: Version 1.0, Nov 23 2016

PROTOCOL SIGNATURE SHEET

A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety, and Efficacy of TS-121 as an Adjunctive Treatment for Patients with Major Depressive Disorder with an Inadequate Response to Current Antidepressant Treatment

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Protocol Amendment 4

By my signature below, I approve this protocol (including appendices).

Approval Signatures:

INVESTIGATOR SIGNATURE SHEET

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Protocol Amendment 4

By signing below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) and I understand that any changes in the protocol must be approved in writing by the Sponsor and the IRB before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Approval Signature:

Principal Investigator: _____ _____

Name Date

_____

Name of Facility

_____

Address

_____

City, State, Zip Code

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Phone Number

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STUDY CONTACT PAGE

Sponsor Contact:	[redacted]
CRO Project Manager:	
CRO Medical Monitor	

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2 LIST OF ABBREVIATIONS

Term	Definition	Term	Definition
ACTH	Adrenocorticotropic hormone	**FDA**	Food and drug administration
ADT	Antidepressant therapy	**GCP**	Good clinical practices
AE	Adverse event	**GGT**	Gamma glutamyltransferase
ALP	Alkaline phosphatase	**GPCRs**	G-protein coupled receptors
ALT	Alanine aminotransferase	**HAM-A**	Hamilton anxiety scale
AST	Aspartate aminotransferase	**HAM-D**	17 items Hamilton depression scale
ATRQ	Antidepressant treatment response questionnaire	**HDL**	High density lipoprotein
AVP	Arginine vasopressin	**HIPAA**	Health insurance portability and accountability act
BMI	Body mass index	**HIV**	Human immunodeficiency virus
bpm	Beats per minute	**HPA**	Hypothalamus-pituitary-adrenal
BUN	Blood urea nitrogen	**HS-CRP**	High sensitivity C-reactive protein
C	Cortical cataract	**IATA**	International air transport association
CFR	Code of federal regulations	**ICF**	Informed consent form
CGI-I, S	Clinical global impression-Improvement, -Severity	**ICH**	International conference on harmonization
Cl	Chloride	**IL**	Interleukin
C_{max}	Maximum plasma concentration	**IRB**	Institutional review board
Con Med	Concomitant medication	**IUD**	Intrauterine device
CPK	Creatine phosphokinase	**IWRS**	Interactive web response system
CRA	Clinical research associate	**K**	Potassium
CRF	Corticotropin-releasing factor	**kg**	Kilograms
CRF	Case report form	**LC-MS/MS**	Liquid chromatography-tandem mass spectrometry
CRO	Clinical research organization	**LDH**	Lactate dehydrogenase
C-SSRS	Columbia suicidality severity rating scale	**LDL**	Low density lipoprotein
CTNI	Clinical trials network and institute	**LOCS**	Lens opacities classification system
CV	Curriculum vitae	**LogMAR**	Logarithm of the minimum angle of resolution
CYP	Cytochrome P450	**MAD**	Multiple ascending dose
DMP	Data management plan	**MADRS**	Montgomery Asberg depression rating scale
DNA	Deoxyribonucleic acid	**MCH**	Mean corpuscular hemoglobin
DSM	Diagnosis and statistical manual of mental disorders	**MCHC**	Mean corpuscular hemoglobin concentration
ECG	Electrocardiogram	**MCV**	Mean corpuscular volume
eC/PRO	Electronic clinician and patient rated outcome	**MDD**	Major depressive disorder
ECT	Electroconvulsive therapy	**MDMA**	3,4-methylenedioxy-N-methylamphetamine
EDTA	Ethylenediaminetetraacetic acid	**MedDRA**	Medical dictionary for regulatory activities
EOT	End of treatment	**MGH**	Massachusetts general hospital
ET	Early termination	**MINI**	MINI-International neuropsychiatric Interview
ETDRS	Early treatment diabetic retinopathy study	**mg**	Milligrams

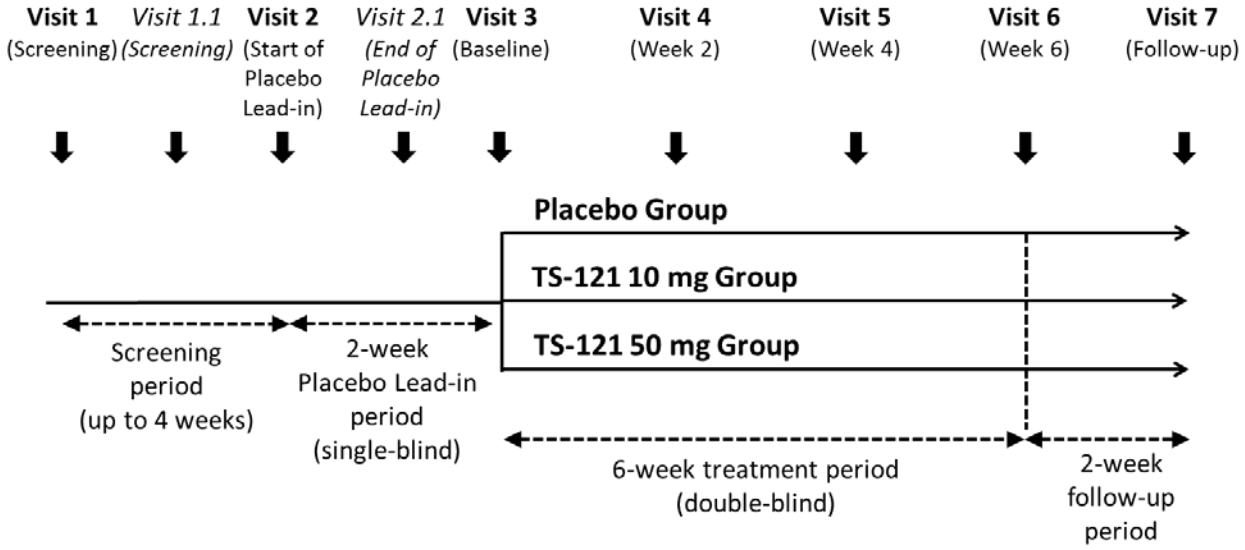
Term	Definition	Term	Definition
Mg	Magnesium	**RDW**	Red cell distribution width
mL	Milliliter	**RO**	Receptor occupancy
mmHg	Millimeter of mercury	**rpm**	Revolutions per minute
MMRM	Mixed model repeated measures analysis	**rTMS**	Repetitive transcranial magnetic stimulation
MS	Medical services	**SAD**	Single ascending dose
msec	Milliseconds	**SAE**	Serious adverse event
Na	Sodium	**SAP**	Statistical analysis plan
NDA	New drug application	**SDQ**	Symptoms of depression questionnaire
NC	Nuclear color	**sec**	Seconds
NESS	New England survey systems	**SGOT**	Serum glutamic-oxaloacetic transaminase
NO	Nuclear opalescence	**SGPT**	Serum glutamic-pyruvic transaminase
P	Posterior subcapsular cataract	**SNRI**	Serotonin norepinephrine reuptake inhibitor
PCP	Phencyclidine	**SOP**	Standard operational procedure
PET	Positron emission tomography	**SSRI**	Selective serotonin reuptake inhibitor
PD	Pharmacodynamics	**THC**	Tetrahydrocannabinol
PGx	Pharmacogenomics	**TNF-α**	Tumor necrosis factor alpha
PHI	Protected health information	**V_{1a}**	Vasopressin 1a
PK	Pharmacokinetics	**V_{1b}**	Vasopressin 1b
PO	Per os	**V_2**	Vasopressin 2
QTcB	Bazett's corrected QT interval	**WBC**	White blood cell
QTcF	Fridericia's corrected QT interval	**WHO**	World health organization
RBC	Red blood cell		

3 SYNOPSIS

Protocol Title	A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of TS-121 as an Adjunctive Treatment for Patients with Major Depressive Disorder with an Inadequate Response to Current Antidepressant Treatment
Protocol Number	TS121-US201
Phase of Development	2a
Number of Study Sites	Approximately 25 US sites
Study Drug	TS-121: An oral, investigational new drug with antagonistic activity of the vasopressin 1b receptor (V_{1b} receptor)
Indication	Major Depressive Disorder (MDD)
Number of Patients	Approximately 180 randomized male and female MDD patients between 18 and 65 years of age inclusive • Placebo Group: 60 patients • TS-121 10 mg Group: 60 patients • TS-121 50 mg Group: 60 patients
Objectives	<u>Primary Objectives</u> • To evaluate the safety and tolerability of TS-121 compared to placebo in MDD patients • To evaluate the efficacy of two dose levels of TS-121 compared to placebo on MDD symptoms in MDD patients <u>Exploratory Objective</u> • To evaluate the effectiveness of biomarkers in predicting TS-121 response with retrospective stratification of patients via baseline values of HPA axis and inflammatory biomarkers
Safety assessments	Safety and tolerability will be assessed from the time the patient is administered the investigational product through the final study procedure. Safety variables for assessment will include: • Adverse events • Physical examination • Columbia Suicide Severity Rating Scale (C-SSRS) • Body weight • Vital signs

	• Clinical laboratory tests (hematology, biochemistry and urinalysis) • 12-lead electrocardiogram (ECG) • Ophthalmological examinations
Efficacy assessments	<u>Primary Endpoint</u> • Change in MADRS total score from Visit 3 (Baseline) to Visit 6 (EOT) <u>Secondary Endpoints</u> • Changes from Visit 3 (Baseline) to Visit 6 (EOT) for CGI-S, SDQ, and HAM-A total scores • Percentage of CGI-I improvers (“Very much improved” or “Much improved”) • Percentage of MADRS responders (≥ 50% reduction in total score)
Pharmacodynamic and Pharmacokinetic assessments	<u>Exploratory Endpoints</u> • Pharmacokinetic data from Visit 6 may be explored relative to study results (mental health assessments and/or laboratory values) • Change from Visit 3 (Baseline) to Visit 6 (EOT) for plasma copeptin and inflammatory markers (TNF-α, IL-1, IL-6, HS-CRP) • To evaluate the effectiveness of biomarkers in predicting TS-121 response with retrospective stratification of patients via baseline values of HPA axis and inflammatory biomarkers consisting of: o Hair cortisol o Salivary cortisol o Urine cortisol o Plasma copeptin, and o Inflammatory markers (TNF-α, IL-1, IL-6, HS-CRP)

Study Design:



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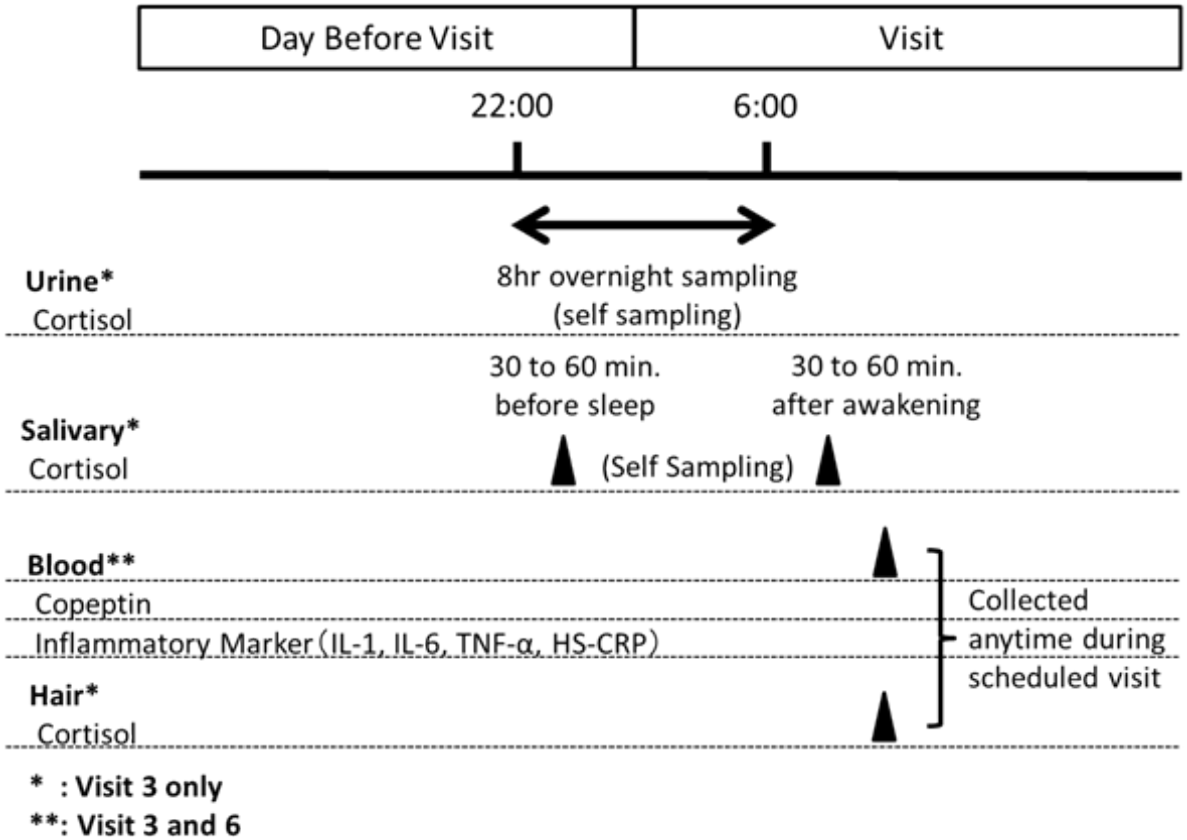

