A PHASE 1, RANDOMIZED, PLACEBO CONTROLLED, MULTIPLE ASCENDING DOSE (MAD) STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TMP-301 IN HEALTHY SUBJECTS

Protocol Number:	TMP-301-HNV-101
Altasciences Project Number:	TPM-P1-726
Investigational Product:	TMP-301
Phase of Development:	1
Sponsor:	Tempero Bio Inc. 1111 Broadway, Suite 1300 Oakland, CA 94607 United States

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonization and all applicable federal and local regulations.

Protocol Version		Date
Amendment 4 **Version 4.0**	**Final**	**October 02, 2023**

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STUDY SYNOPSIS

Name of Sponsor/Company:	Tempero Bio Inc.
Name of Product:	TMP-301
Title of Study:	A Phase 1, Randomized, Placebo Controlled, Multiple Ascending Dose (MAD) Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TMP-301 in Healthy Subjects
Study Development Phase:	1
Objectives:	**Primary objective:** • To assess the safety and tolerability of TMP-301 following multiple ascending oral doses **Secondary objectives:** • To assess the pharmacokinetics (PK) profile of TMP-301 following multiple ascending oral doses **Exploratory objectives:** • To assess endpoints related to TMP-301 mechanism of action • To evaluate Cytochrome P1A2 (CYP1A2) genotypes and their association with phenotypes for potential impact on metabolism and to identify biomarkers of potential response to TMP-301 • Identify TMP-301 metabolites in urine
Endpoints:	**Primary endpoints:** The primary objective will be assessed with the following endpoints: • Adverse events (AE) • Clinical laboratory tests • Vital sign measurements • 12-lead electrocardiograms (ECG) • Physical examinations • Psychiatric assessments (Brief Psychiatric Rating Scale [BPRS], Clinician Administered Dissociative States Scale [CADSS], Columbia Suicide Severity Rating Scale [CSSRS], Modified MiniMental State Examination (3MS), and Visual Analogue Scale [VAS]) **Secondary endpoints:** The secondary objective will be assessed with the following endpoints: • Day 1: Partial areas defined as AUC_{0-12} and AUC_{0-24}; maximum concentration (C_{max}), time of maximum concentration (T_{max}), concentration at 12 h (C_{12}), concentration at 24 h (C_{24}) where $C_{24} = C_{trough\ Day2}$ • Day 14 (or last day of dosing): AUC_{ss} from time zero to the time the end of the (12 or 24 hour) dosing interval ($AUC_{0-TAU,ss}$). For BID cohorts, $AUC_{0-TAU,ss} = AUC_{0-12,SS}$, and for QD cohorts, $AUC_{0-TAU,ss} = AUC_{0-24,SS}$; $C_{avg,\ ss}$, $C_{max,ss}$, $T_{max,ss}$, $C_{12,ss}$, C_{24ss}, and $C_{min,SS}$, all at steady-state (SS), along with apparent total plasma clearance (CL/F) and apparent volume of distribution (V_z/F)

	Additional PK evaluations will include:
	• Accumulation ratio derived as:
	  • $AR\_AUC_{0\text{-}12\ BID} = AUC_{0\text{-}12,ss} / AUC_{0\text{-}12,\ Day\ 1}$
	  • $AR\_AUC_{0\text{-}24QD} = AUC_{0\text{-}24,ss} / AUC_{0\text{-}24,\ Day\ 1}$
	  • $AR\_C_{max} = C_{max,ss} / C_{max,FD,\ Day\ 1}$
	  • $AR\_C_{12} = C_{12,ss} / C_{12,\ Day\ 1}$
	  • $AR\_C_{24} = C_{24,ss} / C_{24,\ Day\ 1}$
	
	Estimations of dose proportionality at steady state. Dose–normalized PK parameters (C_{max}, C_{12}, C_{24}, and $AUC_{0\text{-}12}$ and $AUC_{0\text{-}24}$, when appropriate) will be assessed graphically for dose-proportionality
	
	• Estimation of time to achieve steady state. (C_{trough} will be displayed graphically and summarized descriptively by day to assess for steady state)
	
	• As a marker of CYP1A2 activity, the ratio of paraxanthine to caffeine concentration (at 4 hours post caffeine dose) will be reported on Day -1 and Day 14. Change in CYP1A2 activity will be derived as CYP1A2_ratio = paraxanthine/caffeine concentration day 14 / paraxanthine/caffeine concentration day -1
	• Identify TMP-301 metabolites in urine

Investigational Product, Dose, and Mode of Administration (proposed):	TMP-301 50 mg capsules Mode of administration: Oral In cohort 1, twice daily (bid) 50 mg, and in cohort 2 once daily (qd) 50 mg dose of TMP-301 will be administered orally with approximately 240 mL of water. Cohort 3 and 4 doses TBD.
Placebo, Dose, and Mode of Administration:	Placebo-to-match TMP-301 Mode of administration: Oral
Study Design:	This is a single center, double-blind, placebo-controlled, fixed-sequence, multiple ascending dose (MAD) study.
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per subject): Screening: Day -28 to Day -3 (up to 27 days) Treatment period: Doses will be administered from Day 1 to Day 14 Subjects will reside at the clinical unit from Day -2 (PM) to Day 18 (AM). Subjects will return on Day 25 for a follow-up visit and End of Study (EOS) procedures. Total study duration: up to 53 days (including Screening)
Safety Meetings for Dose Adjustments:	Following completion of each cohort, a Safety Review Committee (SRC) will review all available safety and PK data (through Day 15, 24 hours post last dose) to evaluate progression to the next dose cohort. The SRC will be comprised of the Investigator (or designee) at the Investigational site, the Study Manager and the Sponsor's medical personnel at a minimum. Additional advisors could be invited as required. During the study, each prescheduled cohort may be conducted at the dose outlined in the protocol or may be adjusted to a lower or equivalent dose, on the basis of safety, tolerability, and PK data (if available) reported in the previous cohorts. An optional dose titration cohort may be added.
Study Population:	Healthy adult subjects

Planned Number of Subjects:	A maximum of 32 subjects will be included in the study. Each of the 4 cohorts will include 8 subjects.
Bioanalysis:	TMP-301, caffeine and paraxanthine plasma concentrations will be measured by validated bioanalytical methods.
Pharmacokinetic Analysis:	The PK analysis will be fully detailed in a Statistical Analysis Plan (SAP).
Statistical Analysis:	The statistical analysis will be fully detailed in a SAP.

STUDY ADMINISTRATIVE STRUCTURE

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1. INTRODUCTION

1.1. Study Rationale

TMP-301 is a selective negative allosteric modulator (NAM) for the metabotropic glutamate (mGlu) receptor 5 subtype (mGlu5) being developed by Tempero Bio Inc., for the treatment of substance abuse disorders. TMP-301 has been studied in 2 completed studies including a single-ascending dose (SAD) study to evaluate PK and safety/tolerability (HTL001242-101) and a PET imaging study to correlate exposure of a single dose of TMP-301 with mGlu5 RO (HTL001242-103).

The present study is a multiple ascending dose (MAD) study to evaluate the safety, tolerability, pharmacokinetics (PK) of TMP-301 in healthy subjects. There will be up to 4 dose cohorts, and within each cohort subjects will be randomly assigned to receive either active drug or placebo. Study subjects will be administered active drug or placebo once daily (qd) or twice daily (bid) for 14 days (note: only the AM dose is administered on Day 14).

In this study, genetic samples will be collected for possible exploratory pharmacogenetics research that may be conducted to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes). If conducted, these studies would aim to better identify inherited genetic factors which may predict response to treatment with TMP-301, predict relative susceptibility to drug-drug interactions, predict genetic predisposition to side effects, or provide more information regarding TMP-301 in the disease state and how subjects may respond to TMP-301.

1.2. Background

The mGlu receptors are a family of GPCRs involved in the modulation of synaptic transmission and neuronal excitability throughout the CNS[1] and as such play important neuromodulatory roles throughout the nervous system. As a consequence, they have been recognised as attractive targets for therapeutic intervention for a number of psychiatric, neurological and substance abuse disorders.[2] These receptors provide a mechanism by which the neurotransmitter glutamate can modulate cell excitability and synaptic transmission via second messenger signalling pathways. There are 8 mGlu receptors which are subdivided into 3 groups (I, II, and III) based on their sequence similarity and pharmacology. mGlu5 and mGlu1 belong to group I mGlu receptors.[3] Activation of mGlu5 by glutamate stimulates the G protein-coupled pathways increasing intracellular inositol trisphosphate concentration and calcium mobilisation.[3]

There is significant preclinical evidence suggesting that mGlu5 inhibition is beneficial in substance use disorders. Mice with mutations in the gene that encodes mGluR5 are deficient in cocaine self-administration behaviors.[4,5] Similarly, mGluR5 antagonists decrease cocaine self-administration, cue-induced relapse and conditioned place preferences [6,7] while agonists of mGluR5 trigger relapse.[8] The effect of mGluR5 antagonism extends to other substance use disorders. Rodent studies indicate that the mGluR5 antagonist MPEP can reduce alcohol consumption [9] and opiate self-administration.[10]

Human clinical evidence is also consistent with a role for mGluR5 receptors in substance use disorders. Studies with [11C]ABP688, a PET ligand for mGluR5, in human cocaine users have found a reduction in mGluR5 availability during abstinence that is correlated with the duration of

abstinence.[11] [18]FPEB, another mGluR5 PET ligand, has been used to show that alcohol-dependent patients have decreased cerebral mGluR5 levels during abstinence. [12,13] In contrast, higher striatal mGluR5 availability was observed in relapsers than in abstainers and mGluR5 reduction was associated with reduced craving scores during abstinence, indicating that mGluR5 reduction could reduce craving and prevent relapse. Finally, a Phase 2 clinical study of the mGlu5 inhibitor mavoglurant, in patients with cocaine use disorder (CUD), demonstrated a reduction in the proportion of cocaine use days and alcohol use days in patients receiving mavoglurant relative to patients receiving placebo (NCT03242928 [14]). These findings suggest that a pharmacological blockade of mGluR5 could be a therapeutic approach for modulating cocaine or alcohol-seeking behavior and preventing relapse.

1.3. Summary of Nonclinical Pharmacology

Full details on nonclinical pharmacology are provided in the Investigator's Brochure (Section 4.1).

1.4. Summary of Nonclinical Safety Pharmacology

Full details on nonclinical safety pharmacology are provided in the Investigator's Brochure (Section 4.1.4).

1.5. Summary of Nonclinical Pharmacokinetics

Full details on nonclinical pharmacokinetics are provided in the Investigator's Brochure (Section 4.2).

1.6. Summary of Nonclinical Toxicology

Full details on nonclinical toxicology are provided in the Investigator's Brochure (Section 4.3).