*** : Visit 3 only**
****: Visit 3 and 6**

Study Design and Procedures	This multicenter study is comprised of a screening period of up to 4 weeks, with a 2-week single-blind placebo lead-in period followed by a 6-week randomized, double-blind, placebo-controlled treatment period with a 2-week follow-up period, comparing the safety, efficacy, pharmacokinetics, and exploratory pharmacodynamics of TS-121 to placebo as an adjunctive treatment for patients with MDD. Patients must remain on the same single antidepressant (SSRI, SNRI or bupropion) for 6 weeks, and fixed dose for 4 weeks prior to Visit 1.1. Patients will remain on their current antidepressant therapy (ADT) with a fixed dose throughout the course of the study. **Visit 1 (Screening):** Patients will visit the site for screening assessments and an initial review of study requirements. In addition to confirming the diagnosis of MDD by MINI, a trained site rater will employ the 17-items Hamilton depression scale (HAM-D), which will be subsequently confirmed through an additional HAM-D assessment conducted by a central rater (Visit 1.1) prior to a 2-week placebo lead-in period. Patients will schedule a phone call for central rater assessments. **Visit 1.1 (Screening)**: The central rater will contact the patient as scheduled, and will administer the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) for assessment of current ADT, adequacy of duration and dose of prior and current ADT, as well as degree of improvement. The central rater will also complete the HAM-D assessment and SAFER inventory for confirmation of placebo lead-in eligibility. Results will be communicated to the site prior to Visit 2. **Visit 2 (Start of Placebo Lead-In):** Following initial eligibility confirmation, qualified patients will return to the site initiating a 2-week, single-blind placebo lead-in period. Patients will be instructed to take 3 capsules of investigational product (placebo) once-daily in the morning and to maintain their current ADT regimen for two consecutive weeks. Patients will download AiCure software to their smart phone or receive an AiCure device that will monitor medication adherence during the 2-week placebo lead-in period (and for the duration of the 6-week treatment period) using AiCure's interactive mobile device technology. An ophthalmologist will conduct a thorough eye examination (including slit lamp under mydriasis). Patients will be provided with supplies and instructions for at-home collection of saliva and urine for exploratory HPA axis assessment. Patients will schedule another phone call for central rater assessments (Visit 2.1), and Visit 3 will be scheduled. **Visit 2.1 (End of Placebo Lead-In)**: Response to placebo will be assessed using HAM-D by a central rater via phone. Results will be communicated to the site prior to Visit 3. The current HAM-D score and change in HAM-D score from Visit 1.1 to Visit 2.1 will be used to determine eligibility. **Visit 3 (Baseline):** After completing the placebo lead-in period, patients will return to the site for baseline evaluations. Outpatient biological samples will be collected. Laboratory, safety and efficacy assessments will be performed. Placebo lead-in dosing compliance will be assessed. Following confirmation of eligibility, patients will be randomly assigned to receive TS-121 10 mg, 50 mg, or placebo in a 1:1:1 ratio. Patients will be instructed to continue taking investigational product once-daily in the morning and to maintain their current

	ADT regimen. Visit 4 will be scheduled. **Visits 4 (Week 2):** Patients will return to the site for safety and efficacy assessments. Drug accountability and dispensing of a new supply of investigational product will be performed. Compliance with the dosing schedule will be assessed. Visit 5 will be scheduled. **Visit 5 (Week 4):** Patients will return to the site for safety and efficacy assessments. Drug accountability and dispensing of a new supply of investigational product will be performed. Compliance with the dosing schedule will be assessed. Visit 6 will be scheduled, which includes an ophthalmological examination. **Visit 6 (Week 6):** Patients will return to the site for end-of-treatment safety, efficacy, pharmacokinetic, and exploratory pharmacodynamic assessments. Final drug accountability will be performed. Visit 7 will be scheduled, which includes an ophthalmological examination. **Visit 7 (Follow-up):** Patients will return to the site for a follow-up evaluation of safety and efficacy assessments approximately two weeks after Visit 6.

4 BACKGROUND INFORMATION

4.1 Introduction

Depression is ranked as the leading cause of disability worldwide by the World Health Organization (WHO Fact Sheet No. 369; Oct. 2012). In particular, major depressive disorder (MDD) is a psychiatric illness that is characterized by the occurrence of one or more major depressive episodes, along with an absence of any history of manic, mixed, or hypomanic episodes. It is a serious, often recurrent medical condition, which is associated with a 15.9% lifetime risk of suicide attempt (Chen, 1996). Results of the World Mental Health Survey Initiative (2011) found that the average lifetime incidence of DSM-IV major depressive episodes was 14.6%, with a 12-month prevalence of 5.5% in higher income counties (Bromet, 2011).

Stress has also been hypothesized to be a pivotal factor in the pathophysiology of depression, specifically by way of the hypothalamus-pituitary-adrenal (HPA) axis, which appears to be a prominent mechanism by which the brain reacts to both acute and chronic stress through feedback loops involving several neuroendocrine hormones, including adrenocorticotropic hormone (ACTH) and cortisol. In addition, both corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) both of which are produced in the paraventricular nucleus of the hypothalamus (Vale, 1981; Aguilera, 2000), are considered primary factors in the regulation of HPA axis activity. Receptor subtypes for these neuropeptides, which may be involved in the regulation of HPA axis activity, have attracted much attention as potential targets for the treatment of depression and anxiety.

Despite the availability of numerous pharmacological and psychological treatment options, fewer than 50% of all patients with depression show full remission with optimized treatment, including trials on numerous medications with and without concurrent psychotherapy (Rush, 2006). Thus, there is a clear need for efficacious and well-tolerated agents to treat and prevent recurrent episodes of depression, and current research continues to investigate novel molecular and cellular mechanisms of depression.

TS-121 (drug substance code [redacted]) is an investigational new drug with antagonistic activity of the vasopressin receptor 1b (V_{1b} receptor), which plays a role in the modulation of stress and mood. Based on nonclinical studies conducted by Taisho Pharmaceutical Co., Ltd. Research Center (Japan), TS-121 appears to be a promising candidate for clinical development with a novel mode of action that may benefit MDD patients.

4.2 Mechanism of Action of Vasopressin Receptor 1b (V_{1b} Receptor)

AVP, a cyclic nonapeptide, together with CRF, are principal factors in the regulation of ACTH release from the anterior pituitary (Aguilera, 2000), and have been reported to play an important

role in mood regulation. AVP is synthesized in the parvocellular division of the paraventricular nucleus of the hypothalamus, which is linked to activation of the HPA axis, and upon stress exposure. AVP is released from the median eminence into the pituitary portal circulation, where it strongly potentiates the effects of CRF on the release of ACTH. Clinically, the plasma AVP levels are elevated in patients with MDD, compared with healthy controls (de Winter, 2003), (van Londen, 1997). In previous studies, subjects with melancholic-type or anxious-retarded depression exhibited elevated plasma AVP levels. Plasma AVP levels are also reportedly positively correlated with cortisol levels during depression, particularly in suicide victims (Inder, 1997).

AVP exerts its effects via three receptor subtypes: V_{1a}, V_{1b} and V_2. These subtypes are G-protein coupled receptors (GPCRs) (Serradeil-Le Gal, 2002b). Among them, the V_{1b} receptor is mainly expressed in the anterior pituitary and is thought to be involved in the regulation of HPA axis activity and emotional processes (Lolait, 1995). Indeed, SSR149415, a non-peptide V_{1b} receptor antagonist with high affinity and potent antagonistic activity for the V_{1b} receptor (Griebel, 2005), has been reported to attenuate increases in plasma ACTH induced by CRH+AVP (Serradeil-Le Gal, 2002a), and to exhibit antidepressant- and anxiolytic-like activities in a variety of rodent models of depression and anxiety, with more pronounced effects in models involving stressful situations (Serradeil-Le Gal, 2002a; Griebel, 2005; Iijima, 2007). Therefore, blockade of V_{1b} receptor may provide a novel approach to treating stress-related disorders such as depression and anxiety disorders.

[redacted] is a potent and selective antagonist of V_{1b} receptor, both in *in vitro* and in *ex vivo* studies, and has been shown to possess antidepressant activity in several animal models of depression, including one which mimics severely impaired HPA axis function.

Additional details can be found in Section 3 of the Investigator's Brochure.

4.3 Name and Description of Investigational Product

[redacted] is the name of the active ingredient of TS-121.

[redacted]

4.4 Summary of Nonclinical and Clinical Findings

4.4.1 Summary of Nonclinical Findings

To date, a series of single and repeat dose oral toxicity studies in rats and dogs have been conducted to assess the systemic toxic potential of [redacted] and to support Phase 1 and Phase 2 clinical studies. Though the relevance to human subjects is not yet fully understood, the findings presented below were noted in nonclinical studies.

Additional details are described in the Sections 7.3.1 and 7.3.2 of the Investigator's Brochure.

[redacted]

[redacted]

4.4.2 Summary of Clinical Findings

Three Phase 1 studies, a single ascending dose (SAD) study (TS121-US101), a multiple ascending dose (MAD) study (TS121-US102), and a positron emission tomography (PET) receptor occupancy study (TS121-US103) have been conducted. Overall, 78 healthy male and female adult subjects were administered TS-121 to date. A top dose of 50 mg for 10 days was deemed safe and well tolerated. There were no deaths or serious adverse events reported in any of the studies.

Treatment emergent ventricular arrhythmias have been reported following single and multiple dose administrations of TS-121.

No safety trends were observed in clinical laboratory, vital signs, or physical examinations. In consideration of the nonclinical findings at the time of the MAD study, comprehensive eye examinations were performed; no abnormalities in the eyes relating to lens opacity were reported, including at the highest dose level of 50 mg for 10 days.

Additional details are described in Sections 8 and 9 of the Investigator's Brochure.

4.4.3 Known and Potential Risks to Human Subjects

Though the relevance to human subjects is not yet fully understood, nonclinical findings suggested that potential risks include cataract, hepatotoxicity, effects on the gastrointestinal system and effects on the renal system. To date, no apparent trends related to these potential risks were noted in the clinical studies.

Treatment emergent ventricular arrhythmias have been reported following single and multiple dose administrations of TS-121. During the SAD study (TS121-US101), two subjects exposed to 2.5 mg of TS-121 had defined intervals of ventricular arrhythmias while on telemetry. Plasma levels were approximately 50% of C_{max} values (40 to 70 ng/mL). The events were without symptoms, resolved without intervention, and produced no residual effects. The events were considered mild in intensity and possibly related to the study drug. One subject was discontinued from the trial, and one subject completed the trial.

In the MAD study (TS121-US102), one subject showed a single episode of 4 consecutive premature ventricular contractions without symptoms while on telemetry approximately 15 hours

after receiving 50 mg dose of TS-121 on Day 9. The investigator assessed the episode as a clinically significant event and described the event as mild and possibly related to TS-121. The subject completed the trial with no additional events.

In a PET receptor occupancy study (TS121-US103), no abnormal ECG results were reported following single TS-121 doses of up to 50 mg. See Sections 8 and 9 of the Investigator's Brochure for additional information.

4.5 Study Rationale

This multicenter study is comprised of a screening period of up to 4 weeks, with a 2-week single-blind placebo lead-in period followed by a 6-week randomized, double-blind, placebo-controlled treatment period with a 2-week follow-up period, comparing the safety, efficacy, pharmacokinetics, and exploratory pharmacodynamic effects of TS-121 to placebo as an adjunctive treatment for patients with MDD. To assess for primary effect of TS-121 vs. placebo, patients must remain on the same ADT for 6 weeks, and fixed dose for 4 weeks prior to screening. Patients will remain on their current antidepressant treatment and dose throughout the course of the study.

The study employs multiple quality attributes to reduce placebo response and to monitor patient compliance. Placebo response in MDD trials is well documented. The study employs a 2-week placebo lead-in to enrich the population with placebo non-responders. Additionally, to reduce investigator bias, a central rater assessment will be employed during the screening and the placebo lead-in periods to evaluate initial eligibility and to assess placebo response by use of the HAM-D. Furthermore, central raters will remain involved in the trial with oversight of the MADRS instrument during the treatment period. Patient compliance with dosing will be assessed during the placebo lead-in through completion of the trial by use of AiCure platform of real-time dose monitoring.

TS-121 is postulated to work primarily through the HPA axis. Biomarkers for HPA axis will be assessed at Visit 3, prior to randomized treatment administration, to assess potential screening and/or stratification factors in future trials. There is insufficient predictive knowledge of MDD patients' HPA axis biomarkers and MDD patient response to V1b receptor antagonist. Therefore, a post-hoc exploratory analysis may be conducted comparing patient response to baseline patient profiles.

[redacted] is a high affinity antagonist for the human vasopressin receptor 1b (V1b receptor) that has been shown to work in a number of animal models for depression, suggesting that TS-121 may be a useful treatment option for individuals experiencing MDD. TS-121 dose selection was based on accumulated experience from preclinical studies and three previous clinical trials. The SAD study (TS121-US101) and MAD study (TS121-US102) provide safety and tolerability

support for the current doses. [redacted]

5 STUDY OBJECTIVES

5.1 Primary Objectives

- To evaluate the safety and tolerability of TS-121 compared to placebo in MDD patients
- To evaluate the efficacy of two dose levels of TS-121 compared to placebo on MDD symptoms in MDD patients

5.2 Exploratory Objective

- To evaluate the effectiveness of biomarkers in predicting TS-121 response with retrospective stratification of patients via baseline values of HPA axis and inflammatory biomarkers

6 STUDY DESIGN

6.1 Study Design

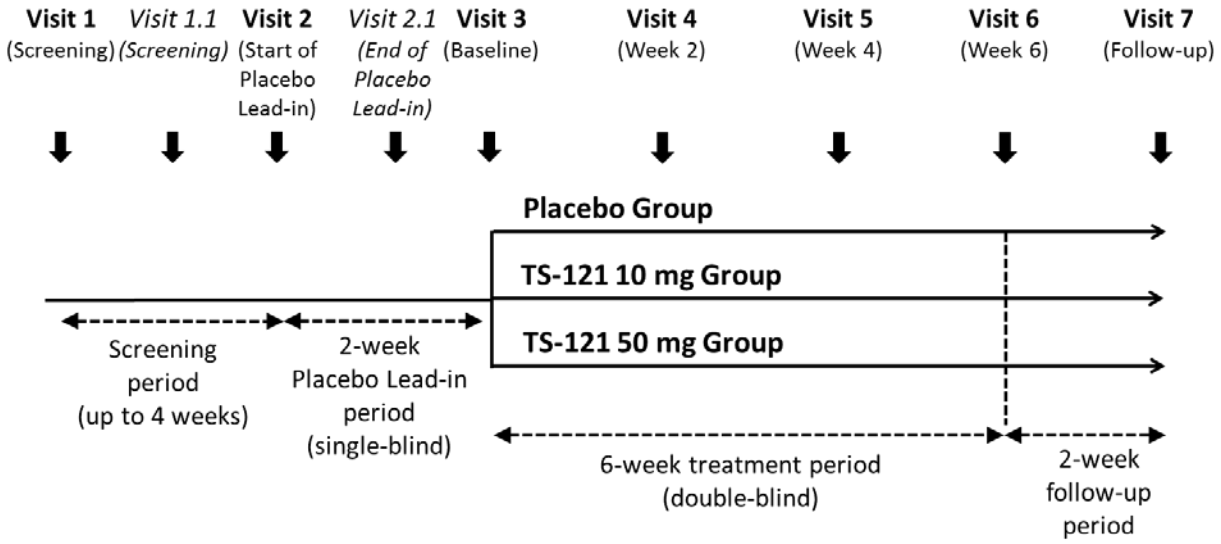

Figure 1. Study Design

6.2 Randomization Procedure

A subject number will be assigned to each patient at the time of informed consent at each site. At Visit 3 (Baseline), following completion of the 2-week placebo lead-in, patients who continue to meet all entry criteria will be assigned a randomization number by IWRS. A patient cannot be assigned more than one randomization number. Patients will retain their subject and randomization numbers for the duration of the study.

Each eligible patient at Visit 3 will be randomly assigned to receive either TS-121 10mg, 50mg or placebo in a ratio of 1:1:1. The kit number dispensed by IWRS will correspond to the assigned treatment.

Treatment assignments of patients will be held by IWRS throughout the study.

6.3 Blinding

To maintain the blind, matching placebo capsules will be provided for the TS-121 capsules. The placebo lead-in period will be single-blind for patients. Following completion of the placebo lead-in period, the treatment period will be double-blinded (neither the investigator nor the patient will have knowledge of the treatment assignment). The sponsor and CRO study personnel, including those involved in monitoring, data management and data analysis will also

be blinded to the treatment assignment during the trial.

6.4 Unblinding

The randomized investigational product administered to each patient will not be known to the patient or to study site personnel, except for:

- Designated IWRS personnel including study-independent personnel from the CRO (if applicable)
- Designated personnel for drug packaging
- The bioanalytical laboratory performing the PK analysis

Under normal circumstances, the blind should not be broken until all patients have completed the study and the database has been locked and finalized. The blind may be broken if specific emergency treatment would be indicated by knowing the treatment status of the patient. The blind may also be broken for events of clinical significance (see Section 11.3). In the event that the sponsor decides to break the blind for events of clinical significance, the sponsor must inform the investigator of the unblinding. The date, time and reason for the unblinding must be documented in the study source records and recorded on the CRF. If data are unblinded, access to the unblinded data should be limited to maintain data integrity of the study. Additional details will be described in the safety plan.

6.5 Early Discontinuation

Patients may discontinue study participation at any time in this trial. All randomized patients who prematurely discontinue participation after receiving at least one dose of investigational product will return to the site for an Early Termination Visit as early as possible after discontinuation, and separately, for a follow-up visit approximately 14 days after their last dose.
Patients who discontinue prior to randomization at Visit 3 will be considered screening failures. If discontinued once entering the placebo lead-in period at Visit 2 but prior to randomization, discontinued patients will be required to undergo a physical examination and completion of the C-SSRS before being discharged from the study.

7 STUDY POPULATION

7.1 Study Population

This study will screen approximately 300 patients and randomize approximately 180 MDD patients. These patients are defined by the inclusion and exclusion criteria described in the following sections.

7.1.1 **Inclusion Criteria**

Patients must meet all of the following criteria to be eligible for enrollment:

1. Adult males and females between 18 and 65 years of age inclusive (at time of initial informed consent)
2. Patients with a current diagnosis of MDD by DSM-5, confirmed through a structured interview using MINI
3. Patients who receive the same antidepressant (SSRI, SNRI or bupropion monotherapy) for the current episode for at least 6 weeks of continuous treatment prior to Visit 1.1 and at least 4-weeks on a fixed dose prior to Visit 1.1 (the dosing duration and appropriateness of the dosage will be confirmed at Visit 1.1 by the central rater using MGH ATRQ)
   [Note: Patients who currently receive 2 or more antidepressants are excluded with exception of Trazodone (≤ 50 mg/day) for sleep as outlined in Section 8.3. Fluvoxamine is prohibited as it is a moderate CYP 3A4 inhibitor (see exclusion criterion #14 and Appendix 1)]
4. Patients willing to remain on the same primary ADT and fixed dose throughout the course of the study
5. Patients who meet the total score on the HAM-D as listed below (as determined by Site or Central Raters):
   - HAM-D ≥ 18 at Visit 1 (Site)
   - HAM-D ≥ 18 at Visit 1.1 (Central)
   - HAM-D ≤ 25% improvement from Visit 1.1 to Visit 2.1 (Central)
   - HAM-D ≥ 18 at Visit 2.1 (Central)
6. Patients who are rated as eligible based on the SAFER Inventory conducted at Visit 1.1
7. Female patients of childbearing potential must agree to use one of the accepted barrier methods of contraception (listed below) during the study (including the screening period prior to receiving trial medication), for at least 90 days following the last dose.
   - condom (male or female) with spermicide
   - diaphragm or cervical cap with spermicide and condom (male)

[Note: Oral contraception, vasectomy of the partner and IUD alone are not considered sufficient contraception. One of the aforementioned barrier methods listed above must be used. Females who are not currently sexually active must also consent to use one of these accepted methods of contraception should they become sexually active while participating in the study.]

Female patients of non-childbearing potential must be either surgically sterile or post-menopausal (absence of *spontaneous* menses for 12 consecutive months)

Male patients with partners of childbearing potential must agree to use appropriate and effective measures of contraception (e.g., condom plus diaphragm with spermicide; condom plus spermicide) and/or refrain from donating sperm from Visit 2 and for at least 90 days following the last dose.

8. Body Mass Index (BMI) ≥ 18 and ≤ 38 kg/m^2 at Visit 1 using the following formula: weight (kg) / [height (m)]^2
9. Patients who are able and willing to provide written informed consent and authorization for protected health information disclosure in accordance with Good Clinical Practice
10. Patients who are able to read, speak and understand English

7.1.2 **Exclusion Criteria**

Patients are to be excluded from study participation if they meet any of the following exclusion criteria:

1. Patients with first episode of depression >60 years of age
2. Patients with inadequate response to ≥2 prior antidepressant treatments (not including current antidepressant) of at least 4 weeks duration each for the current episode at Visit 1 (to be confirmed at Visit 1.1 by the central rater using MGH ATRQ)
3. Patients whose current depressive episode is diagnosed with psychotic features, catatonic features, post-partum (primary onset), or is secondary to a general medical disorder
4. Patients with a diagnosis of any of the following DSM-5 class disorders
    - Schizophrenia spectrum and other psychotic disorders
    - Bipolar and related disorders
    - Anxiety disorders
      [Note: Co-morbid generalized anxiety disorder and social anxiety disorder will be allowed in the study if the primary diagnosis is MDD, and if in the opinion of the

investigator, the comorbid anxiety is not likely to interfere with the subject's ability to participate in the trial or affect study outcome]

- Obsessive-compulsive and related disorders
- Trauma- and Stressor-related disorders

5. Patients who received electroconvulsive therapy (ECT) within 12 months of Visit 1, received more than one course of ECT in their lifetime or plan to receive ECT during the study
6. Patients who received repetitive transcranial magnetic stimulation (rTMS) within 12 months of Visit 1 (Screening) or plan to receive rTMS during the study
7. Patients who plan to initiate or terminate cognitive or behavioral psychotherapy or alter the frequency of ongoing therapy during this study
8. Patients who have attempted suicide within the past 6 months
9. Patients who have a C-SSRS suicidal ideation score of 5 or "yes" response for any of the C-SSRS suicidal behavior questions at Visit 1 or Visit 3
10. Patients with history or presence of intellectual disability, pervasive developmental disorder, cognitive disorder, neurodegenerative disorder (e.g., Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease), or brain injury
11. Patients with any history or complication of convulsive disorder (e.g., epilepsy)
12. Patients with history or presence of medical conditions associated with HPA dysfunction (e.g., Cushing syndrome)
13. Patients who are undergoing treatment with drugs that might influence HPA axis function, including psychotropic medications, benzodiazepines, metyrapone, lithium and/or corticosteroids
    [Please refer to Section 8.3 for a more detailed list of prohibited concomitant medications]
14. Patients who need/plan to take moderate to strong CYP3A4 inhibitors/inducers (food, beverages, medications and supplements) during this study (see Appendix 1)
15. Patients who work night shifts or need to work night shifts during the trial
16. Females who are pregnant, intend to become pregnant (within 90 days of the last dose), or who are breastfeeding
17. Patients with significant hepatic, renal, cardiovascular, hemodynamic, pulmonary, gastrointestinal, hematological, locomotor, immunologic, ophthalmologic, metabolic, neurological, or endocrine disease that in the opinion of the investigator would confound participation or study results

18. Patients with clinically significant ECG* findings at Visit 1 or Visit 3, or hematology, biochemistry, or urinalysis abnormalities at Visit 1 (abnormal laboratory values considered to be not clinically significant as per the investigator are acceptable)
    [* Note: QTcF interval of > 450 msec in males or > 470 msec in females, will be the basis for exclusion from the study; ECG may be repeated once for confirmatory purposes, if an initial value is obtained that exceeds the values specified]
19. Patients with history or presence of cataract (lens opacities with vision disturbances), glaucoma, chronic inflammatory eye disease, significant eye trauma, any ophthalmic surgical procedure (e.g. cataract or glaucoma) or any ocular laser surgery in either eye
20. Patients with lens opacity based on ophthalmological examination performed at Visit 2 as listed below:
    - Nuclear opalescence (NO) with a LOCSIII classification > 3.0 in either eye
    - Nuclear color (NC) with a LOCSIII classification > 3.5 in either eye
    - Cortical lens opacities (C) with a LOCSIII classification > 2.0 in either eye
    - Posterior subcapsular lens opacities (P) with a LOCSIII classification > 0.3 in either eye
21. Patients with a history (within 5 years) or presence of malignancy at Visit 1 [Note: History (within 5 years) of non-metastatic, non-progressive basal and/or squamous cell carcinoma of the skin, in situ cervical and prostate cancer are exceptions (currently in remission)]
22. Patients with history of alcohol or illicit substance abuse / dependence within 12 months of Visit 1 or positive urine drug results at Visit 1
    [Note: Patients with positive urine drug results may be eligible at investigator's discretion if the results are reasonably explained as false positive]
23. Patients with history and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or HIV antibodies 1 and 2 at Visit 1
24. Patients who have received treatment with an investigational product or device that has not received regulatory approval for any indication, or who have participated in a clinical research study within 90 days prior to Visit 1
25. Patients who have been previously administered TS-121
26. Investigative site personnel or their immediate families (spouse, parent, child or sibling whether biological or legally adopted)
27. Taisho employee or their immediate families (spouse, parent, child or sibling whether

biological or legally adopted)

28. Patients with poor treatment compliance (<75%) in taking the investigational product between Visit 2 and Visit 3
    [Note: Treatment compliance should be calculated as the percentage of days a patient is compliant in taking the full daily dose of investigational product (3 capsules/day)]
29. Any patient not able to meet study requirements

7.1.3 **Replacement Patients**

Patients withdrawn for safety or tolerability will not be replaced. Patients discontinued due to other reasons, e.g., dosing compliance, may be replaced at the discretion of the sponsor in order to achieve the study objectives.