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2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	**Primary**
• To assess the safety and tolerability of TMP-301 following multiple ascending oral doses	The primary endpoint is safety assessed after multiple-dose administrations by: • Adverse events (AE) • Clinical laboratory tests • Vital sign measurements • 12-lead electrocardiograms (ECG) • Physical examinations • Psychiatric assessments (Brief Psychiatric Rating Scale [BPRS], Clinician-Administered Dissociative States Scale [CADSS], Columbia Suicide Severity Rating Scale [C-SSRS], Modified Mini-Mental State Examination (3MS) and Visual Analogue Scale [VAS])
Secondary	**Secondary**
• To assess the pharmacokinetics (PK) profile of TMP301 following multiple- ascending- oral doses	The secondary objective will be assessed with the following endpoints: • Day 1: Partial areas defined as AUC_{0-12} and AUC_{0-24}; maximum concentration (C_{max}), time of maximum concentration (T_{max}), concentration at 12 h (C_{12}), concentration at 24 h (C_{24}) where $C_{24} = C_{trough\ Day2}$ • Day 14 (or last day of dosing): AUC_{ss} from time zero to the time the end of the (12 or 24 hour) dosing interval ($AUC_{0-TAU,ss}$). For BID cohorts, $AUC_{0-TAU,ss} = AUC_{0-12,SS}$, and for QD cohorts, $AUC_{0-TAU,ss} = AUC_{0-24,SS}$; $C_{avg,\ ss}$, $C_{max,ss}$, $T_{max,ss}$, $C_{12,ss}$, C_{24ss}, and $C_{min,SS}$, all at steady-state (SS), along with apparent total plasma clearance (CL/F) and apparent volume of distribution (V_z/F) •
Exploratory	**Additional PK evaluations**
• To assess endpoints related to TMP-301 mechanism of action • To evaluate CYP1A2 genotypes and their association with phenotypes for potential impact on metabolism and to identify biomarkers of potential response to TMP-301. • Identify TMP-301 metabolites in urine	• Accumulation ratio derived as: o $AR\_AUC_{0-12\ BID} = AUC_{0-12,ss} / AUC_{0-12,\ Day\ 1}$ o $AR\_AUC_{0-24QD} = AUC_{0-24,ss} / AUC_{0-24,\ Day\ 1}$ o $AR\_C_{max} = C_{max,ss} / C_{max,FD,\ Day\ 1}$ o $AR\_C_{12} = C_{12,ss} / C_{12,\ Day\ 1}$ o $AR\_C_{24} = C_{24,ss} / C_{24,\ Day\ 1}$ • Estimations of dose proportionality at steady state. Dose–normalized PK parameters (C_{max}, C_{12}, C_{24}, and AUC_{0-12} and AUC_{0-24}, when appropriate) will be

OBJECTIVES	ENDPOINTS
	assessed graphically for dose-proportionality • Estimation of time to achieve steady state. (C_{trough} will be displayed graphically and summarized descriptively by day to assess for steady state) • As a marker of CYP1A2 activity, the ratio of paraxanthine to caffeine concentration (at 4 hours post caffeine dose) will be reported on Day -1 and Day 14. Change in CYP1A2 activity will be derived as CYP1A2_ratio = paraxanthine/caffeine concentration day 14 / paraxanthine/caffeine concentration day -1

3. STUDY DESIGN

3.1. Adaptive Features and Risk Management of Study Design

The rationale of having the following adaptive features is based on the hypothesis-forming approach of this clinical trial. Dose escalation or de-escalation, including titration, categories will be adapted as follows:

Table 1: Adaptive Features and Boundaries

Adaptive study design category	Adaptive Features	Boundaries
Dose adjustment	Doses for the subsequent cohorts will be determined/adapted based on tolerability, and PK data (if data through Day 15 permits and is available) collected in previous cohort.	Doses are intended to escalate; however, they may be adjusted to a lower, an equivalent dose or a higher dose as per the adaptive features. For any cohort the mean maximum systemic exposure should not exceed or be predicted to exceed an AUC_{0-24} of 16,200 h.ng/mL at steady state and/or a maximum serum concentration predicted to exceed a C_{max} of 783 ng/mL[a]
The number of MAD cohorts	The quantity of MAD cohorts may be adapted	The maximal number of different dose level cohorts will be 4.
Dose Titration	Dose titration may be added in this study based on interim safety data reviews and tolerability to the study drug.	Based on safety/tolerability findings in any of the previous cohorts, a 14 day dose titration cohort (7 days at initial dose + 7 days at higher dose) may be added.
Dosing with meals	Dosing may be done in a fasted or fed state.	At the selected dose level, the predicted effect of food on exposure will not exceed the thresholds described above.

Abbreviations: MAD = multiple ascending dose; PK = Pharmacokinetics.
[a]Exposure limits were based on 28D Rat NOAEL exposures, with an additional 10x safety factor.

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3.2. Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) is defined as the highest dose that can be administered without clinically significant adverse events (AEs). The MTD will be determined by dose escalation until the stopping criteria are met as outlined in Section 4.3.2.1.

The MTD is defined as the highest dose that does not cause unacceptable side effects.

3.3. Overall Study Design

This study will be a randomized, double-blind, placebo controlled, fixed sequence, MAD study. The study will be conducted in a single clinical research unit (CRU). The study will consist of up to 4 cohorts. Each cohort will consist of 8 subjects (6:2 for active: placebo), for a maximum total sample size of approximately 32 subjects. Subjects will only participate in 1 cohort.

Screening will occur within approximately 28 days prior to the first scheduled study drug administration. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria and who consent to participation will be admitted to the CRU for baseline evaluations prior to dosing. All baseline safety results should be available prior to the first study drug administration.

In cohort 2, subjects will be fasted overnight for 10 hours prior to the morning dose, followed by a 2 hour fast. Subjects were fasted for 2 hours prior to dosing and 2 hours following the evening dose for the cohort 1 (50 mg bid). If dosing in a fed condition is selected for cohort 3 or 4 (see section 3.1), subjects will be fasted overnight for approximately 9 hours, then given standard breakfast followed by study treatment dosing 30 minutes after initiation of breakfast.

Each subject will be randomly assigned to 1 of the following cohorts:

- Cohort 1: Group 1 (6 subjects): 50 mg of TMP-301 bid
  Group 2 (2 subjects): placebo (matching TMP-301) bid
- Cohort 2: Group 3 (6 subjects): 50 mg of TMP-301 qd
  Group 4 (2 subjects): placebo (matching TMP-301) qd
- Cohort 3: Group 5 (6 subjects): Dose regimen of TMP-301 to be determined
  Group 6 (2 subjects): placebo (matching TMP-301)
- Cohort 4: Group 7 (6 subjects): Dose regimen of TMP-301 to be determined
  Group 8 (2 subjects): placebo (matching TMP-301)

Safety will be assessed and blood samples for PK will be collected throughout confinement. Subjects will be discharged from the CRU on Day 18. Subjects will return to the CRU on Day 25 for a follow-up visit and EOS procedures.

Caffeine (100 mg) will be included as probe CYP1A2 substrate in cohort 2 and subsequent cohorts. Ratio of plasma paraxanthine/caffeine will be determined in a blood sample 4 hours after administration of caffeine at baseline (Day-1) and on day 14.

The maximum duration of subject participation, including Screening, will be approximately 53 days.

Subjects who terminate the study early will perform follow-up procedures at the time of Early Termination.

Based on safety and tolerability findings in any of the cohorts, a 14-day dose titration cohort to evaluate the impact on TEAEs may be added as an additional cohort (7 days titration + 7 days stable dosing).

The schedule of activities (SoA) of the study is described in Table 3.

3.4. Study Treatments

The following treatments will be administered according to Table 2.

- IP: TMP301 oral capsule
- Placebo: Matching placebo

Table 2: Dose Cohorts

Cohort	N (Active:Placebo)	Dose	Fasting Status	Drug Administration
1	6:2	Twice daily dose of 50 mg	Fasting Pre & 4 hours post dose	Twice daily TMP-301 or placebo dosing from Days 1 to 13 and once in the morning on Day 14 (for a total of 27 consecutive study drug administrations) or Once daily TMP-301 or placebo to be administered in the mornings of Days 1-14.
2	6:2	Once daily dose of 50 mg	Fasting Pre & 2 hours post dose or Fed 30 minutes pre-dose	
3 (Optional)	6:2	Dose and regimen to be determined		
4 (Optional)	6:2	Dose and regimen to be determined		

Caffeine (100 mg) will also be administered to enrolled subjects as part of the study on Day -1 and Day 14.

4. SUBJECT POPULATION

Subjects meeting all the inclusion criteria and none of the exclusion criteria at Screening may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to the first study drug administration.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

4.1. Inclusion Criteria

1. Provision of signed and dated informed consent form (ICF)
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Healthy adult male or female
4. If male, meets one of the following criteria:
   a. Is able to procreate and agrees to use one of the accepted contraceptive regimens and not to donate sperm from the first study drug administration to at least 90 days after the follow-up visit. An acceptable method of contraception includes one of the following:
      – Abstinence from heterosexual intercourse
      – Male condom with spermicide or male condom with a vaginal spermicide (gel, foam, or suppository)

   Or

   b. Is unable to procreate; defined as surgically sterile (ie, has undergone a vasectomy at least 180 days prior to the first study drug administration)
5. If female, meets one of the following criteria:
   a. Physiological postmenopausal status, defined as the following:
      – absence of menses for at least 12 months prior to the first study drug administration (without an alternative medical condition); and
      – Follicle stimulating hormone (FSH) levels ≥ 40 mIU/mL at Screening;

   Or

   b. Surgical postmenopausal status, defined as the following:
      – bilateral oophorectomy, salpingectomy, or tubal ligation; hysterectomy
6. Aged at least 18 years but not older than 59 years, inclusive, at the time of informed consent
7. Body mass index (BMI) within 18.5 kg/m^2 to 32.0 kg/m^2, inclusively
8. Minimum body weight of at least 50.0 kg

9. Non- or ex-smoker *(An ex-smoker is defined as someone who completely stopped using nicotine products for at least 90 days prior to the first study drug administration)*
10. Must be willing to abstain from drinking coffee or caffeine containing beverages during the study, except where part of the study procedures
11. Has supine blood pressure and pulse rate within the following ranges after 5 minutes rest: systolic blood pressure 90 to 140 mmHg, diastolic blood pressure 50 to 90 mmHg, and pulse rate 45 to 90 bpm at Screening and at check in
12. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on the physical examination (including vital signs) and/or ECG, as determined by an Investigator
13. Has clinical laboratory test results within the reference ranges of the testing laboratory, with the exception of results outside the reference ranges that are deemed not clinically significant by the Investigator (or designee) at Screening and check-in

4.2. Exclusion Criteria

1. Female who is lactating
2. Female who is pregnant according to the pregnancy test at Screening or prior to the first study drug administration
3. Female using the following systemic contraceptives: oral, patch or vaginal ring, in the 28 days prior to the first study drug administration and during the study
4. Female using hormone replacement therapy in the 28 days prior to the first study drug administration and during the study
5. Female using the following systemic contraceptives: injections or implant, or hormone releasing intrauterine device in the 13 weeks prior to the first study drug administration and during the study
6. Drinking excessive amounts of tea, coffee, chocolate, and/or beverage or eating food containing caffeine (> 2 cups/day)
7. Use of tobacco or nicotine containing products (including but not limited to; cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 90 days prior to the first study drug administration and the inability to abstain from nicotine containing products until the follow-up visit.
8. Past or current history of any mental, behavioral, or neurodevelopmental disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or significant risk of developing a psychosis (assessed by PRIME screen) or a personal history of psychotic symptoms (hallucinations or delusions) with or without a formal psychiatric diagnosis. Subjects with family history of significant mental, behavioral, or neurodevelopmental disorders unless determined by the Investigator (or designee) and agreed by the Medical Monitor to be non-clinically significant (NCS) will be excluded.

9. History or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, gastrointestinal, neurological, respiratory, or endocrine disorder, unless determined by the Investigator (or designee) and agreed by the Medical Monitor to be NCS
10. Active or history of cardiovascular or cerebrovascular disease, including hypertension, angina, ischemic heart disease, transient ischemic attacks, bundle branch block, evidence of myocardial ischemia, stroke, and peripheral arterial disease sufficient to cause symptoms and/or require therapy to maintain stable status
11. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee)
12. Active neoplastic disease or history of any neoplastic disease within 5 years of Screening (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitely treated with standard of care)
13. Active infection (eg, sepsis, pneumonia, abscess) or a serious infection (eg, resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to dosing
14. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed)
15. Any of the following at Screening and/or prior to the first study drug administration:
    a. QT interval corrected for heart rate using Fridericia's method (QTcF) > 450 ms confirmed by repeat measurement
    b. QRS duration > 110 ms confirmed by confirmed by repeat measurement
    c. PR interval > 220 ms confirmed by repeat measurement
    d. Findings which would make QTc measurements difficult or QTc data uninterpretable
    e. History of additional risk factors for torsades de pointe (eg, heart failure, hypokalemia, family history of long QT syndrome)
16. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
17. Positive test result for alcohol, cotinine, and/or drugs of abuse at Screening or prior to the first drug administration
18. Positive screening results to HIV Ag/Ab combo, hepatitis B surface antigen or hepatitis C virus tests
19. Any other clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of an Investigator, increase the subject's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data
20. Intake of an IP in the 28 days prior to the first study drug administration
21. Use of any prescription drugs in the 28 days prior to the first study drug administration, that in the opinion of an Investigator would put into question the status of the participant as healthy

22. Use of St. John's wort in the 28 days prior to the first study drug administration and during the study
23. Consumption of any foods or beverages which alter CYP1A2 activity, e.g., barbecued food or cruciferous vegetables, such as broccoli and cauliflower, within 14 days prior to (first) check-in (a list of prohibited foods will be provided to subjects)
24. Consumption of any foods or beverages containing Seville-type oranges, grapefruit, or poppy seeds within 7 days prior to (first) check-in
25. Receipt of blood products within 2 months prior to check-in
26. Donation of 1 unit of blood to American Red Cross or equivalent organization or donation of over 500 mL of blood in the 56 days prior to the first study drug administration
27. Donation of plasma in the 7 days prior to the first study drug administration
28. Poor peripheral venous access
29. History or significant hypersensitivity to TMP301 or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
30. Subjects who, in the opinion of the Investigator (or designee; including input from subjects' general practitioner, as applicable), should not participate in this study
31. Subject hospitalized for any reason in a period of 30 days before the start of the study
32. Subjects who are investigational site staff members or directly involved in the conduct of the study and their family members or subjects who are employed by the Sponsor

4.3. Withdrawal Criteria

4.3.1. Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the subjects to be dosed. Subjects withdrawn before first treatment administration will not be followed up and will not undergo End-of-Study/Early Termination assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

4.3.2. After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an Investigator or Sponsor. If such withdrawal occurs, or if the subject fails to return for visits, an Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject

is withdrawn, the Investigator should make every effort to perform a final study visit 7 days after the last administration of the investigational product (IP) and complete the assessments and procedure outlined in the SOA. Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic, where possible. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to the study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will not be replaced.

In the case of a clinically significant illness detected during the trial (including Coronavirus Disease 2019 [COVID]-19 diagnosis), the Principal Investigator (or delegate) will, in concert with the Sponsor, determine the most appropriate course of action on an individual basis. Evaluations will include but are not limited to:

- The safety of the subject and other study participants
- The possible effect the illness would have on the results gathered during the trial, and their ability to be appropriately analyzed or interpreted
- The possibility of suspending participation then re-initiating it after recovery
- The implication of any inclusion or exclusion criteria that would contradict possible actions
- The implication of any adherence to regulatory guidelines that may be affected by actions decided, for example group effect analysis
- The sample size calculation, current number of subjects, and possibility of replacement subjects

Evaluations and decision-making for subject removal will be documented in the study file, reported to the Sponsor, reviewed during cohort safety evaluation and discussed where appropriate in the Clinical Study Report (CSR).

4.3.2.1. Stopping Rules

4.3.2.1.1. Individual Subject Stopping Rules

A subject will be withdrawn, and study treatment discontinued, if any of the following criteria are met:

- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee).

  Any clinically relevant sign, symptom, or intercurrent illness that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

- Non-compliance with the study restrictions or other unanticipated logistical event that might affect subject safety or study assessments/objectives, or as considered applicable by the Investigator (or designee).
- Occurrence of a serious adverse event associated with active IP administration.
- A subject experiences increased ALT or AST ≥3 × ULN.
- A subject has a creatinine > 1.2 x ULN or an increase in serum creatinine by ≥ 30 µmol/L (or 0.34 mg/dL) within 24 hours or an increase in serum creatinine to ≥ 1.5 x baseline within 7 days.
- A subject has an increase of > 60 msec from baseline (predose on Day 1 of each treatment period, as applicable) in QTcF.
- A subject with any QTcF > 500 msec confirmed by the average of 2 additional ECG recordings performed at least 5 minutes apart, or other clinically significant conduction disturbance or arrhythmia.
- A subject has a heart rate < 45 bpm or heart rate > 130 bpm, confirmed by a repeat assessment
- A subject has a systolic blood pressure < 80 or > 155 mmHg, or a diastolic blood pressure > 100 mmHg, confirmed by a repeat assessment

In the event of a subject meeting any of the above withdrawal criteria, the Sponsor's Medical Monitor may deem it necessary for unblinding to occur.

4.3.2.2. Trial Stopping Rules

During active dosing of a cohort, the Investigator must contact the Sponsor immediately to discuss whether to suspend dosing if an AE or laboratory abnormalities indicate that continued dosing of subsequent subjects would not be tolerated or would jeopardize the subjects' safety. The Sponsor alone may suspend dosing at any time for any reason.

Active dosing of all subjects within a cohort must be stopped with any of the following:

- If 1 SAE occurs in a subject receiving active IP
- If 'severe' non-serious adverse reactions (ie, severe non-serious adverse events considered as, at least, possibly related to TMP-301) in 2 subjects in the same cohort, independent of within or not within the same system-organ-class.
- One or more subjects fulfill Hy's law defined as increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (confirmed with repeat testing) where no other reason can be found to explain the combination of increases, e.g., elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis, or administration of another drug.
- Occurrence of 1 death attributable to the study treatment

If any of the above scenarios occur, all active dosing will stop, and no new cohorts will be initiated. Further discussion will then occur within the SRC, and a safety review will be

conducted. Following the SRC review, the study may continue if the Investigator and Sponsor agree it is safe to proceed. If the study is stopped, the MTD will be declared at the next lowest dose that was found to be safe and tolerable.

Following completion of a dosing cohort, a safety evaluation will take place to determine if it is safe to dose escalate in a subsequent cohort. If any of the following occur, no subsequent dose escalation will occur:

- ≥2 subjects within the same cohort meet the same individual subject stopping rule at least possibly related to study treatment (see section 4.3.2.1.1).
- ≥2 subjects within the same cohort experience any severe AEs at least possibly related to study treatment.
- ≥2 subjects within the same cohort experience clinically significant laboratory abnormalities of the same character at least possibly related to study treatment.
- ≥1 subjects with a serious adverse event considered at least possibly related to study treatment.

If cohort dose escalation is stopped, the MTD will be declared as the next lowest dose that was found to be safe and tolerable.

4.4. Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming food or beverages containing Seville-type oranges, grapefruit, or poppy seeds within 7 days prior to (first) check-in and during the study.
- Subjects will eat only the food provided by the study site during confinement at the CRU.
- Subjects will not be permitted to use tobacco or nicotine containing products (including but not limited to; cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 90 days prior to the first study drug administration and must be willing to abstain from nicotine containing products until the follow-up visit.
- Subjects will be prohibited from consuming alcohol for 48 hours prior to dosing and throughout the study. Throughout the study, in case of any doubt about alcohol consumption, a test for alcohol may be performed if requested by an Investigator.
- Subjects will be prohibited from consuming any foods or beverages which alter CYP1A2 activity (e.g., barbecued food or cruciferous vegetables, such as broccoli and cauliflower) for 14 days prior to check-in and through the end of the study (a list of prohibited foods will be provided to subjects).
- Subjects must abstain from caffeine for 48 hours prior to check-in and will be prohibited from drinking coffee or caffeine containing beverages throughout the study, except when caffeine is being administered as part of the study procedures.

- Males who are sexually active will be made aware of the possible male-mediated fetal toxicity associated with the study drug. Male subjects will be expected to use an acceptable contraceptive regimen and not to donate sperm as described in Section 4.1.

4.5. Concomitant Treatment

In addition to the drugs prohibited as per the exclusion criteria (Section 4.2), subjects will also be prohibited from taking any over the counter (OTC) products for 14 days prior to the first dosing and for the entire duration of the study.

Medications that are substrates, inhibitors, or inducers of CYP1A2 are specifically prohibited (including, but not limited to, those containing caffeine (except where part of the study design), tizanidine, theophylline, naproxen, fluvoxamine, cimetidine, fluoroquinolones, or ticlopidine).

Occasional use of paracetamol/acetaminophen at doses ≤ 2 grams/day will be permitted at the Investigator's discretion.

Except for medication which may be required to treat AEs, no other treatment, medication, or dietary supplement (including herbal/vitamin supplements) other than the study drugs will be allowed from the first dosing until all study activities and evaluations have been completed.

Subjects will be instructed to notify the study site about any new medications taken after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject case report form (CRF). The drug name and dose taken will be noted. An Investigator or delegate and/or the Sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

5. STUDY TREATMENTS

5.1. Investigational Products

All IPs, including the placebo, will be provided by the Sponsor.

5.1.1. TMP-301

5.1.2. Placebo

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5.2. Investigational Product Management

5.2.1. Packaging, Labeling and Dispensing

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5.2.2. Storage and Handling

All study drugs will be shipped from the sponsor or sponsor resources to the CRU's pharmacy.

TMP-301 should be stored between 2°C and 8°C and kept in a tightly closed container. The product should not be used if expired and should not be frozen.

The CRU's pharmacy will maintain an inventory record of the IPs received, stored (in a secure restricted area), and dispensed. IPs will be provided to study subjects only.

5.2.3. Method of Assigning Subjects to Treatment Groups

Altasciences will generate the randomization code with a computer program according to the study design, the number of subjects and the number of treatments. Within each cohort, subjects will be randomized (3:1) to receive TMP-301 or placebo. The random allocation of each IP to each subject will be done in such a way that the study is balanced. Once generated, the randomization code will be final and will not be modified.

Subjects who sign the ICF and are randomized but do not receive the study treatment may be replaced. Subjects who sign the ICF, are randomized and receive the study treatment, and subsequently withdrawn as a result of AEs thought to be related to the study drug will not be replaced. Subjects who sign the ICF, are randomized and receive the study treatment, and are subsequently withdrawn for reasons not related to the study drug may be replaced.