8 TREATMENT OF PATIENTS

8.1 Investigational Product

Physical characteristics of the investigational product are listed in Table 1. A detailed description of the investigational product as well as a listing of excipients is included in Section 4.2.1 of the Investigator's Brochure.

Table 1. Investigational product description

INVESTIGATIONAL PRODUCT	DESCRIPTION
TS-121 capsules (drug units of 10 mg and 20 mg)	White, opaque, hard gelatin capsule
Matching placebo capsule for TS-121	White, opaque, hard gelatin capsule

8.1.1 Packaging and Labeling

Investigational product (TS-121 and matching placebo) will be provided as Size 2, white, hard gelatin capsules. TS-121 capsules will contain 10 and 20 mg active pharmaceutical ingredient. The investigational product will be packaged in child resistant blister packs and assembled as patient kits. Each kit will be labeled as required in 21 CFR Section 312.6.

Each blister pack will contain a 1-week supply of investigational product, and will include an additional 2-day supply to account for visit windows. In total, a 2-week supply of investigational product (2 blister packs) will be dispensed to the patient at each visit.

8.1.2 Handling, Dispensing, and Administration of Investigational Product

The investigational product should be stored in a secure area at room temperature and protected from moisture, freezing and excessive heat. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to eligible study patients. The investigational product must only be dispensed from the study site by authorized personnel as indicated in the site delegation log.

Patients will be instructed to take their daily dose by mouth once in the morning, preferably after breakfast. In case a patient misses dosing in the morning, the patient should skip the dose for that day and resume taking the investigational product on the morning of the next day. Patients will maintain current ADT dosing schedules. Compliance will be monitored using the AiCure platform (see Section 8.1.3). The patient will be instructed to take 3 capsules as described in Table 2 in addition to their ongoing ADT.

Table 2. Investigational product administration

Group	Dose strength and number of capsules to be administered
TS-121 10 mg	TS-121 (drug unit of 10 mg) capsule; 1 capsule TS-121 Placebo capsule; 2 capsules
TS-121 50 mg	TS-121 (drug unit of 10 mg) capsule; 1 capsule TS-121 (drug unit of 20 mg) capsule; 2 capsules
Placebo (including investigational product for Placebo Lead-in period)	TS-121 Placebo capsule; 3 capsules

8.1.3 Treatment Compliance

Designated study personnel will dispense the investigational product. Accountability and compliance verification should be documented in the site drug accountability log.

Patients must maintain adherence to scheduled dosing according to inclusion and exclusion criteria during the placebo lead-in period. Patient compliance with the placebo lead-in and randomized treatment will be monitored by the AiCure platform. Daily dosing by patients will be monitored using mobile device technology. Using smartphones, the site will be able to confirm each investigational product ingestion along with the patient's current ADT. Built-in reminders and a communication system will allow real-time intervention in the event of dosing interruptions. See Section 9.2.9 for additional information on the AiCure platform.

8.1.4 Investigational Product Accountability

The Investigator is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. The dispensing of investigational product (TS-121 and placebo) must be documented on a Drug Accountability Form which should include:

- Number of patient kits received
- Amount currently being stored
- Kit numbers
- Dates and initials of person/s responsible for each investigational product inventory entry/movement
- Patient identifiers for dispensing and return
- Number of kits returned to sponsor or sponsor's authorized designee

8.1.5 Return or Destruction of Investigational Product

All unused, partially used, or unopened supplies of investigational product will be returned from each site to the sponsor's designee and will be destroyed upon sponsor request. Documentation and certificates of drug destruction will be forwarded to the sponsor, as applicable. Confirmation of receipt of returns will be sent to study sites.

8.2 Concomitant Drug Therapy

All concomitant medications taken during the study will be recorded on the CRF for each patient, along with the indication (reason taken), dosage information and start and stop dates. Allowed concomitant medications include any prescription or over-the-counter medication not specifically excluded by the protocol. Patients requiring excluded drugs will be discontinued from the study. For a list of prohibited concomitant drugs, see Section 8.3.

If the patient requires concomitant medication for an AE, it must be reported in the patient's study source records and captured electronically. Any changes to concomitant medications during the study must be clearly recorded and the reason for the change should be documented.

8.3 Prohibited / Restricted Concomitant Therapy

Any antidepressants other than the current single SSRI, SNRI or bupropion will be prohibited throughout the study. Dosage of the current SSRI, SNRI or bupropion must remain unchanged throughout the study.

Trazodone (≤ 50 mg/day), in addition to the current ADT will be permitted if it is prescribed to be taken regularly as a sleep aid, has been initiated at least 3 months before the screening visit (Visit 1), and the medication and dosage is to remain unchanged throughout the study (a PRN dosing regimen of trazodone will not be allowed).

Beyond the patient's current ADT, drugs that might influence HPA axis function, including benzodiazepines, metyrapone, lithium and/or corticosteroids, as well as psychotropic medications or drugs that treat excluded mental disorders are prohibited from Visit 1 to 7. Strong/moderate inhibitors/inducers of CYP3A4 are prohibited from Visit 2 to 6. See Section 17 (Appendix 1) for a list of CYP3A4 excluded medications. The use of non-benzodiazepine hypnotics (i.e., zolpidem, zaleplon, zopiclone and eszopiclone) is permitted if treatment has been initiated before the study and the medication and dosage remains unchanged throughout the study.

The study is designed to assess HPA axis $V1_b$ receptor treatment, and will limit potential confounding comorbidities and treatments beyond SSRI, SNRI or bupropion. Benzodiazepines are excluded due to clear evidence of the effect on HPA axis with short-term use, and unknown effects of long-term use on HPA axis. Likewise, metyrapone is excluded, due to primary

pharmacology effecting HPA axis; its primary indication of Cushing's syndrome is also excluded. Lithium is excluded for effects on HPA axis and primary use in excluded mental disorders. Corticosteroids are excluded due to primary effects on HPA axis. Moderate to strong CYP3A4 inhibitors or inducers are excluded, based on preclinical *in vitro* testing. See Section 6.5 of the Investigator's Brochure for additional information on testing.

8.4 Duration of Patient Participation

This study is comprised of a screening period of up to 28 days, a 2-week placebo lead-in, a 6-week treatment period and up to 2-weeks for a follow-up visit. Eligible patients will be entered into a 2-week placebo lead-in at Visit 2, and if all entry criteria are met, randomized at Visit 3. Patients will remain in the treatment period of the study until Visit 6, and will return for a follow-up visit at Visit 7. Patients will participate in the study for approximately 3 months.

8.5 Discontinuation Criteria and Procedures

In accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and the United States Food and Drug Administration (FDA) Regulations, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution.

The investigator and sponsor also have the right to withdraw patients from the study for reasons including the following:

- Significant protocol violation on the part of the investigator or patient;
- Unblinding by the patient, investigator or unauthorized site personnel;
- Self-withdrawal, or refusal by the patient to continue treatment or observations;
- Unacceptable toxicity;
- Decision by the investigator that termination is in the patient's best medical interest and/or for safety reasons;
- Unrelated medical illness or complication(s);
- Sponsor decision to discontinue the study.

If it is determined that a patient is at imminent risk of suicide, the investigator should evaluate for discontinuation as outlined in Section 11.3.1. Patients with a CGI-I score of 6 or 7 at any time during the study should be evaluated for possible discontinuation from the study as outlined in Section 11.4.

The sponsor may choose to terminate the study at any time for any reason. Should a patient decide to withdraw, all efforts will be made to complete and report the required observations as

thoroughly as possible.

Should a patient discontinue prior to completion of the study, the reason for the withdrawal should be recorded. An early discontinuation evaluation should be made at the time of the patient's withdrawal according to the procedures outlined in Section 6.5. In the event that the patient cannot return for the follow-up visit, the site should make all necessary attempts to contact the patient to follow any adverse events.

9 STUDY PROCEDURES AND OBSERVATIONS

9.1 Study Procedures and Observations

Procedures	Visit 1**** (Screening) Day -28 to Day -7	Visit 1.1**** (Screening) Day -13 to Day -2	Visit 2 (Start of Placebo Lead-in) Day 1	Visit 2.1 (End of Placebo Lead-in) Day 13 (±2)	Screen* failure ONLY End of Study	Visit 3** (Baseline) Day 15 (+3)	Visit 4 (Week 2) Day 29 (±3)	Visit 5 (Week 4) Day 43 (±3)	Visit 6 (Week 6) Day 57 (±3)	Visit 7 (Follow-up) Day 71 (±3)	ET***	
											ET	Follow Up
Site Visit	X		X		X	X	X	X	X	X	X	X
Informed Consent (Study, PGx, HIPAA)[a]	X											
Demography	X											
Inclusion and Exclusion Criteria	X		X			X						
Evaluation of Medical and Psychiatric History	X		X									
Evaluation of Prior Medication History	X											
Serology Screen	X											
Urine Drug Screen	X					X						
Urine Pregnancy (all females)	X		X			X	X	X	X	X	X	X
Height	X											
Body Weight	X		X			X	X	X	X	X	X	X
Body Mass Index (BMI)	X											
Physical and Neurological Examination	X				X	X			X	X	X	X
Ophthalmological Examinations[b]			X						X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X				X	X	X	X	X	X	X	X
MINI	X											
HAM-D (SITE Rater)	X											
MGH ATRQ (Central Rater)		X										
HAM-D (Central Rater)		X		X								
SAFER Inventory (Central Rater)		X										
MADRS[c]						X	X	X	X	X		

Procedures	Visit 1**** (Screening) Day -28 to Day -7	Visit 1.1**** (Screening) Day -13 to Day -2	Visit 2 (Start of Placebo Lead-in) Day 1	Visit 2.1 (End of Placebo Lead-in) Day 13 (±2)	Screen* failure ONLY End of Study	Visit 3** (Baseline) Day 15 (+3)	Visit 4 (Week 2) Day 29 (±3)	Visit 5 (Week 4) Day 43 (±3)	Visit 6 (Week 6) Day 57 (±3)	Visit 7 (Follow-up) Day 71 (±3)	ET***	
											ET	Follow Up
MADRS Central Rater Oversight						X ←				→ X		
CGI-S						X	X	X	X	X		
CGI-I							X	X	X	X		
HAM-A						X	X	X	X	X		
SDQ						X	X	X	X	X		
Vital Signs (seated)	X		X			X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)	X					X	X	X	X	X	X	X
Clinical Laboratory Tests	X					X	X	X	X	X	X	X
Exploratory Safety Assessments			X			X	X	X	X	X	X	X
Hair Cortisol Level						X						
Plasma Copeptin Level						X			X			
Salivary Cortisol Level (at home)[d]			Dispense Kit			X						
Urine Cortisol Level (pooled for 8 hr at home)[d]			Dispense Kit			X						
Inflammatory Markers (TNF-α, IL-1, IL-6, HS-CRP)						X			X			
Pharmacokinetic Blood Sampling [redacted])									X			
Pharmacogenomic Blood Sampling						X						
Placebo administration under single-blind			X ←			→ X						
Randomization						X						
Investigational product dispensing, accountability and compliance check[e]			X			X	X	X	X			
Dose administration under double-blind						X ←			→ X			
Drug adherence (AiCure)[f]			X ←						→ X			
Adverse Event Inquiry & Reporting			X ←							→ X	X	X

Procedures	Visit 1**** (Screening) Day -28 to Day -7	Visit 1.1**** (Screening) Day -13 to Day -2	Visit 2 (Start of Placebo Lead-in) Day 1	Visit 2.1 (End of Placebo Lead-in) Day 13 (±2)	Screen* failure ONLY End of Study	Visit 3** (Baseline) Day 15 (+3)	Visit 4 (Week 2) Day 29 (±3)	Visit 5 (Week 4) Day 43 (±3)	Visit 6 (Week 6) Day 57 (±3)	Visit 7 (Follow-up) Day 71 (±3)	ET***	
											ET	Follow Up
Concomitant Medication Inquiry & Reporting	X ◄	———	———	———	———	———	———	———	———	► X	X	X

* End of Study (Screen failure only): Patients who discontinue between Visits 2 and 3 only will undergo the procedures specified above.