5.2.4. Blinding

The randomization code may be made available to the personnel of the bioanalytical facility The treatment assignment will not be known by the study participants.

Furthermore, the randomization code will not be available to the physician and clinical staff involved in the collection, monitoring, revision, or evaluation of AEs, as well as clinical staff who could have an impact on the outcome of the study, and including the pharmacokineticist (or delegate), until database lock, or designation that unblinding information is required by the SRC to determine the next dose.

The preparation of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an Investigator for further treatment to the subject or to complete a SAE report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

The results of the PK analyses will be made available only to the personnel responsible for evaluating the safety data before proceeding with the next dose level.

5.2.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be maintained. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

At the conclusion of the study, all unused IPs and all medication containers will be returned to the Sponsor unless the Sponsor has approved other arrangements. Drug accountability will be performed at the completion of the trial.

5.3. Administration of Study Drug

For cohort 1, the study drug will be administered twice daily (12 hours apart) on Days 1-13 and once in the morning on Day 14. For cohort 2 (and Cohorts 3-4 if done) the study drug will be administered once daily in the morning on Days 1-14. The date and time of each dose will be recorded. For each subject, all scheduled post dose activities and assessments will be performed relative to the time of the first study drug administration.

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On Day -1, caffeine will be administered at approximately 9:00 am with approximately 240 mL of water at ambient temperature test. On Day 14, caffeine will be administered with the study drug and approximately 240 mL of water.

5.3.1. Treatment Compliance

The study drug will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's standard operating procedures (SOPs).

5.4. Meals

Food intake will be controlled for each confinement period and for all subjects.

Subjects will be required to fast overnight for 10 hours prior to the morning dose and for at least 2 hours following dosing. Subjects will also be required to fast for 2 hours prior to the evening dose and 2 hours following dosing for bid dosing.

For cohort 3 and 4, dosing may be conducted in the fed state (see section 3.1). In that case, subjects will be required to fast overnight for approximately 9 hours. Each subject will be served

a standard breakfast, and the study treatment will be administered 30 minutes after initiation of the meal.

Fluid intake other than water will be controlled for each confinement period and for all subjects.

Each dose of TMP-301 will be administered with approximately 8 oz or 240 mL or water. Water will be permitted as needed except from 1-hour predose until 1 hour after dosing (except for water consumed for the dose administration). For cohort 3 and 4, if dosing is conducted in the fed state, there will be no water restriction during the meal.

5.5. Other Protocol Restrictions

Subjects will remain in bed (seated or semi-reclined) for at least the first 4 hours following drug administration. However, should AEs occur, subjects may be placed in an appropriate position. During this interval and after the 4-hour period, subjects will be permitted to get up under supervision. Subjects will not engage in strenuous activity at any time during the confinement periods.

6. STUDY PROCEDURES

An overview of the study activities for each participant is detailed in Table 3.

Subjects may leave the clinical site on Day 18. However, they may be advised to stay at the clinical site for safety reasons, if judged necessary by the Investigator or delegate in charge.

Unless otherwise stated in the protocol, the Standard Operating Procedures (SOPs) of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. When the nominal time for multiple events occurs simultaneously, the events will be staggered using their acceptable windows (acceptable windows for each assessment are specified in the following sections of this protocol), with priority given to those events related to primary study endpoints.

Any deviation from protocol procedures should be noted in the source documentation, recorded as a protocol deviation, and compiled for reporting in the CSR.

Table 3: Schedule of Activities

Study Procedures	Screening	Check-in	Baseline Caffeine test	Day 1	Days 2-3	Day 4	Days 5-6	Day 7	Days 8-13	Day 14	Days15-17	Discharge	Follow-up/EOS visit
Day	Days-28 to -1	Day -2	Day -1									Day 18	Day 25[z] (±2 days)
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Admission to Unit		X											
Demographic Data	X												
Medical History	X	X[a]											
Psychiatric History	X												
Physical Examination	X	X[b]										X[p]	
Psychiatric Examinations[c]	X[c]												
Urinary Drug Screen	X	X											
Alcohol Urine Test	X	X											
Serology	X												
Pregnancy Test[d]	X	X										X	
FSH[e]	X												
Height and body weight	X[f]											X	X
Genotyping sample[g]				**X**									
Exploratory Biomarkers sample				X[h]	X[h]			X[h]		X[h]		X	
Check-in		X											
Check-out												X	
Nonresidential visit	X												X
Randomization		X											
TMP-301 or Placebo[i]				X	X	X	X	X	X	X			
Caffeine 100 mg oral			X							X			
Caffeine Plasma sampling			4 hr post dose							4 hr post dose			

Study Procedures	Screening	Check-in	Baseline Caffeine test	Day 1	Days 2-3	Day 4	Days 5-6	Day 7	Days 8-13	Day 14	Days15-17	Discharge	Follow-up/EOS visit
Plasma PK Sampling[j,k,l]				X	X	X	X	X	X	X	X	96.00[aa]	X
Urine Sampling[l]				X						X	X		
Adverse Event Recording	X	X		X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medication Monitoring	X	X		X	X	X	X	X	X	X	X	X	X
Clinical chemistry, Hematology, and Urinalysis[m]	X	X		X	X	X	X		X	X	X	96.00 [aa]	X
Vital Signs: Blood Pressure, Pulse Rate and Oral Body Temperature[n,o]	X	X		X	X	X	X	X	X	X	X	96.00 [aa]	X
12-lead ECG[q,r]	X			X	X	X	X	X	X	X	X	96.00 [aa]	X
VAS Alertness Scale[s,t]				X				X		X		96.00 [aa]	
BPRS, CADSS[t,u,v,x]	X	X		X				X		X			
3MS[t,v,w,x]	X	X		X				X		X			
C-SSRS[y]	X	X		X	X		X	X	X		X	X	X
Discharge												X	

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CADSS = Clinician-Administered Dissociative States Scale; 3MS = Modified Mini-Mental State; C-SSRS = Columbia-Suicide Severity Rating Scale**;** ECG = electrocardiogram; FSH = follicle-stimulating hormone; PK = pharmacokinetic(s).

[a] Interim medical history.
[b] Symptom directed physical examination and at Investigator discretion.
[c] Clinical Interview for DSM-5 (SCID-5 CT) will be conducted by appropriately trained staff. This psychiatric examination will include an assessment of premorbid personality, personal and developmental history, alcohol and substance use history, forensic history, past psychiatric history. The PRIME questionnaire will also be administered to screen for risk of psychosis. A psychiatric exam (full or partial) can take place at any time during the study at the discretion of the PI, if there is a relevant concern.
[d] In all females. Serum pregnancy test at Screening and urine pregnancy tests at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] In all females to determine postmenopausal status.
[f] Height measured at Screening only.
[g] The genotyping samples will be stored and may be processed and analyzed to assess genotyping of drug metabolizing systems.
[h] Day 1 at pre-dose, 1, 4, and 8 hours; day 2 pre-dose; and days 7 and 14 at pre-dose, 1, 4, and 8 hours.
[i] For BID Cohorts: Dosing twice daily interval from Day 1 to Day 13, two intakes separated by 12.00 hours (note: only the AM dose is administered on Day 14). For QD Cohorts: Dosing once daily in the morning from Day 1 to Day 14.
[j] Timing of PK blood samples may be changed based on emerging data.
[k] At each protocol specified timepoint for PK (including predose baseline) out to 12.00 hours postdose. (Section 6.2).

[l] Serial blood will be collected on Day 1, and 14 at predose, 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, and 12.00 hours. Trough (predose AM) and 8 hr and 12 hr samples will be collected on Days 2, 7 and 11. Trough samples (predose AM) will be collected on Days 5, 9 and 12. Additional PK samples will be drawn after the last dose on Day 14 at 24.00 (Day 15), 28.00 (Day 15), 48.00 (Day 16), 52.00 (Day 16), 72.00 (Day 17), and 96.00 (Day 18) hours postdose and Day 25 at the follow-up EOS visit (Day25 ± 2 days). Urine will be collected on Day 1 (0 to 4, 4 to 8, 8 to 12, 12 – 24 hr) and Day 14 (0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48 (Day 15), and 48 – 72 hr (Day 16)). See Table 4.

[m] Day 1 predose, then 24.00 (Day 2) and 72.00 hours (Day 4) postdose, then every 2 days (Days 6, 8, 10, 12, 14, 16) post dose at approximately 10 am ± 1 hour.

[n] Days 1 and 7: Prior to morning dosing and 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, and 12.00 hours. Days 2, 4, 6, 8, 10, and 12: Prior to dosing and 4.00 and 12.00 hours postdose. Day 14: Prior to dosing and 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00 (Day 15), 48.00 (Day 16), 72.00 (Day 17), 96.00 (Day 18) hours postdose.

[o] At baseline on Day 1, predose vital sign measurements (except oral body temperature) will be conducted in triplicate (with an interval of approximately 10 - 30 minutes between each recording). The average value of each parameter will be considered as baseline value.

[p] Symptom-directed physical examination.

[q] Days 1 and 7: Predose and at 4.00, 6.00, 8.00, and 12.00 hours postdose. Days 2, 4, 6, 8, 10, and 12: Predose and 4.00 and 12.00 hours postdose. Day 14: Prior to dosing and 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00 (Day 15), 48.00 (Day 16), 72.00 (Day 17), 96.00 (Day 18) postdose.

[r] At baseline in Day 1 predose, ECG recordings will be conducted in triplicate at (-45, -30, and -15 minutes). The average value of each parameter will be considered as baseline value.

[s] Day 1, 7, and 14: Predose then 4.00, 6.00, and 12.00 hours postdose and Day 18.

[t] May also be conducted at other times if deemed appropriate based on emerging data.

[u] Check-in, then 6.00 and 24.00 hours postdose on Day 1, Day 7, and Day 14.

[v] Conducted as part of the psychiatric examination.

[w] Check-in , and 24.00 hours postdose on Day 1, Day 7, and Day 14.

[x] Subjects will be screened within 28 days prior to dosing. A psychiatric examination will be performed at Screening by a suitably trained psychiatrist or appropriately trained staff using a clinical interview. This will include an assessment of premorbid personality, personal and developmental history, alcohol and substance use history, forensic history, past psychiatric history, and mental state examination.

[y] Every other day from Day 1 to discharge.

[z] Approximately 1 week after last dose.

[aa] 96 hours after the last (Day 14) dose

6.1. Safety Assessments

Safety assessments will include physical examination, psychiatric assessments, vital signs, 12-lead ECG, clinical laboratory tests, and AE monitoring. At the discretion of an Investigator, additional safety assessments may be performed as needed to ensure subject safety.

The Investigator or delegate in charge will be present at the clinical site for at least the first 4 hours following first drug administration and will remain available at all times throughout the study.

6.1.1. Medical History

The medical history at Screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, sex, race, body weight, height, and BMI) and baseline characteristics. Alcohol and smoking habits will also be recorded.

6.1.2. Psychiatric History

Clinical Interview for DSM-5 (SCID-5 CT) will be conducted by appropriately trained clinical staff at Screening. This psychiatric examination will evaluate the subject's psychiatric history and include an assessment of premorbid personality, personal and developmental history, alcohol, and substance use history, forensic history, past psychiatric history.

The 12 question PRIME screen will be self-administered by subjects at Screening. After completion, study staff will review the subject's responses. A positive screen is a score of 6 on any one question or a score of 5 on any two questions. Subjects with a positive PRIME screen will be excluded from the study, as they are considered at high risk of developing psychosis (see Appendix 13).

6.1.3. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as outlined in Table 3.

The physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, gastrointestinal, brief neurological and general appearance, unless a symptom-oriented physical exam is indicated.

6.1.4. Vital Signs

Vital signs will be measured as outlined in Table 3. Baseline vital signs (as well as subsequent predose and/or post-dose 24 hours) will be measured approximately 2 hours prior to dosing. All other vital signs will be assessed within +/- 20 minutes of the nominal time point.

Blood pressure and pulse rate will be measured after being in supine position for at least 3 minutes. Efforts will be made to apply the blood pressure cuff when the subject is placed in supine position for ECG collection. Repeat measurements may be performed at investigator's discretion to verify out of range or suspect values, including during screening and check-in.

6.1.5. 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed as outlined in Table 3.

Predose and/or post-dose 24 hour ECGs should be completed approximately 2 hours prior to the morning dose. All other ECG assessments should be completed within +/- 20 minutes of the nominal time point. ECG assessments will be collected after being in supine position for at least 10 minutes.

6.1.6. Pharmacogenetic and Exploratory Biomarkers Sampling

A blood sample will be collected for CYP 1A2 or other genotyping on Day 1 as outlined in Table 3. Blood samples will also be collected on Day 1 and during designated times (per Table 3) during the treatment period for exploratory biomarker analysis.

6.1.7. Laboratory Evaluations

Laboratory evaluations will be performed as outlined in Table 3.

The laboratory evaluations to be conducted for this study are presented in Appendix 6. Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

The Investigator or delegate in charge will assess each abnormal value to determine if it is clinically significant. Postdose clinically significant laboratory values will be reported as AEs, if applicable, as judged by the Investigator or delegate in charge. Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the CSR, based on report requirement.

6.1.8. Brief Psychiatric Rating Scale (BPRS)

The BPRS scale is designed for the assessment of psychiatric symptoms or disorders (eg, depression, anxiety, hallucinations, and unusual behavior).

The scale must be administered by a psychiatrist or other individual that is suitably qualified by education or training. See Appendix 7 for a sample assessment. The assessment will be performed as outlined in Table 3.

The BPRS will be completed at check-in on Day -2 and at approximately 6.00 and 24.00 hours after dosing on Day 1. The BPRS will also be completed approximately 6.00 and 24.00 hours after dosing on Days 7 and 14. The acceptable window for BPRS will be within 2 hours following the 6.00 hours nominal timepoint and approximately 3 hours prior to next dose for the 24.00 hour timepoint.

All the 24.00 hour post-dose assessments are intended to be completed prior to next day dosing as applicable.

PD procedures should be carried out in the following order when required: (1) 3MS, (2) CADSS, (3) BPRS, (4) C-SSRS.

6.1.9. Clinician-Administered Dissociative States Scale (CADSS)

The CADSS scale is designed for the assessment of dissociative states in adults.

The scale must be administered by a psychiatrist or other individual that is suitably qualified by education or training. See Appendix 8 for a sample assessment. The assessment will be performed as outlined in Table 3.

The CADSS will be completed at check-in on Day -2 and at approximately 6.00 and 24.00 hours after dosing on Day 1. The CADSS will also be completed approximately 6.00 and 24.00 hours after dosing on Days 7 and 14. The acceptable window for CADSS will be within 2 hours following the 6.00 hours nominal timepoint and approximately 3 hours prior to next dose for the 24.00 hours timepoint.

All the 24 hours post-dose assessments are intended to be completed prior to next day dosing as applicable.

PD procedures should be carried out in the following order when required: (1) 3MS, (2) CADSS, (3) BPRS, (4) C-SSRS.

6.1.10. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults.

To monitor for a history of (the past 2 years to present) or for the emergence of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at the time points indicated in Table 3.

The questionnaire must be administered by a psychiatrist or other individual that is suitably qualified by education or training. See Appendix 9 for a sample C-SSRS – Baseline/Screening version assessment and Appendix 10 for a sample postdose C-SSRS (Since Last Visit Version) assessment.

The C-SSRS will be completed at screening, check-in on Day -2 and it will be assessed approximately 3 hours prior to dosing on Days 1, 3, 5, 7, 9, 11, 13, 15, 17 and on day 18 prior to discharge, and at the follow-up/EOS visit.

PD procedures should be carried out in the following order when required: (1) 3MS, (2) CADSS, (3) BPRS, (4) C-SSRS.

If there is a positive result for suicidality on the C-SSRS after Screening (defined by a subject answering “yes’ to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), the subject will be evaluated by an Investigator or medically qualified sub-investigator for continuation in the study.

If a subject becomes suicidal during the study, an Investigator or medically qualified sub-investigator should provide the appropriate treatment to the subject.

6.1.11. Modified Mini-Mental State Examination (3MS)

The 3MS is an examination designed for the assessment of dementia in adults.

The examination must be administered by a psychiatrist or other individual that is suitably qualified by education or training. See Appendix 11 for a sample assessment. The assessment will be performed as outlined in Table 3.

The 3MS will be completed at check-in and at approximately 24.00 hours after dosing on Day 1. The 3MS will also be completed approximately 24.00 hours after dosing on Days 7 and 14. The

acceptable window for 3MS will be approximately 3 hours prior to next dose for the 24 hours timepoint.

All the 24 hours post-dose assessments are intended to be completed prior to next day dosing as applicable.

PD procedures should be carried out in the following order when required: (1) 3MS, (2) CADSS, (3) BPRS, (4) C-SSRS.

6.1.12. Visual Analogue Alertness Scale (VAS)

The VAS alertness scale is designed to assess the alertness of subjects across a continuum scale with values from 0 to 10.

The scale will be administered by the VAS team or other individual that is suitably qualified by education or training. See Appendix 12 for a sample assessment. The assessment will be performed as outlined in Table 3.

The VAS should be completed prior to TMP-301 administration and at approximately 4.00, 6.00, and 12.00 hours after dosing on Days 1, 7, and 14. This assessment will also occur on Day 18 prior to discharge.

6.1.13. Rescue Therapy

A crash cart with the necessary resuscitation equipment, including parenteral naloxone, will be available in case of a medical emergency.

In the event of a psychiatric emergency, the Investigator may use medication to treat psychosis, agitation or anxiety. Details for the recommended medication to treat these emergencies can be found in Appendix 14 : Psychiatric Emergency Management.

6.2. Pharmacokinetic Assessments

The complete blood sampling schedule is presented in Table 4.

Evaluation of CYP 1A2 activity using caffeine as a CYP 1A2 probe substrate. Paraxanthine/caffeine ratio will be measured at baseline (day -1) and day 14, from 4h blood sample post caffeine dose (100 mg).

Table 4: Pharmacokinetic Blood and Urine Sampling Schedule

	Nominal Time[a] (hours)	
Day	**Blood**	**Urine**
Day 1[a]	0.00	Day 1

	Nominal Time[a] (hours)	
	0.50	0 to 4 4 to 8 8 to 12 12- 24
	1.00	
	2.00	
	3.00	
	4.00	
	6.00	
	8.00	
	12.00	
Days 2, 7, 11	0.00	No Urine Collection
	8.00	
	12.00	
Days 5, 9, and 12	0.00	No Urine Collection
Day 14	0.00	Day 14 0 to 4 4 to 8 8 to 12 12- 24 24-48 (Day 15) 48-72 (Day 16)
	0.50	
	1.00	
	2.00	
	3.00	
	4.00	
	6.00	
	8.00	
	12.00	
	24.00 (Fasted) (Day 15)	
	28.00 (Fed) (Day 15)	
	48.00 (Fasted) (Day 16)	
	52.00 (Fasted) (Day 16)	
	72.00 (Day 17)	
	96.00 (Day 18)	
	264.00 (Day 25 ± 2 days)	

[a]Nominal times listed are relative to the morning dose on the corresponding day.

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula, which will be placed in the vein of the subject.

The time of PK blood sample collection will be calculated relative to the time of treatment administration. The actual time of all PK blood draws will be recorded in case report form and reported for all subjects.

Windows for timed PK blood sample collections are presented in Table 5. PK samples collected outside of the pre-specified windows will be documented as protocol deviations. Since actual times are to be used for the PK analysis, deviations will be reflected in the analysis unless indicated otherwise upon review of the data.

Table 5: Acceptable Windows for Timed PK Blood Specimen Collection Procedures

Elapsed Time	Accepted Window
Pre-dose	Up to –2 hours
> 0 hour to ≤ 30 minutes	± 10 minutes
> 30 minutes to ≤ 4 hours	± 10 minutes
> 4 hours to ≤ 12 hours	± 10 minutes
> 12 hours to ≤ 24 hours	± 10 minutes
> 24 hours to ≤ 72 hours	± 2 hours
> 72 hours	± 4 hours

TMP-301 concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method.

6.2.1. Pharmacokinetic Sample Processing, Storage and Shipping

Blood samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

7. ADVERSE EVENTS DOCUMENTATION

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an Investigator considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an Investigator)

7.2. Severity Assessment

All AEs will be graded per the FDA's Guidance for Industry on Toxicity Grading for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. Causality Assessment

An Investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 6.

Table 6: Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the IP that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the IP. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the IP. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

AE = adverse event; IP = investigational product; SAE = serious adverse event

7.4. Adverse Event Monitoring

This section described the general process of adverse event monitoring. For specific psychiatric adverse event monitoring and management of psychiatric emergencies, see Appendix 14: Psychiatric Emergency Management.

For the purposes of this study, the monitoring period for AEs extends from Screening until the EOS visit. From screening to the first dose of the study, AEs will be recorded as screening events or as part of the medical history, as applicable. AEs occurring after initiation of study drug will be indicated as TEAEs in the CSR.

Subjects will be questioned on their health status at the beginning of each study period and before each departure from the clinical site. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found or is deemed mild and safely resolving.

In the case of AEs deemed related to the IP, every effort will be made to determine the final outcome.

It is an Investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 or higher.

Concomitant medications will be coded using the World Health Organization drug dictionary (WHO-DDE March 2021 or later).

7.5. Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by an Investigator or delegate (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Pregnancy that occurs within 90 days after the follow-up visit in a female partner of a male study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by the clinical site that such pregnancy occurred during the course of the study or right after. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the safety of the subject's female partner, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to the Sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

7.6. Serious Adverse Event Reporting

For the purposes of this study, any psychiatric emergency (see Appendix 14 : Psychiatric Emergency Management) will be considered a SAE and will be reported as outlined below.

The CRU will notify any SAE to the Sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the IPs. Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

The notification should be directed to the following Sponsor representative:

Commercially Confidential Information

An SAE will be considered “unexpected” if the AE is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

The CRU will determine whether any serious unexpected, related AE must be reported to the Institutional Review Board (IRB). If so, the event will be reported via fax or email within 15 calendar days of an Investigator or staff becoming aware of the event.

The Sponsor will determine whether the SAE must be reported in an expedited manner to the applicable regulatory agencies. If so, the Sponsor will report the event to those agencies and to all participating Investigators.