** Visit 3 must be performed after obtaining results for Visit 2.1.

*** The Early Termination (ET) visit should be performed as early as possible after discontinuation. ET follow-up visit will also be necessary approximately 14 days after the patient's last dose.

**** Visit 1 must be performed prior to Visit 1.1.

[a] Informed consent for PGx must be obtained prior to blood collection at Visit 3.

[b] Ophthalmological Examination: LOCS III assessment must be conducted by an ophthalmologist. Best corrected visual acuity (BCVA) must be performed by the ophthalmologist, optometrist or trained ophthalmic technician. Examination can be performed within -5 days of study Day 1 (Day -5 to Day 1) as Visit 2 assessment.

[c] MADRS should be conducted prior to any other mental health assessments and safety/PK/PD assessments.

[d] Urinary and Salivary Cortisol: Dispense kits at Visit 2.

[e] Investigational product dispensing, accountability and compliance checks: Accountability and compliance checks will be performed at Visits 3 to 6. Administration of the investigational product for the placebo lead-in period will start on the morning following Visit 2 (study Day 2). Administration of the investigational product for the treatment period will start on the morning following Visit 3 (study Day 16).

[f] Drug Adherence: Daily dosing by patients of current ADT and investigational product (TS-121 or placebo) will be monitored using AiCure technology on the patient's smart phone or a device provisioned by the site (See Section 8.1.3, Treatment Compliance).

9.2 Study Assessments

9.2.1 Explain Study and Obtain Written Informed Consent

The investigator or qualified designee will explain the study and all study requirements to the patient, answer all of his/her questions, and obtain written informed consent before performing any study-related procedure. A copy of the informed consent will be given to the patient. Date of consent will be recorded in the patient's study source records and captured electronically.

9.2.2 Review Inclusion/Exclusion Criteria Including Concomitant Medications

The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the patient qualifies for the study at all specified visits. All appropriate treatment will be discussed with the patient. All medications used during the study will be recorded in the patient's study source records and captured electronically.

9.2.3 Demographics

The patient's age (at the time of informed consent), ethnicity, gender and race will be recorded in the patient's study source records and captured electronically.

9.2.4 Medical History

A detailed medical and/or surgical history will be obtained by the investigator or qualified designee and will be recorded in the patient's study source records and captured electronically. Medical history should include information on hepatic, renal, gastrointestinal, and cardiovascular disorders, eye disease, and/or any other clinically significant medical condition. New or existing medical conditions reported prior to first administration of the investigational product will be captured as medical history, whereas any new, untoward, or worsening medical condition reported after first administration of the investigational product will be captured as adverse events.

9.2.5 Psychiatric History

History and/or presence of mental illness will include assessment of onset of symptoms and behaviors, prior mental health history, treatments, history of physical or sexual abuse or perpetration issues, history of alcohol or illicit drug use, and history of family psychiatric illness, will be recorded in the patient's study source records and captured electronically. New or existing psychiatric condition reported prior to first administration of the investigational product will be captured as psychiatric history, whereas any new, untoward, or worsening psychiatric conditions reported after first administration of the investigational product will be captured as adverse events.

9.2.6 Diagnostic and Screening Assessments

9.2.6.1 Serology Screen

A blood sample will be collected at screening for Hepatitis B surface antigen, HIV screening and serum antibodies to hepatitis C. Tests will be performed according to standard local procedures. A plan must be in place at the site(s) for the management of a positive test result according to local requirements. Test results will be recorded in the patient's study source records and captured electronically.

9.2.6.2 Height

Height will be measured at Visit 1 only. The height measurement will be recorded in centimeters (cm) in the patient's study source records and captured electronically.

9.2.6.3 Body Mass Index (BMI)

BMI should be calculated using the following formula and recorded in the patient's study source records only:

$$\text{BMI} = \text{Weight (kg)}/\text{Height (m)}^2$$

Height (cm) and weight (kg) used to calculate BMI should be up to one decimal place.

9.2.6.4 Urine Drug Screen

A urine sample will be collected at Visit 1 to screen for controlled substances, and will also be collected at Visit 3 for confirmatory purposes. The following controlled substances will be tested: amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, marijuana (THC), phencyclidine (PCP), and ecstasy (MDMA). Negative drug screens are required for study eligibility. Test results will be recorded in the patient's study source records and captured electronically.

[Note: Patients with positive urine drug results may be eligible at investigator's discretion if the results are reasonably explained as false positive]

9.2.6.5 Urine Pregnancy

For all female participants, urine pregnancy samples will be tested at specified visits. Patients with a positive pregnancy test at screening or prior to the first dose will not be allowed to enter into the study (screen failure). Patients with a positive pregnancy test any time after first dose will be discontinued from the study. The pregnancy will be monitored and recorded according to Sections 9.1 and 11.4.

9.2.6.6 Screening and Baseline Mental Health Assessments

9.2.6.6.1 MINI-International Neuropsychiatric Interview (MINI)

The MINI (Version 7.0.2) will be administered by the investigator at Visit 1. The results of the MINI interview are to be recorded in the patient's study source records only.

9.2.6.6.2 17-Item Hamilton Rating Scale (HAM-D)

The HAM-D (October 2010 for the DUAG-8 project) is completed with a structured interview guide by the clinician based on his/her assessment of the patient's symptoms. The 17-item version of the HAM-D will be used to determine illness severity in order to fulfill the inclusion criteria.

An initial HAM-D will be conducted by the investigator or designee (trained site rater) at Visit 1 to support the diagnosis of MDD as per the MINI by providing information on severity. A remote HAM-D interview will then be conducted by central raters at Visit 1.1 as a part of phone interview and at Visit 2.1. Central Rater interviews will be performed remotely, and the patient will be contacted at an off-site location. Sites will be notified of the results prior to next visits. Results are to be captured electronically and included in the patient's study records.

9.2.6.6.3 MGH Antidepressant Treatment Response Questionnaire (MGH ATRQ)

The MGH ATRQ (TAISHO_ATRQ 2.7.2017) is a clinician-rated questionnaire examining antidepressant treatment history using specific anchor points to define the adequacy of both dose and duration of each antidepressant trial, as well as the degree of symptomatic improvement obtained with each trial. It will also be used to assess the adequacy of current ADT for the trial. Results are to be captured electronically and included in the patient's study records.

9.2.6.6.4 SAFER Interview

To ensure that appropriate patients are entered into the trial, a central rater interview will be conducted by phone. The assessments administered will be the SAFER Inventory (Taisho TS121-US201), and includes the HAM-D and the MGH ATRQ (detailed above). The interview will be performed remotely by the central rater, and the patient will be contacted at Visit 1.1. Sites will be notified of the results prior to Visit 2. Results are to be captured electronically and included in the patient's study records.

9.2.7 Safety Assessments

9.2.7.1 Adverse Events

See Section 11.1 on capture and reporting of Adverse Events.

9.2.7.2 Physical Examination

A routine physical examination will be performed at the visits indicated in Section 9.1.

The results of the physical examination are to be recorded in the patient's study source records. Any abnormalities noted prior to first administration of the investigational product will be listed as medical history. Findings after first administration of the investigational product that meet the criteria of an AE (Section 11.1) will be captured as AEs.

The physical examination will include, but not be limited to, assessments of the following:

- General Appearance
- Head/ Face
- Eyes
- Ears/Hearing
- Nose
- Mouth, Teeth and Throat
- Neck & Thyroid
- Vascular/Circulatory
- Abdomen
- Skin, Hair, and Nails
- Musculoskeletal: Extremities, Spine
- Lymphatic
- Chest/Lungs

9.2.7.3 Neurological Examination

The comprehensive neurological examination will include assessments of the following:

- Cranial Nerves Function: Reactivity to Light, Accommodation of pupils, and Extraocular Eye Movements
- Coordination: Finger to Nose, Finger Tapping, Rapid alternating Hand Movements, Gait, and Romberg Test
- Deep Tendon Reflexes: Brachioradialis, Patellar, and Achilles
- Presence of Tremors: Resting, Postural, and Intension
- Sensory Exam: Pin Prick and Tactile Soft Touch
- Motor System: Spastic gait, Cerebellar ataxia, Sensory ataxia, Akinetic-rigid gait, Step age gait, Upper/Lower body strength

The results of the neurological examination will be recorded in the patient's study record. Any abnormalities noted prior to first administration of the investigational product will be listed as medical history. Findings after first administration of the investigational product that meet the criteria of an AE (Section 11.1) will be captured as AEs.

9.2.7.4 Ophthalmological Examination

Ophthalmological examinations will be performed on all patients at the visits indicated in Section 9.1. The Lens Opacities Classification System III (LOCS III) grading must be conducted by an ophthalmologist, with active certification for LOCS III grading. The Best Corrected Visual Acuity (BCVA) measurement must be conducted by the ophthalmologist, optometrist or a trained ophthalmic technician. LogMAR score should be confirmed by the ophthalmologist. Rating by the same ophthalmologist, optometrist or a trained ophthalmic technician and same equipment is preferred for the duration of the trial for each patient for the LOCS III grading and the BCVA measurement. Ophthalmological examination will include the following:

- BCVA as measured with the ETDRS chart, and scored in LogMAR
- Evaluation of the crystalline lens through a maximally dilated pupil using LOCS III, including the following features;
    - Posterior subcapsular cataract (P)
    - Cortical cataract (C)
    - Nuclear opalescence (NO)
    - Nuclear color (NC)

Examination of the anterior chamber depth, optic nerve head, and the intraocular pressure by applanation tonometry should be performed by the ophthalmologist prior to dilation of pupils. Mydriatics will be used to achieve maximal mydriasis before any retro illumination or slit lamp photographs are obtained. Photographs of both eyes will be captured on all patients at each examination. The ophthalmologist should not review the previous LOCS III assessments until completion of the LOCS III assessment of a current visit.

(See the Ophthalmological Examination Manual for detailed instructions).

Results of the ophthalmological examination will be recorded in the patient's study source records and captured electronically. Any of clinically significant ophthalmological findings defined in Section 11.3.2 will be recorded as AEs. The sponsor will engage a third-party blinded ophthalmologist to review clinically significant ophthalmological findings or consult with the investigators or sponsor Medical Monitor.

9.2.7.5 Body Weight

Body weight will be measured at specified visits indicated in Section 9.1. Results of the body weight are to be recorded in kilograms (kg) in the patient's study source records and captured

electronically.

9.2.7.6 Vital Signs

Vital signs with the patient in a seated position (sitting for ≥ 5 minutes) will be collected at specified visits indicated in Section 9.1.

Vital signs will include systolic and diastolic blood pressure (mmHg), pulse rate (bpm) and oral temperature (°C). Oral temperature should be measured after a minimum of 20 minutes without oral fluids. Vital signs are to be recorded in the patient's study source records and captured electronically.

9.2.7.7 Electrocardiogram

A standard 12-lead ECG (ventricular rate, RR, PR, QRS, QT, QTcB and QTcF) will be performed by the investigator or designee after the patient has been in the supine position for at least 5 minutes at specified visits indicated in Section 9.1. The patient must remain in a supine position while the ECG is obtained. Electrocardiogram tracings and results with investigator's interpretation are to be included and summarized in the patient's study source records. Results will be recorded in the patient's study source records and captured electronically.

On the electrocardiogram should be recorded the date, time, patient demographics (e.g., age, and sex) and subject number.

9.2.7.8 Safety Laboratory Tests

Table 3 summarizes the laboratory tests to be evaluated in the study. All laboratory reports must be reviewed by the investigator, and any abnormalities must be assessed for clinical significance. Abnormal hematology, biochemistry or urinalysis results may be repeated at the investigator's discretion to rule out laboratory error, or to confirm patient eligibility or safety. The results are to be included in the patient's study source records.