If reports of any new and unexpected AEs become available to the Sponsor during the clinical portion of this study (related or not to the present study), the Sponsor has to advise the CRU, through its clinical Investigator, of those events.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

8.1.1. Safety Population

The safety population will include all subjects who received at least 1 dose of one of the IP or placebo.

The number of subjects who were included, who discontinued, and who completed the study will be tabulated. The primary reasons for discontinuation will be provided.

8.1.2. Pharmacokinetic Population

In most cases, the decision of which subjects will be included in the PK analysis is to be taken before the start of the sample analysis by the bioanalytical facility.

The PK population will be described in an SAP. Generally, the PK population includes all the subjects who received the study drug or equivalent and have at least one postdose evaluable concentration values in any biological matrix.

8.2. Demographic Data and Other Baseline Characteristics

Statistics for demographic and baseline data will be detailed in a SAP.

8.3. Safety

8.3.1. Safety Endpoints

The safety endpoint will be assessed by the number, severity, and type of TEAEs.

8.3.2. Safety Analysis

The clinical laboratory tests and the measurements of vital signs, ECGs, physical examinations, psychiatric assessments, and other safety parameters will be used to perform the safety statistical analysis.

8.3.3. Safety Statistical Methodology

Statistics for summary of AEs and safety results will be fully detailed in a SAP.

8.4. Pharmacokinetics

The PK analysis will be carried out according to Altasciences SOPs. Pharmacokinetic data handling and statistical analysis will be fully detailed in an SAP.

8.4.1. Pharmacogenetic Statistical Methodology

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs,

linear and logistic regression) are used for the analyses. Additional data from subsequent clinical trials are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

8.5. Planned Interim Analyses

No formal interim analyses will be performed; blinded safety data will be reviewed by an Investigator and the Sponsor's Medical Monitor following completion of each TMP-301 dose level.

The SAP will describe the planned interim analyses in greater detail.

8.6. Determination of Sample Size

No formal sample size analysis was performed. It is estimated that approximately 24 subjects should be sufficient to meet the objectives of the study.

9. REFERENCES

1. Niswender, C.M. and P.J. Conn, *Metabotropic glutamate receptors: physiology, pharmacology, and disease.* Annu Rev Pharmacol Toxicol, 2010. 50: p. 295-322.
2. Mihov Y, Hasler G. *Negative allosteric modulators of metabotropic glutamate receptors subtype 5 in addiction: a therapeutic window*. International Journal of Neuropsychopharmacology. 2016 Jul 1;19(7).
3. Watkins, J.C. and D.E. Jane, *The glutamate story.* Br J Pharmacol, 2006. 147 Suppl 1: p. S100-8.
4. Bird MK et al., Lohmann P, West B, Brown RM, Kirchhoff J, Raymond CR, Lawrence AJ. *The mGlu5 receptor regulates extinction of cocaine-driven behaviours. Drug and Alcohol Dependence*. 2014 Apr 1;137:83-9.
5. Chiamulera C et al., *Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice.* Nature neuroscience. 2001 Sep;4(9):873-4.
6. Bäckström P, Hyytiä P. *Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking*. Neuropsychopharmacology. 2006 Apr;31(4):778-86.
7. Kumaresan V et al., *Metabotropic glutamate receptor 5 (mGluR5) antagonists attenuate cocaine priming-and cue-induced reinstatement of cocaine seeking*. Behavioural brain research. 2009 Sep 14;202(2):238-44.
8. Moussawi K et al., *N-Acetylcysteine reverses cocaine-induced metaplasticity*. Nature neuroscience. 2009 Feb;12(2):182-9.
9. Hodge CW et al., *The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice*. Psychopharmacology. 2006 Jan;183(4):429-38.
10. Brown RM, Stagnitti MR, Duncan JR, Lawrence AJ. *The mGlu5 receptor antagonist MTEP attenuates opiate self-administration and cue-induced opiate-seeking behaviour in mice*. Drug and alcohol dependence. 2012 Jun 1;123(1-3):264-8.
11. Milella, M.S., et al., *Limbic system mGluR5 availability in cocaine dependent subjects: A high-resolution PET [C-11]ABP688 study*. NeuroImage, 2014. 98.
12. Leurquin-Sterk, G., et al., *Cerebral dopaminergic and glutamatergic transmission relate to different subjective responses of acute alcohol intake: an in vivo multimodal imaging study*. Addiction Biology, 2018. 23(3): p. 931-944.
13. Ceccarini, J., et al., *Recovery of decreased metabotropic glutamate receptor 5 availability in abstinent alcohol-dependent patients*. Journal of Nuclear Medicine, 2019: p. jnumed.119.228825.
14. NCT03242928. Available from: https://clinicaltrials.gov/ct2/show/NCT03242928.
15. Gregory KJ, Dong EN, Meiler J, Conn PJ. *Allosteric modulation of metabotropic glutamate receptors: structural insights and therapeutic potential*. Neuropharmacology. 2011 Jan 1;60(1):66-81.
16. Trenkwalder, C., et al., *Mavoglurant in Parkinson's patients with l-Dopa-induced dyskinesias: Two randomized phase 2 studies.* Mov Disord, 2016. 31(7): p. 1054-8.
17. Berry-Kravis, E., et al., *Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials*. Sci Transl Med, 2016. 8(321): p. 321ra5.
18. ClinicalTrial.Gov, *Long-term, Safety, Tolerability and Efficacy Study of AFQ056 in Adult Patients With Fragile X Syndrome*. ClinicalTrial.Gov Identifier NCT01348087. 2016.

19. Walles, M., et al., *Metabolism and disposition of the metabotropic glutamate receptor 5 antagonist (mGluR5) mavoglurant (AFQ056) in healthy subjects*. Drug Metab Dispos, 2013. 41(9): p. 1626-41.
20. Friedmann, C.T., et al., *Phase II double-blind controlled study of a new anxiolytic, fenobam (McN-3377) vs placebo.* 1980.
21. Itil, T. and M. HUQUE, *The clinical and quantitative EEG effects and plasma levels of fenobam (McN-3377) in subjects with anxiety: an open rising dose tolerance and efficacy study.* 1978.
22. Pecknold, J.C., et al., *Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study.* J Clin Psychopharmacol, 1982. **2**(2): p. 129-33.
23. Kagedal, M., et al., *A positron emission tomography study in healthy volunteers to estimate mGluR5 receptor occupancy of AZD2066 - estimating occupancy in the absence of a reference region.* Neuroimage, 2013. 82: p. 160-9.
24. Kalliomaki, J., et al., *Evaluation of the effects of a metabotropic glutamate receptor 5-antagonist on electrically induced pain and central sensitization in healthy human volunteers.* Eur J Pain, 2013. 17(10): p. 1465-71.
25. ClinicalTrial.Gov, *Study to Investigate the Pharmacodynamic Effect of a Single Dose of AZD2516 in Healthy Male Subjects. ClinicalTrial.Gov Identifier NCT00154634*. 2012.
26. ClinicalTrial.Gov, *AZD2066 Neuropathic Pain - Mechanical Hypersensitivity (NP-MH). ClinicalTrial.Gov Identifier NCT00939094*. 2012.
27. Keywood, C., M. Wakefield, and J. Tack, *A proof-of-concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-oesophageal reflux disease.* Gut, 2009. 58(9): p. 1192-9.
28. Zerbib, F., C. Keywood, and G. Strabach, *Efficacy, tolerability and pharmacokinetics of a modified release formulation of ADX10059, a negative allosteric modulator of metabotropic glutamate receptor 5: an esophageal pH-impedance study in healthy subjects.* Neurogastroenterol Motil, 2010. 22(8): p. 859-65, e231.
29. Carradori, S. and R. Silvestri, *New Frontiers in Selective Human MAO-B Inhibitors*. J Med Chem, 2015. 58(17): p. 6717-32.

APPENDIX 1. ETHICS

Institutional Review Board

This protocol and the ICF will be submitted to an IRB (or Independent Ethics Committee [IEC]) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the European regulation EU 536/2014 and the Tri-Council Policy Statement (Canada).

Subject Information and Consent

Before screening activities commence, each volunteer will be given a copy of the ICF to read, as well as a full explanation of the purpose of the study, the procedures to be carried out, and the potential AE(s). Once this essential information is provided to the volunteer and the Investigator or delegate in charge has the conviction the volunteer understands the implications of participating in the study, and if the volunteer chooses to continue the screening process, they will be requested to sign and date a properly executed ICF prior to enrollment. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify).

Subjects will be given a signed copy of the ICF. If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.
This study includes an exploratory pharmacogenetic component which requires a separate informed consent. The aim of the planned exploratory pharmacogenetics research studies will be to better identify inherited genetic factors which may predict response to treatment with (TMP-301), predict relative susceptibility to drug-drug interactions, predict genetic predisposition to side effects, or provide more information regarding (TMP-301) in the disease state and how subjects may respond to (TMP-301). The pharmacogenetic assessments are exploratory and are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational drug. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new genomic biomarkers.

Subject Confidentiality

Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the Sponsor. In compliance with Federal regulations/ICH GCP Guidelines, it is required an Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for verification of study-related procedures and data. An

Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the subject's confidentiality.

The Sponsor will store the biological samples in a secure storage space with adequate measures to protect confidentiality.
The samples will be retained while research on the study treatment continues but no longer than 5 years (or other period), as per local requirements.
During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

Safety Oversight

Safety oversight will be under the direction of the SRC composed of individuals with the appropriate expertise, including Sponsor's Medical Monitor, and the PI. Additional advisors could be invited as required. The SRC will operate under the rules of an approved dose escalation plan that will be written and reviewed at the organizational meeting of the SRC. At this time, each data element that the SRC needs to assess will be clearly defined. Additionally, the SRC may conduct ad hoc safety reviews at any point during the conduct of the study.

APPENDIX 2. DATA COLLECTION, RETENTION, AND MONITORING

Case Report Forms

The subject level data is entered by the site into a study specific 21 CFR Part 11 compliant electronic clinical database to accurately collect data for each subject included in a clinical trial. Screen failure data may be part of the analysis data at the discretion of the Sponsor, when included in the contracted scope of work.

Data Management and Processing

Data management develops documentation to define activities performed during the data management conduct of the study trial. The electronic data capture (EDC) system is the tool used to conduct all data management data cleaning activities for monitoring, data review and queries. Data management will use a combination of automated programmed edits and manual data review listings to issue queries for non-conforming or discrepant data. Data management activities are performed in accordance with the SOPs and study-specific data management documents.

Database locking is guided by the Data Management Locking Checklist based on the concept that all site activities are complete; data are considered clean and without errors and CRF signoff by the Principal Investigator or delegate has been completed. User access is removed as part of the locking process.

Data from the clinical database will be output as SAS® datasets. All data will be included with the final report provided to the Sponsor.

Quality Control and Quality Assurance

Designated personnel from the quality assurance (QA) unit(s) will be responsible for maintaining QA of the clinical, PK, statistical and bioanalytical facilities to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for GCP, applicable requirements as outlined in the FDA and OECD Principles of Good Laboratory Practice (GLP), and the *Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples* (EMA/INS/GCP/532137/2010).

Designated personnel from each corresponding operation unit will be responsible to maintain and assure the quality control (QC) of all data generated and documented in compliance with the protocol.

Record Retention

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA CFR 312.57 [C]).