Table 3. Summary of Laboratory Tests

Hematology	Biochemistry	Urinalysis
Red Blood Cell count (RBC)	Total Protein	Hydrogen ion concentration (pH)
White Blood Cell count (WBC)	Albumin	Specific gravity
WBC differential	Calcium	Protein
Hemoglobin	Inorganic phosphorus	Glucose
Hematocrit	Cholesterol (total, LDL, HDL)	Ketones
Mean Corpuscular Hemoglobin (MCH)	Triglycerides	Leukocyte esterase

Hematology	Biochemistry	Urinalysis
Mean Corpuscular Hemoglobin Concentration (MCHC)	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Nitrites
Red cell distribution width (RDW)	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Bacteria
Mean Corpuscular Volume (MCV)	Electrolytes (Na, K, Mg, Cl) and Bicarbonate	Occult blood
Platelet count	Blood Urea Nitrogen (BUN)	WBC/high-power field
	Serum glucose (venous)	Crystals
	Uric Acid	Casts
	Total and direct bilirubin	Epithelial cells
	Alkaline phosphatase	Mucous Thread
	Lactate dehydrogenase (LDH)	
	Gamma Glutamyl Transpeptidase (GGT)	
	Creatinine Phosphokinase (CPK)	
	Serum Creatinine	

9.2.7.8.1 Hematology

Blood samples will be drawn for routine hematology at specified visits indicated in Section 9.1.

9.2.7.8.2 Biochemistry

Blood samples will be drawn under fed or fasted conditions for routine biochemistry at specified visits indicated in Section 9.1. Last meal time will be recorded in the patient's study source records and captured electronically.

9.2.7.8.3 Urinalysis

Urine samples will be collected for routine urinalysis at specified visits indicated in Section 9.1.

9.2.7.9 Exploratory Safety Assessments

Blood samples will be collected at visits indicated in Section 9.1. Plasma (0.5mL) will be stored at the central lab for possible exploratory safety assessments based on the current understanding of toxicology. Detailed procedure of collection, processing and storage will be described in the Laboratory Manual.

9.2.7.10 C-SSRS

C-SSRS (Screening, version 1/14/09) which pertains to the previous 6 months will be administered at Visit 1, and then C-SSRS (Since Last Visit, version 1/14/09) which pertains to changes since the last visit will be administered at Visits 3 through 7. C-SSRS will be assessed by a qualified investigator or designee (qualified site rater) at specified visits indicated in Section 9.1. Results will be recorded in the patient's study source records and captured electronically.

9.2.8 Efficacy Assessments

9.2.8.1 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS will be administered specifically with a structured interview guide developed by MGH. The time frame for this scale is the past 7 days.

MADRS will be administered by the investigator or designee (trained site rater) at specified visits indicated in Section 9.1. Site staff administering the MADRS will be certified by CTNI prior to administering the assessment.

The same certified staff is preferred for the duration of the trial for each patient. Results are to be captured electronically and included in the patient's study source records.

9.2.8.1.1 Site Rater Surveillance

In order to insure consistency of ratings administered by the site raters, CTNI will review MADRS assessments conducted by the site raters. These reviews will be conducted by CTNI clinicians. Through a tablet based system provided by the eC/PRO vendor, site raters will be able to record each MADRS as it is administered at the site.

9.2.8.1.2 eC/PRO Services

CTNI will engage NESS (New England Survey Systems) to provide e-C/PRO (electronic Clinician and Patient Rated Outcome) services for the study. NESS will provide tablets programmed with the study assessments for the sites to use for administering the scales. The tablets have a recording function that enables the reviewer to listen to the interview while reviewing the site rater's scoring. The tablet system is FDA 21 CFR Part 11 compliant.

Results of HAM-D, MADRS, MGH ATRQ and SAFER inventory for each question will be captured through the tablet system.

9.2.8.2 Clinical Global Impressions - Severity (CGI-S) and Improvement (CGI-I) Scales

These clinician-rated scales rate the severity of the disorder and the global improvement since beginning of the study. The time frame for these two scales is the past 7 days.

CGI-S and CGI-I will be administered by the investigator or designee (trained site rater) at specified visits indicated in Section 9.1. Results will be recorded in the patient's study source records and captured electronically.

9.2.8.3 Hamilton Anxiety Scale (HAM-A)

HAM-A (SIGH-A, Version 5/92) will be administered by the investigator or designee (trained site rater) at specified visits indicated in Section 9.1. The time frame for this scale is the past 7 days. Results will be recorded in the patient's study source records and captured electronically

for each question.

9.2.8.4 Symptoms of Depression Questionnaire (SDQ)

The SDQ will be completed by the patient at specified visits indicated in Section 9.1. The time frame for this scale is the past 7 days. Results will be recorded in the patient's study source records and captured electronically for each question.

9.2.9 AiCure: Medication Adherence and Reminder System

This trial will employ a medication adherence monitoring platform using AiCure proprietary technology. The platform uses artificial intelligence on smartphones to confirm medication ingestion, with built-in reminders and a communication system that allows real-time intervention in case of drug interruptions. Use of this platform will in no way supersede or replace the physician and/or trial prescribed medication protocol of the patients.

The monitoring platform requires that patients take each dose of the medication using a smartphone. The platform will be provided to a patient preloaded on a smartphone, or downloaded to their device. Study patients will receive a medication reminder at a time within a predefined window to take their medication using the platform. Study patients will follow a series of prescribed steps in front of the front-facing webcam to visually confirm ingestion of the medication.

After local determination by the device of proper medication administration, all video recordings are encrypted and then transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured data and video is reviewable through roles and rules restricted HIPAA-compliant system ensuring privacy of the information. Patients who are found to regularly not take their medication will be contacted by healthcare providers, or other study monitoring personnel for retraining.

9.2.10 Pharmacodynamics Assessments

Samples for PD markers are collected at specified visits indicated in Section 9.1. This study will explore single time points of collection for exploratory analysis to guide future trials and multiple time points of collection for PD effects assessments. All assays will be performed at a central laboratory.

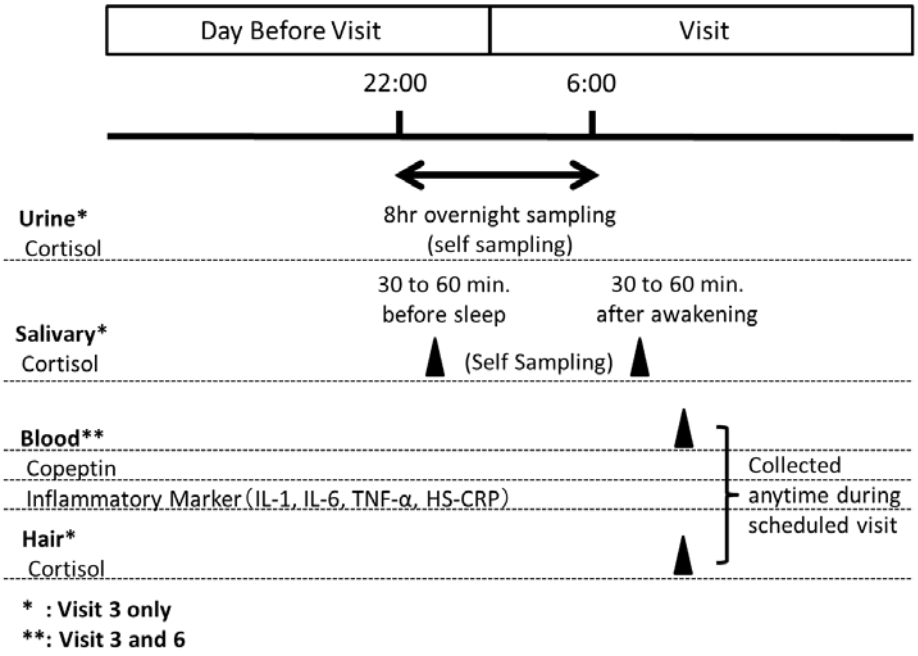

Figure 2. Pharmacodynamic Schedule

9.2.10.1 Plasma Copeptin

Venous blood samples will be collected at specified visits indicated in Section 9.1.

9.2.10.2 Salivary Cortisol

Saliva samples will be self-collected at home for specified visits indicated in Section 9.1. Saliva samples will be collected the day before specified visit at on the following schedule:

- Sample 1: Between 30 and 60 minutes prior to bedtime
- Sample 2: Between 30 and 60 minutes after awakening

No food or drink is permitted for 30 minutes prior to sample collection. Date and time of sample collection, bedtime, time of awakening and time of breakfast will be recorded in the patient's study source records and captured electronically for each sample collected. Detailed processing and handling instructions are available in the Laboratory Manual.

9.2.10.3 Urine Cortisol

Urine samples for urinary cortisol will be collected by the patient at home overnight, starting at 10:00 p.m. on the night prior to Visit 3 and continuing until 06:00 a.m. the next morning (visit day) in order to provide a continuous pooled 8-hour sample. Patients will be given collection materials and instructions at the prior visit. Detailed processing and handling instructions are

available in the Laboratory Manual. Total urine volume will be recorded in the patient's study source records and captured electronically.

9.2.10.4 Hair Cortisol

A single tuft of hair will be collected at the study site with the assistance of study site personnel, according to the schedule in section 9.1 if the patient has a sufficient amount of hair to provide for measurement. Detailed procedures for hair collection, processing and analysis will be documented in the Laboratory Manual.

9.2.10.5 Inflammatory Markers (TNF-α, IL-1, IL-6, HS-CRP)

Venous blood samples will be collected at specified visits indicated in Section 9.1. TNF-α, IL-1, and IL-6, will be analyzed by a central laboratory with standard methodology. C-reactive protein will be analyzed by a high-sensitivity method (HS-CRP) by a central laboratory.

9.2.11 Pharmacokinetics Assessment

9.2.11.1 [redacted] (TS-121)

Plasma samples will be analyzed to determine concentrations of [redacted] using a validated, specific and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The determination of [redacted] will be performed by [redacted].

9.2.11.1.1 Pharmacokinetics: Blood Sampling for [redacted]

A single venous blood sample (approximately 4 mL of whole blood) will be collected for determination of [redacted] pharmacokinetics at Visit 6. The exact dates and times of the blood sampling and the last investigational product administration before blood sampling must be recorded in the patient's study source records and captured electronically.

Blood collection tubes: 4 mL plastic vacuum tubes containing K2 EDTA.

Plasma sample storage vessels: 2 mL polypropylene tubes

After collection, the blood sample will be kept in an ice bath (or other cooling systems, except for refrigerator) until centrifuged. Samples must be centrifuged (4ºC, 3000 rpm, 10 minutes) within 30 minutes after blood collection to obtain plasma. After centrifugation, plasma samples shall be distributed into two polypropylene tubes as follows:

- 0.5 mL (Primary) for [redacted] pharmacokinetic analysis
- 0.5 mL (Backup) for [redacted] pharmacokinetic analysis

All tubes will preferably be stored at or below -70ºC. If -70ºC freezer is not available, all tubes will be stored at or below -20ºC.

9.2.11.1.2 Pharmacokinetics: Shipping for [redacted]

[redacted]

9.2.12 Pharmacogenomic Blood Sampling

A single blood sample (approximately 8.5 mL of whole blood) for pharmacogenomics (PGx) will be obtained from eligible patients consenting to PGx during Visit 3. The dates of the blood sampling will be recorded in the patient's study source records and captured electronically. Instructions for preparation, storage and shipping of the pharmacogenomic samples are found in the Laboratory Manual.

9.3 Visit and Time Windows

Visit and time windows for each visit are summarized in Section 9.1. Visit 1 can be performed from Day -28 to Day -7, and must be performed prior to Visit 1.1. Visit 1.1 can be performed from Day -13 to Day -2. Visit 2.1 has a ±2 day window. Visit 3 has a +3 day window and must be performed after obtaining results for Visit 2.1. All visits after Visit 3 will have a visit window of ±3 days. The ophthalmological examination at Visit 2 can be performed within -5 days of

study Day 1 (Day -5 to Day 1).

10 STATISTICAL METHODS

In addition to this section of the study protocol, a more detailed Statistical Analysis Plan (SAP) will be provided in a separate document. Any revisions (both alternative and additional methods) to the SAP that are used in the final report, and reasons for such revisions, will be described in the final report. This is a pilot project and the results obtained will be used to estimate the effect size and to support future studies.

10.1 Sample Size Determination

The total number of patients enrolled in the study is based on practical consideration and not on statistical power calculations. These sample sizes are considered adequate to meet the study objectives based on clinical considerations and allow for assessments of the safety, efficacy and PD effects of TS-121 in this patient population.

10.2 Analysis Populations

The safety analysis population will include all patients who received at least one dose of investigational product (including placebo during the placebo lead-in period).

The intent to treat population will include all patients who were randomized and received at least one dose of investigational product.

The exploratory PD analysis population will include all randomized patients who completed the assessment and have sufficient mental health assessments completed. This could be independent of receiving the investigational product. Missing data will not be imputed and are to be excluded from the analysis.