Monitoring of the Study

The Sponsor or its representative may monitor the study in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site

will permit trial-related monitoring, audits, institutional review board (IRB)/independent ethics committee (IEC) review, and regulatory inspection(s) by providing direct and/or virtual access, where possible, to source data/documents.

APPENDIX 3. ADMINISTRATIVE PROCEDURES

Liabilities

It is the Sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

COVID-19 Response Plan

Regulatory authorities have recognized that the COVID-19 pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the IP or adhering to protocol-mandated visits and laboratory/diagnostic testing. To accommodate these challenges and mitigate safety risks associated with COVID-19, protocol modifications may be required which include (and are not limited to):

- Conducting the study in multiple (smaller) subject groups;
- Altering the timing of study procedures and subject confinement;
- Modification of standard inclusion or exclusion criteria;

The exact mitigations will be documented in the study Risk Assessment and Mitigation Plan.

Additional health checks including COVID-19 testing, body temperature monitoring, etc. may be performed during the trial, even if not planned within the protocol.

Statement of Investigator

The FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], will be signed by the Investigator, and will be kept on file.

Delegation of Investigator Duties

An Investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

An Investigator will maintain a list of sub-investigator(s) and other appropriately-qualified persons to whom he/she delegates significant trial-related duties.

Should an Investigator delegate the supervision of the IP administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An Investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the clinical site or an Investigator (or delegate) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

APPENDIX 4. PROTOCOL REVIEW AND APPROVALS

TITLE: A PHASE 1, RANDOMIZED, PLACEBO CONTROLLED, MULTIPLE-ASCENDING DOSE (MAD) STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TMP-301 IN HEALTHY SUBJECTS

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with GCP and the applicable regulatory requirements.

_____
Principal Investigator Name (Please Print)

_____ _____
Principal Investigator Signature Date (yyyy/mm/dd)
Altasciences Clinical Kansas Inc.

TITLE: A PHASE 1, RANDOMIZED, PLACEBO CONTROLLED, MULTIPLE-ASCENDING DOSE (MAD) STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TMP-301 IN HEALTHY SUBJECTS

On behalf of the Sponsor, I approve of, and agree to comply with, all of the procedures contained within this protocol.

_____ _____

Dan Meyers MD Date (yyyy/mm/dd)
Chief Medical Officer
Tempero Bio Inc.

APPENDIX 5. LIST OF ABBREVIATIONS

3MS	Modified Mini Mental State Examination
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
bid	twice daily
BMI	body mass index
bpm	beats per minute
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician Administered - Dissociative States Scale
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P1A2
ECG	electrocardiogram
EOS	End of Study
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IU	international unit
kg	kilogram
L	liter

MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliters
mmHg	millimeter of mercury
N/AP	not applicable
ng	nanograms
OECD	Organization for Economic Co-operation and Development
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
PR	time between P and R wave
PRIME	Prevention through Risk Identification, Management, and Education
PT	preferred term
QA	Quality Assurance
QC	Quality Control
QRS	complex between Q and S wave
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Correction Formula
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class
SOP	standard operating procedure
SRC	Safety Review Committee
ST	ST segment of the Electrocardiogram
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	Visual Analogue Scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced

APPENDIX 6. CLINICAL LABORATORY EVALUATIONS

Clinical Laboratory Test Panel	Description
General biochemistry:	Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin total and conjugated bilirubin if total bilirubin is elevated, blood urea nitrogen, calcium, chloride, Creatinine phosphokinase (CPK), Bicarbonate (CO2), creatinine (including eGFR calculated using the CKD-EPI calculation, cholesterol total, glucose, LDH, phosphorous, potassium, protein total, sodium, triglycerides, and uric acid
Coagulation:	Prothrombin time (PT)/INR and partial thromboplastin time (aPTT) levels
Endocrinology:	FSH[1]
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume, and platelet count
Serology[a]:	Human immunodeficiency virus (HIV) Ag/Ab Combo, Hepatitis B surface antigen, and Hepatitis C virus
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, opiates, oxycodone, fentanyl, phencyclidine, and tricyclic antidepressants
Pregnancy test:	Serum pregnancy test or urine pregnancy test

[a]Screening visit only.

APPENDIX 7. BRIEF PSYCHIATRIC RATING SCALE

CLIENT NAME: _____ DATE: _____
CLIENT ID#: _____ MD: _____

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. **SOMATIC CONCERN** Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not. SCORE ☐	10. **HOSTILITY** Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (*Rate attitude toward interviewer under "uncooperativeness"*). SCORE ☐
2. **ANXIETY** Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms. SCORE ☐	11. **SUSPICIOUSNESS** Brief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances. SCORE ☐
3. **EMOTIONAL WITHDRAWAL** Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation. SCORE ☐	12. **HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people. SCORE ☐
4. **CONCEPTUAL DISORGANIZATION** Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning. SCORE ☐	13. **MOTOR RETARDATION** Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level. SCORE ☐
5. **GUILT FEELINGS** Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses. SCORE ☐	14. **UNCOOPERATIVENESS** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation. SCORE ☐
6. **TENSION** Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient. SCORE ☐	15. **UNUSUAL THOUGHT CONTENT** Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes. SCORE ☐
7. **MANNERISMS AND POSTURING** Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here. SCORE ☐	16. **BLUNTED AFFECT** Reduced emotional tone, apparent lack of normal feeling or involvement. SCORE ☐
8. **GRANDIOSITY** Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation. SCORE ☐	17. **EXCITEMENT** Heightened emotional tone, agitation, increased reactivity. SCORE ☐
9. **DEPRESSIVE MOOD** Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints. SCORE ☐	18. **DISORIENTATION** Confusion or lack of proper association for person, place or time. SCORE ☐

APPENDIX 8. CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE

The Clinician Administered Dissociative States Scale (CADSS)

J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ID_____Date_____

Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in this room.
   - 4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   - 0= Not at all.
   - 1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   - 2= Moderate, I feel somewhat detached from my own body, but I am basically alltogether.
   - 3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   - 4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   - 0= Not at all.
   - 1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   - 2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   - 3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   - 4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
   - 0= Not at all.
   - 1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   - 2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   - 3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   - 4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
   - 0= Not at all.
   - 1= Mild, things seem slightly different than normal, although it is barely perceptible.
   - 2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   - 3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   - 4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
   - 0= Not at all.
   - 1= Mild, things seem slightly paler than usual if I think about it.
   - 2= Moderate, colors are somewhat diminished, but still recognizable.
   - 3= Severe, colors are extremely pale, in no way as vivid as they usually are.
   - 4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.

12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.

13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.

14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.

15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.
    2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
    3= Severe, I have lost several segments of time of one minute or more.
    4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
    0= Not at all.
    1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
    2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
    3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
    4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
    0= Not at all.
    1= Mild, things seem to be a little bit more real than normal.
    2= Moderate, things seem to be more real than normal.
    3= Severe, things seem to be very real or have a special sense of clarity.
    4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
    0= Not at all.
    1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
    2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
    3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
    4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
    0= Not at all.
    1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
    2= Moderate, colors seem brighter, about twice as bright as normal.
    3= Severe, colors seem very bright, at least five times as bright as normal.
    4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
    0= Not at all.
    1= Mild, I feel a little bit confused about who I am.
    2= Moderate, I feel confused about who I am, but I basically know who I am.
    3= Severe, I feel very confused about who I am, and at times I wonder if I am a person, or if I am many people.
    4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
    0= Not at all.
    1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
    2= Moderate, I feel like I have different parts which don't quite fit together.
    3= Severe, there are two or more sides to myself which have unique characteristics.
    4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
    0= Not at all.
    1= Mild, there are some recent things which I cannot remember.
    2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
    3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
    4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
    0= Not at all.
    1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
    2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
    3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
    4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past _ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT VERSION

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 11. MODIFIED MINI-MENTAL STATE EXAMINATION

Modified Mini Mental State Examination (3MS)

Teng E.L. and Chui, H.C., (1987).
The Modified Mini-Mental State Examination (3MS)

Directions for use

The questions are put in the order of appearance and the score of each question is managed immediately. In order to obtain co-operation of the patient, it is necessary to install the patient comfortably and to exert a positive reinforcement. It is important not to influence the answers and to avoid the pressure on the items where the patient is in difficulty.

Direction for scoring

For the various parts of the test, the score has to allot depends on the type of question. For the majority of the questions, a point is allotted by correct answer. For the others items, quotation to be allotted is indicated clearly in the test. The difficulty in the attribution of the 3 ms scores is that it combines also the score of the MMSE, which can disturb the user.

The Modified Mini-Mental State (3MS)

3MS	MMS		
		DATE AND PLACE OF BIRTH	
		Date: year _____	0 1 2 3
___	5	month day	
		Place: town _____	
		state_____	0 1 2
___	___	**REGISTRATION**	
3	3	(No. of presentations:)	
		SHIRT, BROWN, HONESTY	0 1 2 3
		(or: SOCKS, BLACK, MODESTY)	
		(or: SOCKS, BLUE, CHARITY)	
		MENTAL REVERSAL	
7	5	*5 to 1*	
		Accurate	2
		1 or 2 errors/misses	0 1
		DLROW	0 1 2 3 4 5
___	___	**FIRST RECALL**	
9	3		
		Spontaneous recall	3
		After "Something to wear"	2
		"SHOES, SHIRT, SOCKS"	0 1
		Spontaneous recall	3
		After "A color"	2
		"BLUE, BLACK, BROWN"	0 1
		Spontaneous recall	3
		After "A good personal quality"	2
		"HONESTY, CHARITY, MODESTY"	0 1
___	___	**TEMPORAL ORIENTATION**	
15	5	*Year*	
		Accurate	8
		Missed by 1 year	4
		Missed by 2-5 years	0 2
		Season	
		Accurate or within 1 month	0 1
		Month	
		Accurate or within 5 days	2
		Missed by 1 month	0 1
		Day of month	
		Accurate	3
		Missed by 1 or 2 days	2
		Missed by 3-5 days	0 1
		Day of week	
		Accurate	0 1
5	5	**SPATIAL ORIENTATION**	
		State	0 2
		County	0 1
		City (town)	0 1
		Hospital/office building/home?	0 1

3MS	MMS		
___	___	**NAMING**	
5	2	(MMS: Pencil ___ Watch ___)	
		Forehead Chin	1 2 3 4 5
		Shoulder ____	
		Elbow _____ Knuckle _____	
___		**FOUR-LEGGED ANIMALS** (30 seconds) 1 point ea.	
10			
___		**SIMILARITIES**	
6			
		Arm-Leg	
		Body part; limb; etc	2
		Less correct answer	0 1
		Laughing-Crying	
		Feeling; emotion	2
		Other correct answer	0 1
		Eating-Sleeping	
		Essential for life	2
		Other correct answer	0 1
___	___	**REPETITION**	
5	1		
		"I WOULD LIKE TO GO HOME/OUT"	2
		1 or 2 missed/wrong words	0 1
		"NO IFS ANDS OR BUTS "	
___	___	**READ AND OBEY "CLOSE YOUR EYES"**	
3	1		
		Obeys without prompting	3
		Obeys after prompting	2
		Reads aloud only (spontaneously or by request)	0 1
___	___	**WRITING** (1 minute)	
5	1		
		(I) WOULD LIKE TO GO HOME/OUT	
		(MMS: Spontaneous sentence: 0 1)	
___	___	**COPYING TWO PENTAGONS** (1 minute)	
10	1		
			Each Pentagon
		5 approximately equal sides	4 4
		5 unequal (>2:1) sides	3 3
		Other enclosed figure	2 2
		2 or more lines	0 1 0 1
			Intersection
		4 corners	2
		Not 4-corner enclosure	0 1
___	___	**THREE-STAGE COMMAND**	
3	3		
		___ TAKE THIS PAPER WITH YOUR LEFT/RIGHT HAND	
		___ FOLD IT IN HALF, AND	
		___ HAND IT BACK TO ME	
___		**SECOND RECALL**	
9			
		(Something to wear)	0 1 2 3
		(Color)	0 1 2 3
		(Good personal quality)	0 1 2 3

APPENDIX 12. VISUAL ANALOGUE SCALE

Each subject will have to complete the Visual Analogue Scale (VAS) Alertness Scale with anchor points of "Very drowsy", "Neither drowsy nor alert", and "Very Alert" before dosing and at various times during study drug administration.