The PK analysis population will include all patients who were randomized and received investigational product with evaluable PK data and may exclude those that are considered invalid due to relevant missing values, or if any other problems occurring during sampling, laboratory analysis, dosing, or AEs that invalidate the concentration measurements

10.3 General Analysis Conventions

For continuous measures, data will be summarized by descriptive statistics. Where appropriate, change from baseline and visit-to-visit will be summarized. For categorical measures, data will be summarized with frequency counts and percentages. All data analyzed will be displayed in detailed listings. No interim analysis is planned.

10.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics including but not limited to age, gender, body weight, height, body mass index, medical history, and psychiatric history will be tabulated by group using descriptive statistics.

10.5 Endpoint Analysis

10.5.1 Safety Analysis

Safety will be assessed based on reported adverse events, abnormal findings from physical and ophthalmological examination, body weight, vital signs measurements, 12-lead ECGs, C-SSRS score and clinical laboratory assessment results. Additional details will be described in the SAP.

10.5.1.1 Adverse Events

Adverse events will be listed by preferred terms and summarized by system organ class with preferred term based on the MedDRA coding system. The number and percentage of patients who experience one or more AEs will be tabulated. The tabulation will be further classified by severity and relationship to investigational product.

10.5.1.2 Clinical Laboratory Values

Laboratory data from each sampling and changes from baseline will be summarized by descriptive statistics. Laboratory analyses will utilize Visit 3 assessments as baseline values. Parameters will be categorized as low, normal, or high according to the laboratory normal range specifications.

Clinical laboratory outlier criteria will be used to identify values and trends of potential medical importance. A summary for the number and percentage of patients with clinical laboratory outliers for each specified laboratory test will be presented. Similar analyses will be performed for clinically noteworthy changes which would show magnitude of change from baseline.

Criteria for clinical laboratory outliers and clinically noteworthy changes will be described in the SAP.

10.5.1.3 Vital Signs

Vital signs at each measured time point and changes from baseline will be summarized by descriptive statistics.

10.5.1.4 Electrocardiogram

Characteristics of cardiac events at each reading and changes from baseline will be summarized descriptively for interval data (ventricular rate, RR, PR, QRS and QTc) will be calculated for each group. The incidence of abnormalities, based on the clinical interpretations from the investigator, will be enumerated.

QTc as corrected by the Fridericia and Bazett methods will be used as the primary measure of change in QT interval. Changes from baseline for each of the ECG parameters will be summarized using descriptive statistics. Borderline and prolonged QTc will be listed and

frequency table provided. Additionally, the numbers of patients with change from baseline in QTc at appropriate visits categorized as <30 msec, 30 to 60 msec, and >60 msec, will be tabulated and summarized by treatment group as will the number of patients with a QTc interval >500 msec.

10.5.1.5 Ophthalmological Examinations

Any of clinically significant ophthalmological findings as defined in Section 11.3 will be analyzed as adverse events.

The LOCS III grading scores and best corrected visual acuity scores observed during the study will be listed.

Additional details will be described in the SAP.

10.5.1.6 C-SSRS

Any suicidal ideation or behavior on the C-SSRS that develops during the study will be listed. Additional details will be described in the SAP.

10.5.2 Efficacy Analysis

10.5.2.1 Primary Endpoint

To evaluate the efficacy of TS-121 compared to placebo on MDD symptoms in MDD patients, Mixed Model Repeated Measures analysis (MMRM)/non-parametric methods will be used to compare the difference between the three treatment groups on the primary endpoint (change in MADRS score) depending on the distribution of the data. On the primary endpoint (change in MADRS score), as assessed at Week 6, a statistically significant GROUP*TIME interaction effect, with greater reductions in MADRS scores in the TS-121 groups, will be interpreted as indicating efficacy (GROUP: Placebo, TS-121 10 mg and TS-121 50 mg, TIME: Week 2, Week 4 and Week 6).

10.5.2.2 Secondary Endpoint

With respect to the secondary outcome variables, the same MMRM/non-parametric methods as described above will also be used to compare the difference between the three treatment groups on the each secondary endpoint depending on the distribution of the data.

Changes from Baseline (Visit 3) to EOT (Visit 6) for the following:

- CGI-S score
- HAM-A total score
- SDQ score

Chi-square test or Fisher's exact test will be used to compare the difference of active treatment groups to placebo group on the following secondary endpoint.

- Percentage of MADRS responders (≥ 50% reduction in total score)
- Percentage of CGI-I improvers ("Very much improved" or "Much improved")

10.5.3 **Pharmacodynamic (PD) Analysis**

With respect to the PD outcome variables, the same MMRM/non-parametric methods as described in Section 10.5.2.1 will be used to compare the difference between the three treatment groups on the each of PD endpoint depending on the distribution of the data.

Changes from Baseline (Visit 3) to EOT (Visit 6) for the following:

- Plasma copeptin
- Inflammatory markers (IL-1, IL-6, HS-CRP, and TNF-α)

Pharmacodynamic biomarkers (salivary cortisol, hair cortisol, plasma copeptin, 8h urinary cortisol and inflammatory markers (IL-1, IL-6, HS-CRP, and TNF-α)) will be evaluated post-hoc to explore relationship of responders and non-responders to baseline characteristics. The analysis will be used to inform, potentially, on future trial design. A separate plan will document analyses of PD samples. All results, including baseline PD biomarkers (salivary cortisol, hair cortisol, plasma copeptin, 8h urinary cortisol and inflammatory markers (IL-1, IL-6, HS-CRP, and TNF-α)), will be listed with relevant metadata.

10.5.4 **Pharmacokinetic (PK) Analysis**

Visit 6 samples will be limited to evaluation of TS-121 PK. The individual plasma concentration of [redacted], the last dosing date and time, and actual sampling date and time will be listed. Additional details will be described in the SAP.

10.5.5 **Pharmacogenomic (PGx) Analysis**

If study results warrants further investigation of genomic variation postulated to be involved in the metabolism, toxicity, pharmacological response, or emerging MDD data to TS-121 or MDD, the sponsor may conduct genetic and other biomedical research on specimens, including genetic analyses (DNA). PGx samples for patients who received TS-121 (including placebo) will be stored for up to 15 years and may be evaluated as information is gained on TS-121 and/or MDD.

11 ADVERSE EVENT REPORTING

11.1 Definitions, Grading & Relationship, Outcome and Follow-up

11.1.1 **Definitions**

Adverse Event (AE): Any untoward medical occurrence in a patient administered an investigational product, and which does not necessarily have a causal relationship to investigational product. An AE can be any unfavorable or unintended sign (including an abnormal finding), symptom, or disease. AEs include any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures (including clinically-significant laboratory test abnormalities). Overdose defined in Section 11.6.1 will also be considered as an AE whether or not it is associated with symptoms or abnormal laboratory results.

Events should be considered AEs if they:

- result in discontinuation from the study,
- require treatment or any other therapeutic intervention,
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Appropriate therapeutic action and follow-up measures will be performed by the investigator in accordance with GCP. These actions and measures will continue until the condition is resolved and/or the etiology is identified. Any non-serious AEs (including laboratory results or other clinical findings) that result in the patient's withdrawal from the study will require the patient to undergo early discontinuation procedures.

Laboratory Abnormalities: It is the responsibility of the investigator to review all laboratory findings for all patients. Abnormal values should be commented upon as to clinical relevance or importance in the study source records or the laboratory report as appropriate. An abnormal laboratory value may be considered an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory abnormalities considered to constitute an adverse event should be reported on the appropriate section of the patient's study source records. Laboratory abnormalities do not need to be listed as separate adverse events if they are considered to be part of a clinical

syndrome that is being reported as an adverse event.

11.1.2 **Grading and Relationship**

The investigator will evaluate all AEs as to their severity, and record the outcome and action taken. The investigator will also judge the likelihood that the AE was related to the investigational product and document this in the patient's study source records. See Table 4 below:

Table 4. Classification of Adverse Events

Severity	**Mild**	awareness of sign or symptom, but easily tolerated
	Moderate	discomfort enough to cause interference with usual activity
	Severe	incapacitating with inability to work or do usual activity
Duration	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued? Interrupted? Dosage increased or decreased? Other action?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience will be provided by an investigator. The investigator's signed/dated initials on the source document supporting the causality noted on the AE form ensures that a medically qualified assessment was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse experience based upon the available information. The greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience:	
	Exposure	Is there evidence that the patient was actually exposed to the test drug such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
	Dechallenge	Was the dose of test drug discontinued or reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. **(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the test drug; or (3) the study is a single-dose drug study.)**
	Rechallenge	Was the patient re-exposed to the test drug in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. **(Note: This criterion is not applicable if:** **(1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study.)**
	Consistency with Investigational Product Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology?
	The assessment of relationship will be reported on the case report forms/worksheets by an investigator according to his/her best clinical judgment, including consideration of the above elements. **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).**	
	Definitely related	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory

	rechallenge procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

11.1.3 **Outcome**

The seriousness of an event is determined by its outcome (e.g., hospitalization, death, etc.). The action taken to treat an AE and the outcome of the action must be recorded. Outcomes may be categorized as shown below:

- FATAL: The termination of life as a result of an adverse event. Death Related to Adverse Event
- NOT RESOLVED: One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated.
- RESOLVED: One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated.
- RESOLVED WITH SEQUELAE: One of the possible results of an adverse event outcome where the patient recuperated but retained pathological conditions resulting from the prior disease or injury.
- RESOLVING: One of the possible results of an adverse event outcome that indicates that the event is improving.
- UNKNOWN: Not known, not observed, not recorded, or refused.

11.1.4 **AE Follow-Up**

Any AEs that are ongoing after the Follow-up Visit should be followed for 30 days, with the exception of serious adverse events that are followed until resolution or stabilization. Information collected after the Follow-up Visit, however, will not be captured in the database, but will be maintained in the patient's study source records and made available upon request.

11.2 Serious Adverse Event Reporting

11.2.1 **Definition of Serious Adverse Event**

A serious adverse event (SAE) is an untoward medical occurrence that at any dose:

- results in death (Note: Death is an outcome and not an event and the cause of death should be listed as the SAE);
- is life-threatening (i.e., the patient was at immediate risk of death from the AE);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/ incapacity; or
- is a congenital anomaly or birth defect (in the child of a patient who was exposed to the investigational product)

Any other important medical event that may result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.2.2 **Serious Adverse Event Reporting Procedure**

If in the opinion of the investigator, the event meets the criteria of an SAE, the following procedures will be followed:

On discovery, all SAEs should immediately (within 24 hours of awareness of the event) be reported to [redacted] by:

- Completing the SAE report form and faxing the documents to [redacted], using the [redacted] SAE fax number below:
  - 24/7 Fax: [redacted]
- Or, by completing the SAE report form and submitting it to [redacted] via email utilizing the address below:
  - SAE Reporting e-mail: [redacted]
- In the event that the site is unable to complete the SAE form to report the event within 24 hours of awareness of the event, the investigator may report the SAE over the telephone and then provide the completed SAE form via (fax/email). If questions arise regarding the reporting procedures or the specifics of the reporting of an event, the site may call utilizing the following number:

  [redacted]

- The following documents will be forwarded to [redacted] within 24 hours of reporting the event:
  1. SAE Report
  2. Con Med CRF page
  3. Medical History page
  4. Any other applicable information
- The sponsor must be notified within 24 hours of awareness of the event as specified in the Safety Plan.
- The initial report of an SAE may be submitted by email. The investigator must provide the minimal information: i.e. the protocol number, subject number, date of SAE, SAE term,

short description of the event, causality (if determined) and the reason why the event is categorized as serious.

- The investigator will also notify the Institutional Review Board (IRB) of the event within the time frame specified in the IRB's Standard Operating Procedures after becoming aware of the SAE. An initial report followed promptly by a complete report will be forwarded to the IRB, or in accordance with the IRB policy.

- The patient will be observed and monitored carefully until (1) the condition stabilizes and/or resolves; (2) its cause is identified; or (3) it is otherwise determined by the Medical Monitor and investigator. Follow-up information relating to the SAE must be submitted to [redacted] by email as soon as additional information related to the event is available.

- If a patient is hospitalized due to the SAE, the hospital discharge summary should be obtained if possible when it becomes available.

- If a death occurs and an autopsy is performed, a copy of the autopsy report should be obtained if possible when it becomes available. All efforts must be undertaken to obtain follow-up information promptly.

Any SAEs occurring from first administration of investigational product through 30 days after last administration must be reported. All SAEs will be reported, whether or not they are deemed to be related to study product. Timely reporting of SAEs will be followed in accordance with regulatory requirements as outlined in the Safety Plan.

11.2.3 **SAE Follow-Up**

If an SAE is reported while the event is still ongoing, the investigator must submit follow-up reports to [redacted] regarding the patient's subsequent course. All SAEs, including those that are ongoing at the end of the study or upon discontinuation must be followed until resolution or stabilization.