Example:

APPENDIX 13. PRIME QUESTIONNAIRE FOR PSYCHOSIS RISK

At screening, all subjects will be administered this 12-item questionnaire to determine their risk of developing psychosis. Responses to all items are scored on a 0-6 scale. Any subject which scores a 6 on any individual item, or 5 on at least 2 items will be considered at high risk of developing psychosis and will be excluded from the study.

For accurate results, the subject must be entirely honest in their response to all 12 questions. Subjects should rate their level of agreement with the statement as follows: Definitely disagree (0), Somewhat disagree (1), Slightly disagree (2), Not Sure (3), Slightly agree (4), Somewhat agree (5), Definitely agree (6).

Items:

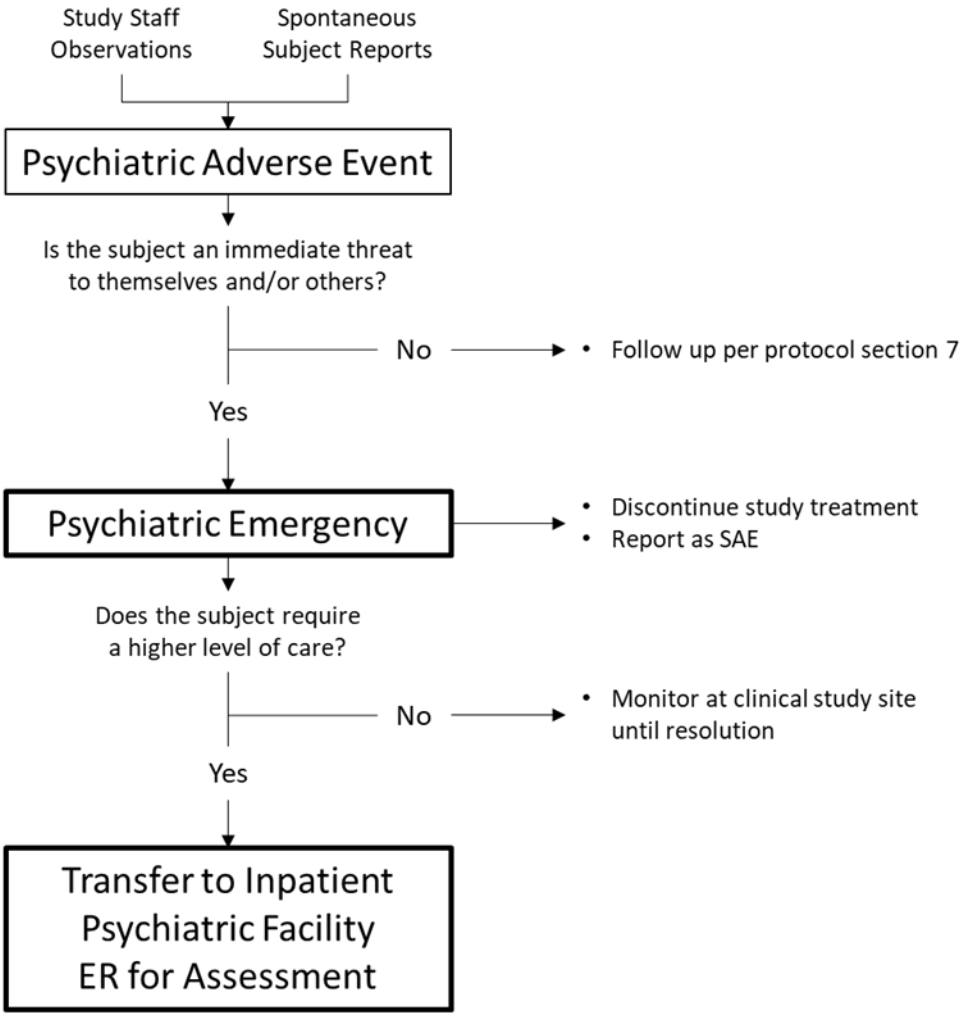
1. I think that I have felt that there are odd or unusual things going on that I can't explain.
2. I think that I might be able to predict the future.
3. I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.
4. I have had the experience of doing something differently because of my superstitions.
5. I think that I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.
6. I have thought that it might be possible that other people can read my mind, or that I can read other's minds.
7. I wonder if people may be planning to hurt me or even may be about to hurt me.
8. I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.
9. I think I might feel like my mind is "playing tricks" on me.
10. I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me.
11. I think that I may hear my own thoughts being said out loud.
12. I have been concerned that I might be "going crazy".

APPENDIX 14. PSYCHIATRIC EMERGENCY MANAGEMENT

Inhibitors or antagonists of mGlu5, including TMP-301, are associated with psychiatric adverse events which can include dissociation and hallucination. Although most psychiatric AEs with this class of drugs are mild, there is a risk of psychiatric AEs evolving into emergencies, where there is an immediate risk of harm to either the treated subject, or others in the subject's surroundings. The purpose of this appendix is to define the procedures for identification and management of potential psychiatric emergencies in subjects enrolled in this study. These procedures have been designed to ensure the safety of subjects and staff and to provide continuity of care through the resolution of the psychiatric emergency.

Figure 2 shows an overview of psychiatric emergency management in this study. The subsequent sections of this appendix provide details of the specific steps in the emergency management procedure. The Investigator(s) implementing this management plan will have 24/7 access to a psychiatrist to assist in the decisions required to implement the plan. Full supporting operational details are described in the psychiatric event monitoring plan (PEMP).

Figure 1: Psychiatric Emergency Management



Psychiatric Adverse Event Monitoring:

Psychiatric AE monitoring follows the same general process of monitoring for any AE as described in Section 7.4 of the protocol. Specifically, subjects will be monitored for evidence of psychiatric AEs from the time of ICF signature to the end of the study in the following ways:

- Study staff observations
  - Open-ended health status questions at the start and end of domiciling periods and observation of subject behavior during domiciling periods
  - Review of subject responses to scheduled BPRS (6.1.8), CADSS (6.1.9), C-SSRS (6.1.10), 3MS (6.1.11) and VAS (6.1.12) assessments
- Spontaneous subject reports of new symptoms or other complaints

If any of these sources raise the suspicion of a psychiatric AE, a formal evaluation by the Investigator will occur to confirm the AE. Once an event is confirmed to be a psychiatric AE, it will be assigned severity (see Section 7.2) and causality (see Section 7.3).

Psychiatric Emergency Determination:

Confirmed psychiatric AEs will be further evaluated by the Investigator to determine if it is also a psychiatric emergency. This determination will be conducted in consultation with a psychiatrist, and will be based on the following criterion:

- Subject is judged to be an immediate threat to themselves and/or others.

Subjects with psychiatric AEs which are not judged to be emergencies will be observed for resolution or worsening of the AE at the clinical study site. If the AE worsens, the subject will be re-evaluated to determine if the psychiatric emergency criterion is met.

Subjects with confirmed psychiatric emergencies will have study treatment immediately discontinued. Furthermore, any psychiatric emergency will be considered a serious adverse event (SAE) and will be reported to health authorities and/or local ethics committee according to relevant regulations.

Psychiatric Emergency Management:

Subjects with confirmed psychiatric emergencies will be evaluated to determine if they require a higher level of management than the clinical study site can provide. This determination will take place between the PI psychiatrist, consulting psychiatrist (if PI is unavailable), and the sponsor's medical monitor.

If a higher level of management is not required, the subject will remain at the clinical study site where they will be monitored and managed under the direction of the Investigator. The subject will be closely monitored until the psychiatric emergency has been resolved, and the subject is no longer judged to be a risk to themselves or others. With the resolution of the psychiatric emergency, the subject will undergo the same process as any other subject who has had study treatment discontinued (see Table 3 for EOS assessments).

Rescue medication can be used to treat psychiatric emergencies with manifestations of psychosis, or significant agitation and/or anxiety. The decision to provide rescue medication will

be at the discretion of the PI, according to their best medical judgement, and in consultation with the sponsor's medical monitor. The following medications can be considered (Neither of these medications are likely to have any interactions with TMP-301):

- Risperidone 0.5 – 2 mg PO every 2 hours prn (≤6 mg total in 24 hours)
- Lorazepam 0.5 – 2 mg PO (or 1 mg IM) every 6 hours prn (≤10 mg total in 24 hours)

If a higher level of management is required, subjects will be directly transferred to an inpatient psychiatric facility emergency room for further evaluation. During transfer, and at all times during the evaluation prior to admission to the facility, the subject will be accompanied by study staff. The clinical study staff, under the direction of the PI, will be in contact with the psychiatric facility to provide key information about the psychiatric emergency as well as the relevant details about the study treatment and procedures. Once admitted to the inpatient psychiatric facility, the subject will be cared for according to the standard procedures of the facility. Clinical study staff will be in regular contact with the facility to receive updates and to provide any additional information required for optimal care of the subject. The subject will be released from the facility once the emergency has resolved, and the subject is judged safe and appropriate to be released in the clinical opinion of qualified experts at the facility, or the subject refuses further treatment. Medical records from the psychiatric facility will be shared with the clinical study site after the subject is released.

Psychiatric Emergency Follow Up:

All psychiatric emergencies will be closely monitored with direct clinical care (either at the clinical study site or the inpatient psychiatric facility) until resolution - when the subject is no longer a risk to themselves or others. The determination of resolution of a psychiatric emergency can be made either at the clinical study site by the study PI or at the inpatient psychiatric facility (either in the emergency room or after an inpatient stay) by appropriately trained medical staff. After the determination of resolution, the patient will be discharged home. The clinical site will call the subject within 24 hours of discharge for a status check. The subject will return to the clinical study site within 7 days of discharge for end of study assessments.

For subjects with an active psychiatric emergency who leave either the clinical study site or inpatient psychiatric facility against medical advice, all reasonable efforts will be made to monitor the subject's status until resolution can be documented. This will include daily phone calls to the subject and/or their family or contacts and home visits where feasible. Every reasonable effort will be made to facilitate the subject's return to appropriate medical care, either at the inpatient psychiatric facility, or at another medical facility where appropriate. Following stabilization and resolution of the psychiatric emergency, the subject will return to the clinical study site within 7 days of discharge for end of study assessments.