11.3 Events of Clinical Significance

Suicidal ideation and behavior, and lens opacity, as defined in the following sections, are considered as Event of Clinical Significance (EOCS). An EOCS should be recorded as an AE. All EOCS, regardless of whether the event meets criteria for SAE, should be reported to [redacted] within 24 hours of becoming aware of the event.

11.3.1 **Suicidal Ideation and Behavior**

Any patient who, based on the investigator's judgment, poses an imminent risk of suicide, as suggested by the C-SSRS suicidal ideation score of 5 or any "yes" response for any of the C-

SSRS suicidal behavior questions should be discontinued from the study (see Section 8.5). Suicidal ideation or behavior should be recorded as AE and reported to [redacted] within 24 hours of becoming aware of the event whether or not the event is considered an SAE or deemed to be related to investigational product. All efforts should be taken to minimize the risk of suicide and the investigator should carefully monitor the patient. Any patients who show evidence of suicidal behavior during the course of the study should be evaluated immediately and/or referred to their attending psychiatrist or to a local emergency room etc. so the patient can receive an appropriate care. The site should have the ability to direct any patient who requires emergency hospitalization to an emergency room or inpatient psychiatric unit. In addition, 24 hour contact information to site personnel should be provided to all patients should they have serious worsening of their condition.

11.3.2 **Lens Opacity**

Class I lens event [increase from baseline in the LOCS III grade of ≥0.5 (Nuclear Opalescence), ≥0.8 (Cortical) or ≥0.5 (Posterior Subcapsular)] and any changes considered to be clinically significant (e.g., incidence of cataract) as per the ophthalmologist will be immediately reported to the investigator. The investigator will report the event to the [redacted] within 24 hours of becoming aware of the event whether or not the event is deemed to be related to investigational product. A Class I lens event should be recorded as an AE and reported as an EOCS.

11.3.3 **EOCS Reporting Procedure**

EOCS reporting procedure is as follows:

- Immediately upon becoming aware of EOCS as defined above, the investigator will report the event by fax/email directly to [redacted] as described in Section 11.2.2.
- The following documents will be forwarded to [redacted] within 24 hours of reporting the event:
  - Results of ophthalmic examination (for lens opacity event only)
  - Slit Lamp and retro illumination Photographs (for lens opacity event only)
  - Any other applicable information

11.4 Worsening of Depression

Significant worsening in depression should be reported as an AE. A CGI-I score of 6 or 7 at any time during the study should be considered as an AE of worsening of depression, and the patient must be evaluated to see if the patient should discontinue the study. In addition, the investigator should document the decision to continue or discontinue the patient, along with a rationale for the decision.

11.5 Pregnancy Reporting

If a patient does become pregnant during the course of the study, the patient should be discontinued immediately. The site must report all pregnancies to [redacted] via email or telephone within 24 hours of receiving the report of pregnancy. The site should record and maintain all relevant information on the appropriate study form, including the follow-up and outcome of the pregnancy.

Pregnancy itself is not regarded as an AE/ SAE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study (with the patient's consent).

Male patients should refrain from fathering a child or donating sperm during the study and for at least 90 days following the last dose. Pregnancy of the patient's partner is not considered to be an AE; however, the outcome of all pregnancies should be followed up and documented if possible.

11.6 Overdose

11.6.1 **Definition of Overdose**

An overdose is defined in this protocol as ingestion of the investigational product (accidental or intentional) of more than 3 capsules in the same calendar day.

Note: In case of a potential overdose, where the patient took investigational product from a combination of more than one row on the medication card but did not exceed 3 capsules in the same calendar day, an AE of "medication error" should be recorded.

11.6.2 **Overdose Reporting**

If an overdose occurs, the overdose should be reported as an AE whether or not it is associated with symptoms or abnormal laboratory results. The event reported should include information on whether the event is accidental or intentional, and if the event is associated with symptoms or adverse reaction.

The investigator will report all reports of overdose to the [redacted] within 24 hours of becoming aware of the overdose whether or not the overdose is intentional.

12 INVESTIGATOR OBLIGATIONS

This study will be conducted in accordance with GCP, Title 21 of the CFR, Part 50, Subparts A and B; Part 56; and Part 312, Subpart D; and the Consolidated Guidance for Industry GCP E6, April 1999; and 1996 ICH GCP E6.

12.1 Ethical Considerations

The investigator will ensure that the study is conducted in full conformance with the FDA standards for human research as specified in 21 CFR 312, Part D (Responsibilities of Sponsors and Investigators) and in accordance with the Declaration of Helsinki.

12.2 Institutional Review Board (IRB) Approval

Prior to initiating the study and receiving investigational product, the investigator must obtain written approval to conduct the study from the appropriate IRB. The investigator must have signed the protocol signature page. When changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigator to the IRB for approval prior to implementation. Protocol administrative changes will also be submitted in writing by the investigator to the IRB for review and notification. The IRB must be informed of all serious and unexpected AEs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

In addition to the IRB approval, other documentation including FDA Form 1572, financial disclosure forms, investigator curriculum vitae (CV), applicable licensure for investigators and sub-investigators, a copy of the IRB approval, letter, and an IRB approved consent form must be collected and filed in the trial master file.

12.3 Informed Consent

12.3.1 **Study Informed Consent**

All potentially eligible patients for the study will be given a copy of the study informed consent form (ICF) to read. All study patients must sign this ICF if he/she decides to participate in the study. The study products will not be released to the patient who has not signed the ICF. The investigator or designee will inform all patients as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his or her medical records may be reviewed. The investigator will explain all aspects of the study in lay language and answer all the patient's questions regarding the study. The investigator must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time. All revisions of the protocol must be reflected in the ICF and reviewed by the IRB. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

12.3.2 Pharmacogenomic Informed Consent

A separate signed informed consent will be administered to cover the conduct of PGx sample collection and analysis. Only patients who have consented to allow PGx research may have sample collected. The patient may choose to participate in the trial, but not participate in the PGx research. Elements of the PGx consent will be included from the sponsor provided template and local policies, regulations and laws.

12.3.3 Health Insurance Portability and Accountability (HIPAA) Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) contains provisions to protect the confidentiality and security of personally-identifiable information that arises in the course of providing health care. In order to understand how HIPAA affects research, there are a few important terms that are defined by the law. A covered entity is the organization that has to comply with HIPAA. Such organizations may be a Hybrid Covered Entity because, in addition to providing health care at medical facilities, it also has other organizational activities such as education and research.

The HIPAA Privacy Rule governs Protected Health Information (PHI) which is defined as information that can be linked to a particular person (ie., is person-identifiable) that arises in the course of providing a health care service.

When PHI is communicated inside of a covered entity, this is called a use of the information. When PHI is communicated to another person or organization that is not part of the covered entity, this is called a disclosure. HIPAA allows both use and disclosure of PHI for research purposes, but such uses and disclosures have to follow HIPAA guidance and have to be part of a research plan that is reviewed and approved by an IRB. An institutionally approved HIPAA authorization must be completed for each patient. The Authorization can be included as part of the main study informed consent, but must have a second signature section in addition to signature section of the study informed consent. The HIPAA authorization will include the following attributes consistent with local privacy requirements:

12.3.3.1 Authorization Core Elements

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
- A description of each purpose of the requested use or disclosure

- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

12.3.3.2 Authorization Required Statements

- A statement of the individual's right to revoke Authorization and how to do so, and, if applicable, the exceptions to the right to revoke Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential risk that PHI will be re-disclosed by the recipient and no longer protected by the Privacy Rule. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

12.4 Patient Confidentiality

All reports and patient samples will be identified only by a coded number to maintain patient confidentiality. All records will be kept confidential to the extent permitted by law. The investigator should keep a separate log of patients, codes, names and addresses. Documents which identify the patient by name (informed consent) should be kept in strict confidence.

Taisho Pharmaceutical R&D Inc. and its vendors agree to keep all patient information confidential. Only coded, blinded data will be released. Data resulting from analysis will be entered into a database that is not accessible to the public. Patient data will be identified only by the subject number or randomization number, and not by other annotation or identifying information. Taisho Pharmaceutical R&D Inc. and its vendors will take every possible step to reduce the risk of releasing information to its customers that would enable the customer to personally identify patients.

12.5 Patient's Financial Responsibilities During the Study

Patients will not be financially responsible for any procedures or tests of any investigational nature. Institutions shall not seek reimbursement for any medical services or for investigational product from any third-party payers if such costs are already covered by payments made under the study agreement.

13 DOCUMENTATION, RECORD KEEPING, AND DATA MANAGEMENT

13.1 Source Data/Documents

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents is defined as the first place that data is captured/recorded. Any and all source data/documents must be maintained and be stored and/or retrievable at the site. Patients' data transferred to the CRF will be identified by a unique subject number. As an exception, if it is necessary to identify the patient for safety or regulatory reasons, Taisho Pharmaceutical R&D Inc. and the investigator are bound to keep this information confidential.

The investigator must maintain source data/documents for each patient in the study. All information appearing on the CRFs must be traceable to its source (paper or electronic), which are generally maintained in the patient's file/record.

Corrections or changes to data that are transcribed or transferred to the CRF must be traceable to source and must be initialed and dated by the (authorized) person making the changes. A reason for the change(s) or any discrepancies must be explained (i.e. audit trial).

13.2 Records Retention

Essential documents must be retained by the investigator for a period of at least two years after the last FDA marketing approval, or at least two years following the withdrawal of the NDA or cessation of investigational product development, or until written approval to destroy the documentation is provided by the sponsor. Taisho Pharmaceutical R&D Inc. will notify the investigator/institution in writing when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include, but are not limited to the documents described in ICH E6 guideline section 8.2 to 8.4.

The documentation must be retained longer, if so required by local law. Investigators must notify the sponsor, in writing, of changes in address, sales or practices or site closures in order to make arrangements for the maintenance of study files.

13.3 Data Management

All data management procedures will be detailed in a separate Data Management Plan (DMP).

14 CHANGES TO THE PROTOCOL AND STUDY TERMINATION

14.1 Protocol Amendment

All changes to the protocol must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by the sponsor and the investigator(s) and submitted for approval to the IRB. A copy of the approval will be provided to the site. Where the local IRB regulations regarding protocol amendments differ from this policy, the local regulations will apply.

14.2 Study Termination

The sponsor and the investigator reserve the right to terminate the study at any time. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of each patient's interest.

15 STUDY MONITORING

15.1 Clinical Monitoring

An initiation meeting will be conducted by the sponsor or an authorized representative (e.g., clinical monitor). During this meeting, the protocol, CRFs, ICF and pertinent aspects of the US Code of Federal Regulations (CFR) will be reviewed with the investigator and all study staff.

Interim monitoring visits will be conducted by a clinical research associate (CRA) during the study at predefined intervals. Upon reasonable notice, the investigator and/or an authorized designee will set aside sufficient time to be available to the CRA to assist with the data query and resolution process, as well as to provide access to any additional records required for source data verification. During the course of the study, the responsible study staff will be available to discuss any matters relating to the conduct of the study.

At each site visit, the CRA will review CRFs and source documents to verify that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. Incorrect, inappropriate, or illegible entries onto the CRFs will be returned to the investigator and/or an authorized designee for correction. Monitoring visit agendas should also leave sufficient time to review the investigator site files for completeness and accuracy, and for investigational product inventories as appropriate.

Further details will be outlined in a clinical monitoring plan.

15.2 Auditing Procedures

A quality assurance audit may be performed by authorized representatives of Taisho Pharmaceutical R&D Inc., a regulatory agency or an IRB. If a regulatory authority requests an audit of the study site, the investigator is required to inform the sponsor and CRO immediately.

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17 APPENDIX 1: Excluded CYP3A4 Concomitant Medications

	Strong	Moderate
INHIBITORS	boceprevir	aprepitant
	cobicistat	cimetidine
	conivaptan	ciprofloxacin
	danoprevir and ritonavir	clotrimazole
	elvitegravir and ritonavir	crizotinib
	grapefruit juice	cyclosporine
	indinavir and ritonavir	dronedarone
	itraconazole	erythromycin
	ketoconazole	fluconazole
	lopinavir and ritonavir	fluvoxamine
	paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	imatinib
	posaconazole	tofisopam
	ritonavir	verapamil
	saquinavir and ritonavir	
	telaprevir	
	tipranavir and ritonavir	
	troleandomycin	
	voriconazole	
INDUCERS	carbamazepine	bosentan
	enzalutamide	efavirenz
	mitotane	etravirine
	phenytoin	modafinil
	rifampin	
	St. John's wort	

(List updated by FDA on 9/26/2016)

Strong Inhibitors: drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold

Moderate inhibitors: drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥2 to <5-fold

Strong Inducers: drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%

Moderate Inducers: drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥50% to <80%

Refer to the following website for details/updates:

[FDA Website] Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo*