TNX-601 ER (tianeptine hemioxalate extended-release tablets)
Clinical Trial Protocol TNX-TI-M201

A Phase 2, Randomized, DoUble-Blind, PLacebo-Controlled, Parallel-Group Study to Evaluate the EffIcacy, SaFety, and Tolerability of TNX-601 ER Monotherapy Versus Placebo in Patients with Major Depressive Disorder (MDD)

"The **UPLIFT**" Study

Original Protocol Release Date: 17 August 2022
Amendment 1: 21 December 2022
Amendment 2: 02 March 2023

Sponsor: Tonix Pharmaceuticals, Inc.
[redacted]

For Tonix:

[redacted]

Version 2.0, 02 March 2023

INVESTIGATOR'S AGREEMENT

I have read the TNX-TI-M201 protocol and agree to conduct the study as outlined. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company: Tonix Pharmaceuticals, Inc.
Name of Investigational Product: TNX-601 ER (tianeptine hemioxalate extended-release tablets)
Name of Active Ingredient: Tianeptine hemioxalate
Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of TNX-601 ER Monotherapy versus Placebo in Patients with Major Depressive Disorder (MDD)
Study center(s): Approximately 30 sites in the United States
Study Population: Male and female patients aged 18 to 65 years (inclusive) with a diagnosis of MDD as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, currently suffering from a major depressive episode (MDE).
Objectives: **Primary:** To evaluate the efficacy of TNX-601 ER (tianeptine hemioxalate extended-release tablets) monotherapy in the treatment of major depressive disorder (MDD) **Secondary:** To evaluate the safety and tolerability of TNX-601 ER (tianeptine hemioxalate extended-release tablets) monotherapy in the treatment of MDD
Methodology: This is a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of TNX-601 ER, 39.4 mg monotherapy, on symptoms of depression in adult patients with MDD. There will be a screening and washout period of up to 35 days, a double-blind treatment period (during which patients will receive either TNX-601 ER or placebo in a 1:1 randomization ratio) of about 42 days, and a posttreatment safety follow-up period of approximately 14 days after discontinuation of study drug. Patients will be consented and screened at Screening (Visit 1) for the study until approximately 300 patients are randomized. Randomization will be performed in a 1:1 ratio to one of 2 treatment arms (daily TNX-601 ER or placebo) after meeting DSM-5 diagnostic criteria for MDD in a current MDE as assessed by the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2) at Screening (Visit 1). The TNX-601 ER dose for all eligible patients will be 1 tablet once daily in the morning, initiated at Baseline (Visit 2). All patients will return to their respective study site for an off-drug, Post Study Follow-up (Visit 6) approximately 2 weeks after discontinuation of study drug. Overall duration in the study for each patient is expected to be up to 13 weeks.
Number of patients (planned): Approximately 300 patients with MDD will be enrolled. Randomized patients who withdraw will not be replaced.

Inclusion Criteria:

1. Female or male aged 18 to 65 years (inclusive).
2. Have a primary DSM-5 diagnosis of current MDD.
   a) The duration of the current MDE must be at least 12 weeks.
   b) Without psychotic or catatonic features.
3. Have a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥28 at Screening (Visit 1), ≥25 at Baseline (Visit 2), and a ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2).
4. No acute or potentially confounding medical disorders based on medical history, physical and brief neurological exam, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG) performed at Screening (Visit 1) and Baseline (Visit 2).
5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [eg, bilateral oophorectomy or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study and for 4 weeks following the last dose of the study drug (TNX-601 ER or placebo):
   a) Hormonal methods, such as oral, implantable, injectable, or transdermal contraceptives, for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before study drug administration;
   b) Intrauterine device (IUD);
   c) Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream).
   d) Bilateral tubal ligation.
   e) Partners of vasectomized males in stable relationships;
   f) Females not involved in heterosexual relationships.
6. Male patients agree to use a reliable method of birth control, as defined above, during the study and for at least 4 weeks following the last dose of TNX-601 ER or placebo.
7. Capable of reading and understanding English and able to provide written informed consent to participate. Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in the optional pharmacogenomic assessment will not affect the patient's eligibility for the main study.
8. Are judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures, including venipuncture, and examinations required by the protocol.

Exclusion Criteria:

1. Psychiatric History:
   a) Diagnosis of DSM-5-defined lifetime bipolar disorder (I, II, or unspecified), schizophrenia, schizoaffective disorder, MDD with psychotic features, other psychotic disorder, or antisocial personality disorder; current (past month) obsessive-compulsive disorder; current (past month) posttraumatic stress disorder; current (past 3 months) anorexia nervosa; lifetime opioid or lifetime sedative-hypnotic use disorders, as confirmed by the MINI 7.0.2.
   b) Diagnosis of borderline personality disorder that is known, suspected, or as suggested by a score of ≥7 on the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD).

c) Patients with comorbid generalized anxiety disorder (GAD), social anxiety disorder (SAD), or panic disorder are excluded only if the GAD, SAD, or panic disorder is considered the primary psychiatric diagnosis, rather than MDD. (If MDD is the primary diagnosis, patients with comorbid GAD, SAD, and panic disorder are allowed for randomization).

2. Increased risk of suicide on the basis of the Investigator's judgment, that is of a severity that is not appropriate for outpatient management, or that warrants additional therapy excluded by the protocol, or if any of the following results are obtained:
   a) High suicidality based on a MINI 7.0.2 Module B score ≥17 (Screening [Visit 1]); or,
   b) Patient answers YES to either MINI question B10 or B11 (Screening); or,
   c) Patient meets criteria for CURRENT Suicidal Behavior Disorder on the MINI 7.0.2 (Screening [Visit 1]); or,
   d) A positive response to the Columbia Suicide Severity Rating Scale (C-SSRS) questions for Type 4 or Type 5 suicide ideation within 6 months of Screening (Visit 1) or at Baseline (Visit 2); or,
   e) Any suicidal behavior in the past 12 months as identified by the C-SSRS at Screening (Visit 1) or between Screening (Visit 1) and Baseline (Visit 2) as identified by the C-SSRS at Baseline (Visit 2); or,
   f) A score of >4 on Item 10 of the MADRS at Screening (Visit 1) or Baseline (Visit 2).
3. Patients with treatment refractory MDD, ie, previously having in their lifetime failed ≥2 treatments with at least 2 different classes of antidepressants of adequate dose, duration, and treatment adherence as assessed by the Investigator at Screening (Visit 1).
4. Positive urine drug screen results for illicit or abused substances other than cannabis at Screening (Visit 1) or Baseline (Visit 2), or history of substance and/or alcohol use disorder during the preceding 12 months as evaluated by the MINI 7.0.2 at Screening (Visit 1).
5. Use of the following concomitant medications:
   a) antidepressants (including St. John's Wort, S-adenosyl methionine, and/or trazodone used as an antidepressant) within 4 weeks of Baseline (Visit 2), except for fluoxetine, which must not be within 6 weeks of Baseline (Visit 2);
   b) Monoamine oxidase inhibitors (MAOIs) within 4 weeks of Baseline (Visit 2);
   c) oral atypical antipsychotics used for antidepressant augmentation within 4 weeks of Baseline (Visit 2). Patients on antipsychotics for other reasons, or patients taking conventional antipsychotics are not eligible;
   d) lithium used for antidepressant augmentation within 4 weeks of Baseline (Visit 2). Patients on lithium for other reasons are not eligible;
   e) stimulants, benzodiazepines, or buspirone within 1 week of Baseline (Visit 2);
   f) trazodone used as a hypnotic within 1 week of Baseline (Visit 2);
   g) patients on chronic opioids are not eligible. Opioid use is not allowed during the study treatment period;
   h) any use of anticonvulsants other than prophylactic use for migraine.
6. Have had electroconvulsive treatment, transcranial magnetic stimulation, vagal nerve stimulation, or treatment with ketamine or esketamine for MDD.

7. Have initiated psychotherapy or have had a change in psychotherapy or other nondrug therapies (such as acupuncture or hypnosis) within 12 weeks prior to Screening (Visit 1) , and/or not willing to refrain from initiating such treatment during the course of the study.
8. A body mass index (BMI) of <18.0 or >40.0 kg/m^2
9. The patient has a history of sleep apnea that is severe, uncontrolled, or untreated. Patients with mild obstructive sleep apnea (eg, apnea/hypopnea index 5-15), and/or patients, whose mild to moderate sleep apnea is well-controlled with CPAP or oral device, are allowed at the discretion of the Investigator.
10. Have any other clinically significant medical, psychiatric, or social condition prior to randomization that, in the opinion of the Investigator, could affect patient safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study. Examples include hematologic disease or cancer with <5 years remission (other than treated carcinoma *in situ* of the cervix, basal cell carcinoma, or Type 1 squamous cell carcinoma of the skin).
11. Diagnosed with clinically significant and currently relevant cardiac disease (eg, arrhythmia that is symptomatic or requires treatment, 2^{nd}- or 3^{rd}-degree AV block, complete right or left bundle branch block, heart failure, or recent myocardial infarction [within the past 2 years]) or QT corrected for heart rate using Fridericia's formula (QTcF) >450 msec (male) or >470 msec (female) on the ECG at Screening Visit 1).
12. Evidence of human immunodeficiency virus (HIV) infection based on medical history.
13. Seizure disorder other than history of childhood febrile seizures.
14. Hypersensitivity to tianeptine, or any of the excipients in the study drug.
15. Moderate or severe comorbid traumatic brain injury (TBI) by history. Based on past history and Investigator's judgment, patients with mild TBI are eligible.
16. Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >2x upper limit of normal (ULN) or bilirubin >1.5x ULN, with the exception of patients with isolated Gilbert's syndrome.
17. Have an estimated glomerular filtration rate (eGFR; CKD-EPI 2021 equation) <60 mL/min at Screening (Visit 1).
18. Have a thyroid stimulating hormone (TSH) level <0.8x the lower limit of normal or >1.3x ULN. Patients with treated thyroid conditions and TSH levels in the aforementioned range will be eligible to participate in the study.
19. Have a Hemoglobin A1c >7.5% ULN at Screening (Visit 1).
20. Have any other clinically significant abnormalities (significant would include laboratory deviations requiring acute medical intervention or further medical evaluation) in laboratory results at Screening (Visit 1), including clinical chemistries, hematology, and any clinical information that, in the judgment of the Investigator, should preclude a patient's participation in the study.
21. Females who are either pregnant or breastfeeding.
22. Site personnel directly affiliated with this study and/or their immediate families.
23. Have participated in an interventional clinical trial within 90 days prior to Screening (Visit 1).

Eligibility Criteria for Randomization:

1. Continue to meet all inclusion/exclusion criteria,
2. MADRS total score ≥25 at Baseline (Visit 2), and
3. ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2).

Investigational product, dose, and mode of administration:

TNX-601 ER (tianeptine hemioxalate extended-release tablet) 39.4 mg, taken orally once daily in the morning with breakfast and continuing without interruption for 6 weeks of double-blind treatment.

Duration of Study Participation:

Up to 5 weeks for screening period, 6 weeks for double-blind treatment period, and 2 weeks for safety follow-up period (total up to 13 weeks)

Reference therapy, dose, and mode of administration:

Placebo, tablet taken orally once daily in the morning with breakfast and continuing without interruption for 6 week of double-blind treatments. Placebo tablets will be devoid of the tianeptine hemioxalate but contain the same inactive ingredients as TNX-601 ER and look identical to TNX-601 ER.

Criteria for evaluation:

Primary Efficacy Endpoint:

The primary efficacy endpoint will be the change from Baseline (Visit 2) in the MADRS total score at Week 6.

Key Secondary Efficacy Endpoints:

- Change from Baseline (Visit 2) in the Clinician Global Impression – Severity (CGI-S) score at Week 6
- Change from Baseline (Visit 2) in the Sheehan Disability Scale (SDS) total score at Week 6

Exploratory Efficacy Endpoints:

- Proportion of patients achieving response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score, assessed at Weeks 2, 4, and 6
- Proportion of patients in remission, defined as a MADRS total score ≤10 at Weeks 2, 4, and 6
- Proportion of patients achieving sustained response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score at both Weeks 4 and 6
- Proportion of patients with a Clinician Global Impression – Improvement (CGI-I) rating of "very much improved" or "much improved" at Weeks 2, 4, and 6
- Mean CGI-I score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) in Patient Global Impression – Severity (PGI-S) score at Weeks 2, 4, and 6
- Proportion of patients with a Patient's Global Impression of Change (PGIC) rating of "very much improved" or "much improved" at Weeks 2, 4, and 6
- Mean PGIC score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) to Week 6 in the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score in females and in males (analyzed separately)
- Change from Baseline (Visit 2) in the MADRS total score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the CGI-S score at Week 2 and Week 4

- Change from Baseline (Visit 2) in the SDS total score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the Hamilton Anxiety Rating Scale (HARS) total score at Weeks 2, 4, and 6Change from Baseline (Visit 2) in each of the 3 domains (work/school; social life; home life or family responsibilities) using the SDS at Weeks 2, 4, and 6
- Proportion of patients with a CGI-S rating of "normal, not at all ill" or "borderline mentally ill" at Weeks 2, 4, and 6
- Proportion of patients with a PGI-S rating of "not present", "very mild", or "mild" at Weeks 2, 4, and 6

Safety and Tolerability:

- Incidence of adverse events (AE) and serious AEs (SAEs) throughout the entire duration of the study
- Incidence of AEs associated with abuse liability using the MADDERS® (Misuse, Abuse, Diversion Drug Event Reporting System)
- Assessment of physical and neurological examination findings
- Changes from Baseline (Visit 2) in ECG results
- Changes from Baseline (Visit 2) in clinical laboratory test results
- Changes from Baseline (Visit 2) in vital signs and weight
- Indications of increased suicidal ideation or behavior as assessed by the C-SSRS
- Changes from Baseline (Visit 2) in patient-rated CSFQ-14 in males and in females, assessed separately
- Change from Baseline (Visit 5/ET) in the Subjective Opiate Withdrawal Scale (SOWS) at the Post Study Follow-up (Visit 6).

Statistical Methods:

Analysis Populations

- Safety Population (SAFETY): All patients who receive at least 1 dose of investigational product, analyzed as treated.
- Intention-to-Treat Population (ITT): All randomized patients who receive at least 1 dose of study drug, analyzed as randomized.

Efficacy Analyses

The primary efficacy analysis will use a Mixed Model Repeated Measures (MMRM) approach to estimate mean change from (Visit 2) in the Total MADRS score evaluated at the Week 6 visit in the TNX-601 ER and placebo arms. The model will include all participants in the ITT population, and the dependent variable will be the observed change from Baseline (Visit 2) in total MADRS score at each postdose visit. Covariates in the model will include the fixed categorical effects of treatment, site, visit, and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. Missing data will be imputed via multiple imputation (MI), and details regarding the MI approach will be described in the Statistical Analysis Plan (SAP).

The primary analysis will be followed by several sensitivity analyses. The key secondary efficacy outcomes will be measured and compared between treatment groups and will be adjusted for multiplicity using a fixed sequence procedure. Further details on sensitivity and secondary analyses can be found in the SAP, as well as the order of the key secondary endpoints.

Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized overall and by preferred term and system organ class. AEs will also be summarized by severity and relationship to study drug. SAEs and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from Baseline (Visit 2) for clinical laboratory test results, vital signs, ECG parameters, and CSFQ-14 scores will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). The number of patients with Baseline (Visit 2) and treatment-emergent suicidal ideation and/or suicidal behavior, based on the C-SSRS, will be summarized by treatment group.

Interim Analysis

An interim analysis will be performed once approximately 50% of the planned patients have enrolled and those patients have either completed the study or discontinued early. The purpose of the interim will be to evaluate the study for futility and potentially increase the sample size to maintain statistical power conditioned on the results of the first 50% of patients. The study team will only be informed of the recommendation from an independent statistical review committee to halt the study for futility, maintain the original sample size, or to increase the sample size (by a fixed, pre-specified amount). All recommendations by the statistical review committee are non-binding.

For the primary and key secondary outcomes, the results from before and after the interim will be combined with Cui, Hung, Wang (CHW) methodology (Cui, 1999). Full details of the interim analysis procedure and steps to maintain treatment blinding of the study team will be described in the SAP and the Interim Analysis Charter and finalized prior to execution of the interim analysis.

Sample Size Estimation

The sample size will be approximately 300 patients with MDD. [redacted]

Pharmacogenomic Analyses

Potential genetic determinants of treatment response will be examined by the assessment of genetic variants in relation to treatment outcome. A blood sample will be obtained from patients who have signed a separate informed consent form (ICF) for the pharmacogenomic analyses.

The first step of the pharmacogenomic analyses will involve whole genome sequencing and analysis for allelic polymorphisms related to treatment response to TNX-601 ER. It is presumed that unused sample will be stored up to 15 years and will potentially be utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-601 ER.

Table 1: Study Design and Schedule of Assessments

Procedures and Evaluations	Screening	Baseline	Double-Blind Treatment Period			Post Study Follow-up
Visit	**1**	**2**	**3**	**4**	**5 or ET**	**6**
Study Week	**-5 to -1**	**0**	**2**	**4**	**6**	**8**
Study Day	**-35 to -7**	**1**	**15 ± 2**	**29 ± 2**	**43 + 2**	**57 + 7**
Screening						
Informed consent	X					
Optional Pharmacogenomics consent	X[g]					
Clinical Trial Subject Registry Consent	X[k]					
Placebo response training[a]	X	X	X	X	X	
Inclusion/exclusion criteria	X	X				
Psychiatric history (MINI 7.0.2)	X					
MSI-BPD	X					
Prior and concomitant medications	X	X	X	X	X	X
Demographics and medical history	X				X[l]	
Vital signs, weight, height[b], and BMI	X	X	X	X	X	X
Physical examination, including a brief neurological exam	X				X	
12-lead ECG	X	X			X	
Pregnancy test[c]	X	X	X	X	X	X
Urine drug screen[d]	X					
Clinical laboratory assessments	X			X	X	
PK				X	X	
Randomization		X				
Study Drug						
Dispense study drug		X[f]	X	X		
Study drug return, compliance, and accountability			X	X	X	
Optional Pharmacogenomics						
Blood sample collection		X[g]	*	*	*	*
Efficacy						
MADRS	X	X	X	X	X	
CGI-S		X	X	X	X	
CGI-I			X	X	X	
HARS		X	X	X	X	
SDS		X	X	X	X	
PGIC			X	X	X	
PGIS		X	X	X	X	
Safety						
AEs		X	X	X	X	X
MADDERS®			X[h]	X[h]	X[h]	X[i]
C-SSRS	X	X	X	X	X	X
CSFQ-14		X			X	
SOWS					X	X[j]

Abbreviations: AE = adverse event; ET = early termination; BMI = Body Mass Index; TSH=Thyroid Stimulating Hormone; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity scale; HARS = Hamilton Anxiety Rating Scale; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; C-SSRS = Columbia-Suicide Severity Rating Scales; ECG = Electrocardiogram; MADRS = Montgomery-Åsberg Depression Rating Scale; MINI 7.0.2 = Mini International Neuropsychiatric Interview, Version 7.0.2; MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; SDS = Sheehan Disability Scale; MADDERS® = Misuse, Abuse, Diversion Drug Event Reporting System; SOWS = Subjective Opiate Withdrawal Scale.

a A placebo response reduction document is presented to patients by study staff for review and discussion at every in-clinic visit from Screening (Visit 1) through end-of Treatment (Visit 5/ET).

b Height to be measured at Screening (Visit 1) only.

c Serum pregnancy test at Screening (Visit 1) and on-site urine pregnancy test at all other visits for all women of childbearing potential, including women who have had bilateral tubal ligation. Serum pregnancy test may be conducted at Investigator's discretion at End of Treatment (Visit 5/ET).

d Performed at Screening (Visit 1) and only at other visits if Investigator suspects drug use or if a prescribed scheduled medication is washed out to participate in the study (eg., benzodiazepines, stimulants, opioids). At Screening, both an on-site urine dip-stick and a central laboratory sample will be obtained.

e Chemistry, Hematology, HbA1c and TSH at Screening. Chemistry and Hematology only at Visit 4 and Visit5.

f Patient will take first dose of study drug at the clinic at the end of Baseline (Visit 2).

g PGx sample ideally taken at Visit 2 but can be taken at any post-Baseline visit as well (*), noting that Baseline (Visit 2) is best due to potential for discontinuation before subsequent visits.

h MADDERS® questionnaires will be administered only if any pre-defined AEs and/or DADEs suspect for misuse, abuse or diversion event is identified, or any drug accountability issues above the pre-defined threshold are identified.

i MADDERS® Medication Use Survey will be administered to all patients at Visit 6.

j To be completed at +1 day, +2 days, +3 days, +6 days, +9 days, and +12 days at home after the Completion of Treatment, and then in-person at the Post Study Follow-up visit.

k The Clinical Trial Subject Registry (CTSR) is a mandatory part of the consent process. A site can elect not to participate in the CTSR, with approval from the sponsor, and there will be no protocol deviations recorded for leaving it out of the procedures.

l Collection of demographics at Visit 5/ET will only include re-collecting current nicotine, alcohol, and THC usage patterns post double-blind treatment.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
CHW	Cui, Hung, Wang
CK	Creatine kinase
CRF	Case Report Form
CRO	Contract Research Organization
CSFQ-14	Changes in Sexual Functioning Questionnaire Short Form
C-SSRS	Columbia Suicide Severity Rating Scale
CTSR	Clinical Trial Subject Registry
DADE	Drug Accountability Discrepancy Event
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (version 5)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HARS	Hamilton Anxiety Rating Scale

Abbreviation or Specialist Term	Explanation
HEENT	Head, Eyes, Ears, Nose, and Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intention-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response
MADDERS®	Misuse, Abuse, Diversion Drug Event Reporting System
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MDD	Major Depressive Disorder
MDE	Major depressive episode
MI	Multiple Imputation
MINI 7.0.2	Mini International Neuropsychiatric Interview, Version 7.0.2
MMRM	Mixed Model Repeated Measures
MR	Modified release
MR1	Modified release prototype 1
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
RBC	Red Blood Cell
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression - Severity
PK	Pharmacokinetic
PRN	*pro re nata* (as needed)
QTcF	QT Corrected for Heart Rate using Fridericia's Formula

Abbreviation or Specialist Term	Explanation
SAD	Social Anxiety Disorder
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Sheehan Disability Scale
SF	Screen Failure
SIGMA	Structured Interview Guide for the MADRS
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedures
SOWS	Subjective Opiate Withdrawal Scale
SSRI	Selective Serotonin Reuptake Inhibitor
TBI	Traumatic Brain Injury
TCA	Tricyclic Antidepressant
TEAE	Treatment Emergent Adverse Event
TNX-601 ER	Tianeptine Hemioxalate Extended-release Tablets
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

5. INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018), with 21 million adults in the United States alone experiencing a depressive episode in 2020 (SAMHSA, 2020). The mechanism of action of virtually all antidepressant pharmacotherapies developed in the prior century involves actions on central monoaminergic systems, including the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs are currently the most prescribed class of antidepressants; however, only about 50% of patients with MDD respond to initial treatment with an SSRI and in only 35-40% is remission from depression achieved (Conway et al, 2015; Trevino et al, 2014; Rush et al, 2006; Trivedi et al, 2006). Following non-efficacy with an initial SSRI, remission is only about 20%, and greater than half have no meaningful benefit with a second-step switch to another monoaminergic antidepressant (Rush et al, 2006). Moreover, there is much support for the hypothesis that depression may involve dysregulation of pathways mediating resilience to stress through neuroplasticity and neurogenesis. Therefore, there is a pressing need for new MDD treatment options with alternative mechanisms of action, particularly those such as tianeptine that appear to protect from or reverse the neurodegenerative effects of stress (McEwen et al, 2010). Moreover, the tolerability profile of tianeptine compares favorably to those of available antidepressants in the United States, without significant sexual side effects, absence of adverse activity on sleep architecture and uniquely providing anxiolysis without associated sedative effects.

Tonix Pharmaceuticals, Inc. (hereafter referred to as "Tonix") is developing tianeptine hemioxalate extended-release tablets (TNX-601 ER) for the indication of MDD. [redacted]

There are currently no tianeptine containing drugs approved in the United States and no ER formulations of tianeptine approved anywhere in the world.

The current study is a Phase 2 study examining whether once daily oral administration of TNX-601 ER is effective in the treatment of MDD.

5.1. Brief Summary of Prior Clinical Experience, Dose Rationale, and Justification of Study Design

[redacted]

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To evaluate the efficacy of TNX-601 ER (tianeptine hemioxalate extended-release tablets) monotherapy in the treatment of major depressive disorder (MDD)

6.2. Secondary Objective

To evaluate the safety and tolerability of TNX-601 ER (tianeptine hemioxalate extended-release tablets) monotherapy in the treatment of MDD.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of TNX-601 ER, 39.4 mg monotherapy, on symptoms of depression in adult patients with MDD in approximately 30 sites in the United States. This study plans to randomize approximately 300 male and female patients aged 18 to 65 years old (inclusive), with current MDD as defined by DSM-5 criteria. During the 6-week double-blind treatment period, patients will receive either TNX-601 ER or placebo in a 1:1 randomization ratio. After the End of Treatment (Visit 5/ET), there will be a 2-week posttreatment safety follow-up period.

The study will be conducted in 4 periods: Screening (Visit 1), Baseline (Visit 2), Treatment (Visits 3-5), and Post Study Follow-up (Visit 6).

Screening (Visit 1)

Patients will be consented and assessed for current MDD as defined by DSM-5 diagnostic criteria, using the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2). Depression severity will be assessed by MADRS. Eligibility will also depend on medical history, physical and neurological examination, use of concomitant medications, and the results of laboratory tests (eg, pregnancy and drug screen, liver, kidney, and thyroid function, electrocardiogram).

If a patient meets all eligibility requirements but is currently taking a prohibited medication, there will be a Screening Period of up to 35 days for drug tapering and washout. For extenuating circumstances and in cases in which a prospective participant is on fluoxetine, the duration of the Screening Period may be increased to up to 49 days with Medical Monitor approval. Medication-free washout time for prohibited medications will be 4 weeks for antidepressants (except for fluoxetine, which will be 6 weeks) and atypical antipsychotics.

Baseline, Randomization, Start of Treatment (Visit 2)

To ensure continued eligibility prior to randomization, patients will be assessed for all inclusion/exclusion criteria, including a MADRS total score of ≥ 25. Patient must also have a ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2). Any

patients not meeting these randomization criteria will be considered a Screen Failure (SF) and will not continue in the study. Eligible patients will be randomized in a 1:1 ratio to one of two treatment arms (once daily oral TNX-601 ER or placebo). At this visit, study drug will be dispensed, and the first dose will be given to eligible patients.

Double-Blind Treatment Period (Visits 3-5)

The Treatment Period will last for about 42 days. Several investigator- and patient-rated scales and safety assessments (eg, C-SSRS, AEs) will be administered at each visit. At each of the 3 visits, study drug compliance and accountability will be assessed by collecting previously dispensed study drug bottle and counting the remaining tablets.

All patients who withdraw early from the study will be encouraged to complete an Early Termination (ET) visit as early as possible for safety evaluations. The patients will also be strongly encouraged to come back for the Post Study Follow-up (Visit 6).

Post Study Follow-up (Visit 6)

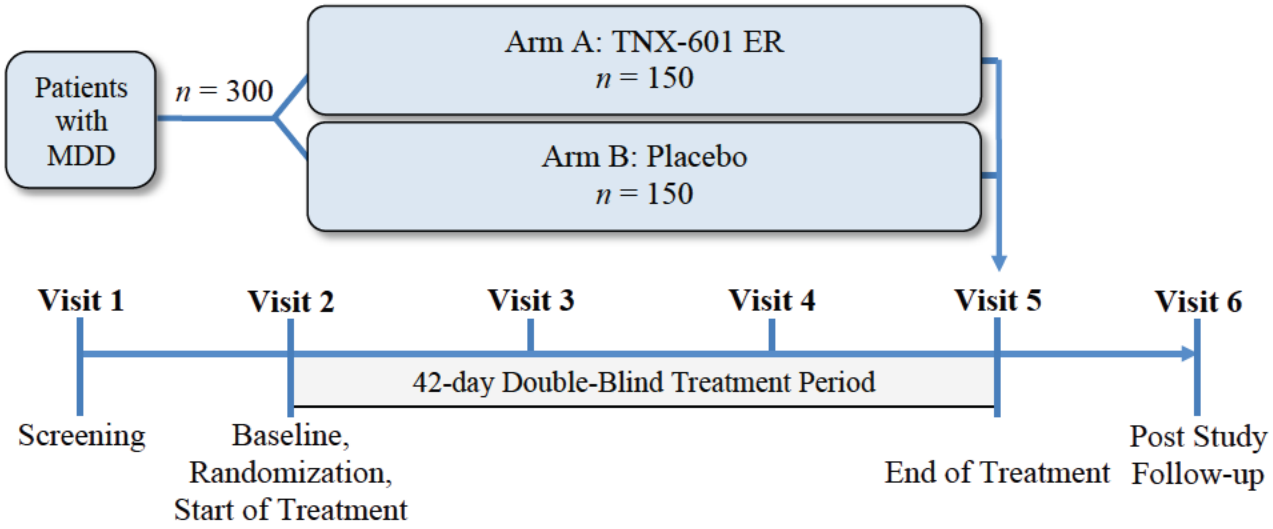
Between discontinuation of study drug and the Post Study Follow-up (Visit 6), potential withdrawal effects will be assessed at home using the SOWS at +1 day, +2 days, +3 days, +6 days, +9 days, and +12 days after the End of Treatment (Visit 5/ET). This includes patients who are early terminated.

Approximately 14 days (+7 days) after discontinuation of study drug, all randomized patients will return to their respective study site for an off-drug, Post Study Follow-up (Visit 6). This visit will include an assessment of prior and concomitant medications, vital signs and weight, pregnancy test, AEs, C-SSRS, and the SOWS.

The overall duration in the study for each patient is expected to be up to 13 weeks.

The study timeline and events schedule are provided in Figure 1.

Figure 1: Study Schema



7.2. Number of Patients and Treatment Assignment

A total of approximately 300 patients will be randomized in a 1:1 ratio to treatment with once-daily oral TNX-601 ER (tianeptine hemioxalate extended-release tablets) or identical placebo tablets, which are devoid of the tianeptine hemioxalate but contain the same inactive ingredients present in the active tablets. Randomization will be stratified by study site.

7.3. Study Endpoints

7.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from Baseline (Visit 2) in the MADRS total score at Week 6.

7.3.2. Secondary Efficacy Endpoints

7.3.2.1. Key Secondary Efficacy Endpoints

The efficacy endpoints listed below are considered key secondary endpoints.

- Change from Baseline (Visit 2) in the Clinician Global Impression – Severity Scale (CGI-S) score at Week 6
- Change from Baseline (Visit 2) in the Sheehan Disability Scale (SDS) total score at Week 6

A fixed sequence procedure will be applied to the key secondary efficacy endpoints to adjust for multiplicity and to control for overall type I error.

7.3.3. Exploratory Efficacy Endpoints

- Proportion of patients achieving response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score, assessed at Weeks 2, 4, and 6
- Proportion of patients in remission, defined as a MADRS total score ≤10 at Weeks 2, 4, and 6
- Proportion of patients achieving sustained response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score at both Weeks 4 and 6
- Proportion of patients with a Clinician Global Impression – Improvement Scale (CGI-I) rating of “very much improved” or “much improved” at Weeks 2, 4, and 6
- Mean CGI-I score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) in Patient Global Impression of Severity Scale (PGIS) score at Weeks 2, 4, and 6
- Proportion of patients with a Patient Global Impression of Change (PGIC) rating of “very much improved” or “much improved” at Weeks 2, 4, and 6
- Mean PGIC score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) to Week 6 in the CSFQ-14 total score in females and in males (analyzed separately)
- Change from Baseline (Visit 2) in the MADRS total score at Week 2 and Week 4

- Change from Baseline (Visit 2) in the CGI-S score at Week 2 and Week 4
- Change from Baseline in the SDS total score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the Hamilton Anxiety Rating Scale (HARS) total score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) in each of the 3 domains (work/school; social life; home life or family responsibilities) using the SDS at Weeks 2, 4, and 6
- Proportion of patients with a CGI-S rating of "normal, not at all ill" or "borderline mentally ill" at Weeks 2, 4, and 6
- Proportion of patients with a PGIS rating of "not present", "very mild", or "mild" at Weeks 2, 4, and 6

7.3.4. Safety and Tolerability

Safety and tolerability will be assessed by:

- Incidence of AEs and SAEs throughout the entire duration of the study
- Incidence of AEs associated with abuse liability using MADDERS®
- Assessment of physical and neurological examination findings
- Changes from Baseline (Visit 2) in ECG results
- Changes from Baseline (Visit 2) in clinical laboratory test results
- Changes from Baseline (Visit 2) in vital signs and weight
- Indications of increased suicidal ideation or behavior as assessed by the C-SSRS
- Changes from Baseline in patient-rated CSFQ-14 in males and in females, assessed separately
- Change from Baseline (Visit 5 or End of Treatment) in the SOWS at the Post Study Follow-up (Visit 6).

7.4. Efforts to Minimize Missing Data

It is important to avoid missing data from clinical trials. The following strategies are designed to minimize dropouts and missing data in this study:

1) Providing patients with greater background on the nature of placebo-controlled clinical trials and explaining that completing this study, regardless of the patient's level of treatment response, is essential to understanding whether TNX-601 ER may be helpful to others in the treatment of MDD. Sites will explain that the study is not designed to benefit the individual patient but, rather, can only provide useful information for future therapeutics.
2) Minimizing the burden on patients, with visits scheduled generally every 2 weeks (with reasonable visit window flexibility).
3) Training of site personnel on the importance of minimizing missing data

4) Providing payment for patients' time and effort at clinic visits, based on the duration of assessments and as approved by the Institutional Review Board. Reimbursement for travel expenses to and from the clinic sites may also be provided to further minimize the financial burden of participating in the study.

5) Utilizing repeated assessments of outcome measures and analytical approaches that most appropriately compensate for missing data.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Informed Consent

A potential patient may be screened for eligibility only after the nature of the study, its purpose, and any other information relevant to the patient's decision to participate have been explained to him or her, and the patient has voluntarily confirmed his or her willingness to participate. If medications are to be withdrawn for the explicit purpose of participation in this study, the patient must first sign an informed consent form (ICF) before the withdrawal or down titration of any medication is initiated.

Informed consent is documented by means of a written, signed, and dated ICF. Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment. Additional information is provided in Section 15.3.

8.2. Inclusion Criteria

Patients enrolled in this study will be volunteer patients. Eligible patients must meet all the following inclusion criteria during the screening period:

1. Male or female aged 18 to 65 years (inclusive).
2. Have a primary DSM-5 diagnosis of current MDD.
   a) The duration of the current MDE must be at least 12 weeks.
   b) Without psychotic or catatonic features.
3. Have a MADRS score ≥28 at Screening (Visit 1), ≥25 at Baseline (Visit 2), and a ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2).
4. No acute or potentially confounding medical disorders based on medical history, physical and brief neurological exam, vital signs, clinical laboratory tests, and 12-lead ECG performed at Screening (Visit 1) and Baseline (Visit 2).
5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [eg, bilateral oophorectomy or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study and for 4 weeks following the last dose of the study drug (TNX-601 ER or placebo):
   a) Hormonal methods, such as oral, implantable, injectable, or transdermal contraceptives, for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before study drug administration;

b) Intrauterine device (IUD);

c) Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream);

d) Bilateral tubal ligation

e) Partners of vasectomized males in stable relationships;

f) Females not involved in heterosexual relationships;

6. Male patients agree to use a reliable method of birth control, as defined above, during the study and for at least 4 weeks following the last dose of TNX-601 ER or placebo.
7. Capable of reading and understanding English and able to provide written informed consent to participate. Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in the optional pharmacogenomic assessment will not affect the patient's eligibility for the main study.
8. Are judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures, including venipuncture, and examinations required by the protocol.

8.3. Exclusion Criteria

1. Psychiatric History:
   a) Diagnosis of DSM-5-defined lifetime bipolar disorder (I, II, or unspecified), schizophrenia, schizoaffective disorder, MDD with psychotic features, other psychotic disorder; antisocial personality disorder; current (past month) obsessive-compulsive disorder; current (past month) posttraumatic stress disorder; current (past 3 months) anorexia nervosa; lifetime opioid or lifetime sedative-hypnotic use disorders, as confirmed by the MINI 7.0.2.
   b) Diagnosis of borderline personality disorder that is known, suspected, or as suggested by a score of ≥7 on the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD).
   c) Patients with comorbid generalized anxiety disorder (GAD), social anxiety disorder (SAD), or panic disorder are excluded only if the GAD, SAD, or panic disorder is considered the primary psychiatric diagnosis, rather than MDD. (If MDD is the primary diagnosis, patients with comorbid GAD, SAD, and panic disorder are allowed for randomization).
2. Increased risk of suicide on the basis of the Investigator's judgment, that is of a severity that is not appropriate for outpatient management, or that warrants additional therapy excluded by the protocol, or if any of the following results are obtained:
   a) High suicidality based on a MINI 7.0.2 Module B score ≥17 (Screening [Visit 1]); or,
   b) Patient answers YES to either MINI 7.0.2 question B10 or B11 (Screening [Visit 1]); or,

c) Patient meets criteria for CURRENT Suicidal Behavior Disorder on the MINI 7.0.2 (Screening [Visit 1]); or,

d) A positive response to C-SSRS questions for Type 4 or Type 5 suicide ideation within 6 months of Screening (Visit 1) or at Baseline (Visit 2); or,

e) Any suicidal behavior in the past 12 months as identified by the C-SSRS at Screening (Visit 1) or between Screening (Visit 1) and Baseline (Visit 2) as identified by the C-SSRS at Baseline (Visit 2); or,

f) A score of >4 on Item 10 of the MADRS at Screening (Visit 1) or Baseline (Visit 2).

3. Patients with treatment refractory MDD, ie, previously having in their lifetime failed ≥2 treatments with at least 2 different classes of antidepressants of adequate dose, duration, and treatment adherence as assessed by the Investigator at Screening (Visit 1).
4. Positive urine drug screen results for illicit or abused substances other than cannabis at Screening (Visit 1) or Baseline (Visit 2), or history of substance and/or alcohol use disorder during the preceding 12 months as evaluated by the MINI 7.0.2 at Screening (Visit 1).
5. Use of the following concomitant medications:

a) antidepressants (including St. John's Wort, S-adenosyl methionine, and/or trazodone used as an antidepressant) within 4 weeks of Baseline (Visit 2), except for fluoxetine, which must not be within 6 weeks of Baseline (Visit 2);

b) MAOIs within 4 weeks of Baseline (Visit 2);

c) oral atypical antipsychotics used for antidepressant augmentation within 4 weeks of Baseline (Visit 2). Patients on antipsychotics for other reasons, or patients taking conventional antipsychotics are not eligible;

d) lithium used for antidepressant augmentation within 4 weeks of Baseline (Visit 2). Patients on lithium for other reasons are not eligible.

e) stimulants, benzodiazepines, or buspirone within 1 week of Baseline (Visit 2);

f) trazodone used as a hypnotic within 1 week of Baseline (Visit 2);

g) patients on chronic opioids are not eligible. Opioid use is not allowed during the study treatment period;

h) Any use of anticonvulsants other than prophylactic use for migraine.

6. Have had electroconvulsive treatment, transcranial magnetic stimulation, vagal nerve stimulation, or treatment with ketamine or esketamine for MDD.
7. Have initiated psychotherapy or have had a change in psychotherapy or other nondrug therapies (such as acupuncture or hypnosis) within 12 weeks prior to Screening (Visit 1), and/or not willing to refrain from initiating such treatment during the course of the study.
8. A body mass index (BMI) of <18.0 or >40.0 kg/m^2.
9. The patient has a history of sleep apnea that is severe, uncontrolled, or untreated. Patients with mild obstructive sleep apnea (eg, apnea/hypopnea index 5-15), and/or patients, whose mild to moderate sleep apnea is well-controlled with CPAP or oral device, are allowed at the

discretion of the Investigator.

10. Have any other clinically significant medical, psychiatric, or social condition prior to randomization that, in the opinion of the Investigator, could affect patient safety, preclude evaluation of response, interfere with the ability to comply with study procedures, or prohibit completion of the study. Examples include hematologic disease or cancer with <5 years remission (other than treated carcinoma *in situ* of the cervix, basal cell carcinoma, or Type 1 squamous cell carcinoma of the skin).
11. Diagnosed with clinically significant and currently relevant cardiac disease (eg, arrhythmia that is symptomatic or requires treatment, 2nd- or 3rd-degree AV block, complete right or left bundle branch block, heart failure, or recent myocardial infarction [within the past 2 years]) or QT corrected for heart rate using Fridericia's formula (QTcF) >450 msec (male) or >470 msec (female) on the ECG at Screening (Visit 1).
12. Evidence of human immunodeficiency virus (HIV) infection based on medical history.
13. Seizure disorder other than history of childhood febrile seizures.
14. Hypersensitivity to tianeptine, or any of the excipients in the study drug.
15. Moderate or severe comorbid traumatic brain injury (TBI) by history. Based on past history and Investigator's judgment, patients with mild TBI are eligible.
16. Have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >2x upper limit of normal (ULN) or bilirubin >1.5x ULN, with the exception of patients with isolated Gilbert's syndrome.
17. Have an estimated glomerular filtration rate (eGFR; CKD-EPI 2021 equation) <60 mL/min at Screening (Visit 1).
18. Have a thyroid stimulating hormone (TSH) level <0.8x the lower limit of normal or >1.3x ULN. Patients with treated thyroid conditions and TSH levels in the aforementioned range will be eligible to participate in the study.
19. Have a Hemoglobin A1c >7.5% ULN at Screening (Visit 1).
20. Have any other clinically significant abnormalities (significant would include laboratory deviations requiring acute medical intervention or further medical evaluation) in laboratory results at Screening (Visit 1), including clinical chemistries, hematology, and any clinical information that, in the judgment of the Investigator, should preclude a patient's participation in the study.
21. Females who are either pregnant or breastfeeding.
22. Site personnel directly affiliated with this study and/or their immediate families.
23. Have participated in an interventional clinical trial within 90 days prior to Screening (Visit 1).

8.4. Randomization Criteria

The following randomization criteria must be satisfied at Baseline (Visit 2) in order for the patient to be eligible to continue in the study. Only those patients meeting the following randomization criteria are eligible for randomization:

1. Continue to meet all inclusion/exclusion criteria
2. MADRS total score ≥25 at Baseline (Visit 2), and
3. ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2).

8.5. Prior and Concomitant Medications

Many concomitant psychiatric medications are prohibited during this study because this study has been designed to evaluate the safety and efficacy of monotherapy with TNX-601 ER tablets for the treatment of MDD. The goal of the study is to recruit patients who are not currently using other medications to treat their MDD, or who are not clearly benefitting from any of the medications that would need to be discontinued in order to enter this study. Since many patients with MDD may already be taking one or more excluded medications when screened, Principal Investigators should use caution when determining whether a patient, in their clinical judgment, can be safely withdrawn from current medications that are being used to treat MDD or are otherwise excluded from the protocol.

Eligible patients will not be receiving treatment with antidepressants (including St. John's Wort, S-adenosyl methionine, and/or trazodone used as an antidepressant), mood stabilizers or anticonvulsants (other than used for migraine prophylaxis) within 4 weeks of Baseline (Visit 2), except for fluoxetine, which must not be within 6 weeks of Baseline (Visit 2). If a patient is receiving oral atypical antipsychotics used for antidepressant augmentation, it must not be within 4 weeks of the Baseline (Visit 2). Eligible patients will not be receiving antipsychotics for other reasons. Eligible patients will also not be receiving stimulants, benzodiazepines, buspirone, or trazodone as a hypnotic within 1 week of the Baseline (Visit 2). In cases in which a stimulant is discontinued for participation and was positive on Screening (Visit 1) urine toxicology, an in-clinic dipstick urine toxicology should be performed prior to randomizing the patient which shows the stimulant was successfully washed out. For benzodiazepine washouts with positive Screening (Visit 1) urine toxicology, a repeat urine toxicology that is sent to the Central Lab must be obtained at least 7 days prior to randomization in an Unscheduled visit showing successful washout of the benzodiazepine. The Central Lab is used rather than urine toxicology dipsticks because the Central Lab can test a greater number of commonly used benzodiazepines.

Similarly, all opioid medications, including tramadol and tapentadol, are excluded medications. Patients on chronic opioids are not appropriate candidates for participation, but there may be patients with occasional as needed (PRN) opioid usage or who were recently on a short course for acute pain who may be appropriate if, in the clinical judgement of the Investigator, they could be safely tapered and remain opioid free for the week before Baseline (Visit 2) and throughout the 6 weeks of treatment and follow up period in the study. In cases in which opioids are tapered and discontinued for the study, an additional urine toxicology by in-clinic dipstick must be obtained prior to randomization showing the opioid was successfully washed out.

The screening period of up to 35 days is provided to ensure a safe tapering rate and discontinuation of excluded medications, per Investigator's discretion, leading up to the 4-week medication-free period (or 1-week medication-free period, depending on the medication) required before Baseline (Visit 2).

8.5.1. Allowed Concomitant Medications

It is ideal to have all patients participating in the study go without any hypnotic agents for the entire double-blind period of the study. Yet there may be instances in which patients' insomnia symptoms need to be addressed with a concomitant treatment. In these instances, non-benzodiazepine sleep aids (eg, zolpidem, zaleplon and eszopiclone) and sedating antihistamines are allowed on a PRN basis during the study but are to be avoided within 24 hours of a clinical visit and generally should not be used more than two to three nights in a row. The Investigator should manage the use of these two classes of permissible hypnotics during the study, encouraging limited use. The dates on which these are used should be captured in concomitant medications at the clinic visits. Chronic nightly use should be avoided whenever possible.

Other prescription or over-the-counter medications not specifically excluded by entry criteria typically may be continued during the study, with the expectation that chronic medications should have been used in a stable fashion for at least 30 days prior to randomization. Sites should contact the Medical Monitor for any questions about whether a concomitant medication may be continued during the study or if it would be acceptable to taper an excluded medication.

Sites will collect data on all concomitant medications (other than antidepressants) taken within 30 days of screening.

8.6. Withdrawal Criteria

In accordance with the Declaration of Helsinki, human patients have the right to withdraw from the study at any time for any reason. The Investigator and Tonix also have the right to remove patients from the study. Additional information regarding withdrawal or discontinuation of patients is described in detail in Section 10.4.1.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug Packaging, and Labeling and Storage

Study drug supplies will be packaged identically so as to maintain the integrity of the study blind. The study drug bottles will be labeled minimally with the following information: study number TNX-TI-M201, sponsor name and address, bottle number, quantity, storage conditions, usage instructions, and caution statements for investigational new drug, eg, Caution: New Drug – Limited by United States Law to Investigational Use and Keep Out of Reach of Children and Pets.

Each study drug bottle will contain 20 tablets. One bottle will be dispensed to each patient at Visit 2 (Baseline), Visit 3 (Week 2), and Visit 4 (Week 4); this will provide the patient with 20 tablets to cover the 2 weeks of dosing between visits, plus additional tablets to cover loss

and/or visit window variability. The patient should be instructed to keep this study drug in a safe location out of extreme environmental conditions and out of the reach of children and pets, and that this drug is not to be taken by any individual other than the study patient. Each patient will also be instructed that they will be expected to return the bottle and all unused study drug at each clinic visit; unused drug will be counted to assess compliance with study drug treatment.

Storage of the study drug at the investigational sites should be under locked and secure conditions with limited staff access. Study drug should be stored at 15-25°C/59-77°F in a temperature/humidity-monitored room.

9.2. Dosing Instructions

Patients will be instructed to take one tablet of their assigned study drug (TNX-601 ER or placebo) orally, each morning and continuing without interruption for 6 weeks. Day 1 study drug will be taken in the clinic. They should swallow the tablets whole, and not crush or chew the tablets. The tablet should be taken in the morning with breakfast. Patients will be reminded that only 1 tablet is allowed per day. Note: In the event that the patient misses a dose, instruct the patient to continue dosing with one (1) tablet the next morning; eg, they should not take more to make up for the missed dose.

9.3. Dispensing Instructions

Each patient who has met the randomization criteria (Section 8.4) will be assigned 1 double-blind treatment bottle at Visit 2 via the Interactive Web Response System (IWRS), with a unique, but otherwise random bottle number that is generated when an authorized staff member successfully completes randomization procedures. Patients will also be assigned a new treatment bottle at Visits 3 and 4 via the IWRS. The bottle numbers provided by the IWRS at these visits will tell the site which treatment bottles have been assigned to the patient.

In the event of loss of study drug, new drug will be provided by the IWRS, when appropriately requested by the site and/or the sponsor or designee.

Study treatments for the double-blind treatment phase are either:

Treatment A: 1 x TNX-601 ER tablet (“TNX-601 ER”) 39.4 mg to be taken orally in the morning.

Or

Treatment B: 1 x placebo tablet (“placebo”) to be taken orally in the morning

9.4. Release of Clinical Study Supplies to the Investigator

Tonix or Tonix’s designee’s standard operating procedures for releasing clinical trial supplies to the site will be followed.

9.5. Study Drug Accountability and Reconciliation

All patients will be expected to bring their bottle of study drug with them to all study visits. At each study visit, the site staff will inspect the drug bottle, and perform a count of the tablets

remaining in the bottles and document this in the patient's record. An assessment of drug adherence should be done by the study staff to ensure that the patient understands all dosing instructions and is taking the drug as prescribed. Patients will be asked for an explanation if the count of returned study drug tablets indicates a discrepancy between the expected number of tablets dosed and the number returned in the bottle. If it is found that the patient is not taking the study drug as expected, the patient will be re-counselled with instructions, and this should be noted in the patients' records. A deviation should be recorded on any patient who is less than 70% compliant with dosing between visits.

If the patient fails to return any of the unused study drug as expected, the Investigator will identify if it matches a MADDERS® triggering event and complete the MADDERS® Supplemental Drug Accountability Form. Patient should be evaluated by the Investigator for the reason for the lower-than-expected tablet number and about potential misuse, abuse, or diversion, and the Investigator will address this accordingly. If more than 1 tablet cannot be accounted for at any of the visits where drug is returned (Week 2, 4, or 6), the Investigator will be asked to evaluate the situation, and a written summary of this evaluation should be added to the source and entered onto the case report form (CRF). Situations where replacement drug is requested, or when more than 1 tablet cannot be accounted for, should be recorded as deviations.

All study drug, including partial and empty bottles, must be maintained at the study site until Tonix or its designee verifies drug accountability and provides instruction for destruction or the return of the investigational product to the Sponsor's drug distribution depot.

Tonix or their designee will perform drug accountability which entails reconciliation between the amount of drug shipped to the study site, study drug assigned and dispensed to the patient (including returned unused assigned study drug), and study supplies that were never dispensed and/or assigned to patients.

10. STUDY VISITS AND PROCEDURES

The overall and detailed schedule for study procedures and visits is provided in Table 1.

10.1. Visit 1 (Screening: Day -35 to -7)

10.1.1. Informed Consent

Before the potential patient has undergone any study-related screening procedures, including any downward titration or withdrawal of medications, the nature of the study and the potential risks associated with it will be explained to the patient, and the patient will be given an opportunity to ask questions to his or her satisfaction. After all questions are answered, but before proceeding further, the patient must read and sign a written ICF. This signed ICF will be retained in the Investigator's study file, and the date the patient signed the form will be entered into the CRF. The patient will be provided with a copy of his or her signed and dated ICF and will also be required to sign all updated informed consents.

The patient will also be presented with a consent to Clinical Trial Subject Registry (CTSR) screening, which is a mandatory part of the consent process.

A site can elect not to participate in the CTSR, with approval from the sponsor, and there will be no protocol deviations recorded for leaving it out of the procedures.

The patient will also be presented with the opportunity to participate in the optional pharmacogenomic assessment. If the patient agrees to participate in the optional pharmacogenomic assessment, a separate signed written ICF must be obtained.

10.1.2. Screening Overview

Screening (Visit 1) will start a variable length screening period. The length of the screening period is to be no shorter than 7 days but may be as long as 35 days in order to accommodate medication taper and discontinuation or other study requirements.

If the patient is eligible to continue in the study, and does not need to discontinue any excluded medication, the patient may be scheduled to return for Baseline (Visit 2) in 7 (or more) days, assuming all screening evaluations have been completed, including confirmation of acceptable laboratory and ECG results. If the patient needs to undergo taper and discontinuation of excluded medication, the Investigator will generate a written down-titration schedule for the patient and will schedule Baseline (Visit 2) such that the date of Baseline (Visit 2) is 1 to 5 weeks after the date of the final dose of any excluded medication. If additional clinic visits are deemed necessary by the Investigator for clinical monitoring of the patient before scheduling Baseline (Visit 2), such visits will be recorded as unscheduled visits.

10.1.3. Patient Numbering

All screened patients will be assigned a unique concatenated 6-digit site-patient number (eg, 202-012) by the IWRS. A screening log or system documenting the following information will be recorded and maintained, and will include the patient's year of birth, screening number, whether the patient was ultimately randomized or not, and if not randomized, the reason the patient was excluded/screen failed.

10.1.4. Screening and Assessments/Procedures

The following screening assessments/procedures will be completed in the following general order:

- Obtain written informed consent to participate
- Review placebo response training with patient
- Obtain demographics, including alcohol, nicotine/tobacco (smoking, vaping and/or chewing), and marijuana use
- Obtain medical history
- Obtain prior and current medication history, including all prior MDD therapies and other treatments for psychiatric indications
- Obtain psychiatric history
    - MINI 7.0.2
    - MSI-BPD

- MADRS, Structured Interview Guide for the MADRS (SIGMA) version); total score of ≥28 required at Screening (Visit 1)
- Perform physical examination, including a brief neurological examination
- Obtain vital signs, height, weight, and BMI
- Draw samples for clinical laboratory tests:
    - Blood for chemistry, hematology, HbA1c, thyroid stimulating hormone (TSH)
    - Blood for serum pregnancy test (for women of child-bearing potential)
    - Urine for Drug Screen (central laboratory)
- Conduct 12-lead ECG
- Administer C-SSRS, Baseline/Screening Version
- Review inclusion/exclusion criteria

Only those patients meeting all of the inclusion and none of the exclusion criteria will be eligible to continue. NOTE: Final determination of eligibility based on clinical laboratory tests will be made when results have been returned.

Sites will be asked to complete and submit to the Tonix medical monitoring team key screening information. This information will be reviewed by the Tonix medical monitoring team to help ensure the selection of well-qualified patients. The specific requirements and timelines associated with this pre-randomization review process will be outlined in a separate document.

Once eligibility has been confirmed and authorization for randomization granted by the Medical Monitor or delegate, eligible patients will return to the clinic for Baseline (Visit 2).

There is no requirement for Follow-Up visits for patients who are SFs. Patients who fail to qualify should have their medication adjusted, as appropriate, per the judgment of the Investigator and be released from the clinic.

Patients that are determined to be a screen fail may be re-screened based on Medical Monitor approval.

10.2. Visit 2 (Baseline: Day 1)

Baseline (Visit 2) should be scheduled 7 to 35 days after Screening (Visit 1). If the patient meets all randomization criteria, the patient will be randomized via the IWRS system to receive double-blind study drug.

10.2.1. Pre-Randomization Assessments

The following assessments must be completed at Baseline (Visit 2) to confirm that the patient is eligible for randomization. Upon arrival at the clinic, the following assessments should be done, in the following general order:

- Assess occurrence of AEs
- Update medical history (with changes since screening noted)

- Assess changes in concomitant medications
- Obtain vital signs and weight
- Review placebo response training with patient
- Administer MADRS. Total score must be ≥25 at Baseline (Visit 2), and there must be ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2).
- Conduct urine drug screen (urine dipstick, only as necessary, if select Screening (Visit 1) tests were positive for excluded medications that required discontinuation prior to randomization, or if Investigator suspects drug use)
- Conduct in-clinic urine pregnancy test (for women of child-bearing potential)
- Collect blood sample for those who consent to participate in the optional pharmacogenomics assessment. (The blood draw for this pharmacogenomics assessment can be done at any in-clinic visit post-Screening; however, it is preferred that the sample is collected at Baseline (Visit 2) whenever possible.)
- Conduct 12-lead ECG
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PGIS
    - CSFQ-14
- Administer the HARS
- Administer the C-SSRS- Since Last Visit Version
- Physician to assess CGI-S (needs to be completed once all other assessments are available for Investigator to review)

10.2.2. Randomization Criteria

Once all pre-randomization assessments have been completed, only those patients who meet all of the following randomization criteria will be eligible to continue:

1) Continue to meet all inclusion/exclusion criteria,
2) MADRS total score ≥ 25 at Baseline (Visit 2),
3) ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2)

If the patient does not satisfy these randomization criteria, the patient has failed to qualify for this study and should be considered a SF, with the reason documented. With Medical Monitor approval, if the patient is otherwise considered a qualified and compliant patient, Baseline (Visit 2) may be delayed to accommodate situations in which extenuating or short-term circumstances do not warrant SF.

If the patient does satisfy these randomization criteria, then continue with the following:

- Randomize the patient via IWRS Randomization System
  - Dispense 2-week supply (1 bottle) of double-blind study drug
- Review patient instructions regarding study drug dosing (Section 9.2)
- Have patient take first dose of study drug (Day 1) and observe for 30 min
- Schedule next study visit

10.3. Visits 3 and 4 (Weeks 2 through 4)

Visits 3 and 4 are similar study visits that are scheduled to be conducted after 2 and 4 weeks of treatment, respectively. Visit 3 should occur on Day 15 ± 2 days and Visit 4 should occur on Day 29 ± 2 days.

The following assessments and procedures are scheduled for these visits in the following general order:

- Collect study drug and assess compliance and accountability
- Assess occurrence of AEs
- Update concomitant medications
- Obtain vital signs and weight
- Review placebo response training with patient
- Administer the MADRS
- Conduct urine pregnancy test (for women of child-bearing potential)
- **Visit 4 only:** Draw samples, fasting or non fasting, for clinical laboratory tests for:
  - Chemistry and hematology
  - PK
- Have the patient complete the following outcome scales (in order):
  - SDS
  - PGIS
  - PGIC
- Administer the HARS
- Administer C-SSRS - Since Last Visit Version
- Administer MADDERS® only if any pre-defined AEs and/or Drug Accountability Discrepancy Events (DADE) suspect for misuse, abuse, or diversion event is identified
- Investigator to assess CGI-S and CGI-I (needs to be completed once all other assessments are available for Investigator to review)

- Dispense new bottle of double-blind study drug as assigned by IWRS

After all assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the next scheduled visit, and be re-instructed, as necessary, on dosing instructions, and reminded to bring study drug back to the clinic at their next visit.

10.4. Visit 5 (Week 6)

End of Treatment (Visit 5) should occur after 6 weeks of double-blind study drug treatment, scheduled at Day 43 + 2 days. The following assessments and procedures are to be completed in the following general order:

- Collect study drug and assess compliance and accountability
- Assess occurrence of AEs
- Update concomitant medications
- Obtain information on current use of alcohol, nicotine/tobacco (smoking, vaping and/or chewing), and marijuana
- Perform physical examination, including a brief neurological examinationObtain vital signs and weight
- Review placebo response training with patient
- Administer MADRS
- Conduct urine pregnancy test (for women of child-baring potential). Serum pregnancy test may be done at Investigator's discretion.
- Draw samples, fasting or non-fasting, for clinical laboratory tests for:
    - Chemistry and hematology
    - PK
- Conduct 12-lead ECG
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PGIS, PGIC
    - CSFQ-14
- Administer the HARS
- Administer C-SSRS-Since Last Visit Version
- Administer SOWS and train the patient on how to report the SOWS at Day +1, +2, +3, +6, +9 and +12 days via the IWRS
- Administer MADDERS® only if any pre-defined AEs suspect for misuse, abuse, or diversion event is identified, or any drug accountability issues above the pre-defined threshold is identified

- Physician to assess CGI-S and CGI-I (needs to be completed once all other assessments are available for Investigator to review)
- Schedule the Post Study Follow-up (Visit 6)

10.4.1. Early Termination (ET)

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason, and they will be advised of this right. The Investigator and Tonix also have the right to remove patients from the study. Specific reasons for removal of a patient from the study could include, but are not limited to:

- An AE
- An illness that, in the judgment of the Investigator or Tonix, might invalidate the study results or place the patient at risk
- The request of the patient, Investigator, or Tonix, whether for administrative or other reasons
- Pregnancy

This study will attempt to obtain as complete information as possible on all participating patients. An effort must be made to contact the Medical Monitor prior to any patient's early termination. Each reason for early termination will be reviewed. Patients who wish to terminate their participation in the study early should be strongly encouraged to come to the clinic for an ET Visit, and a Follow-up visit. The purpose of the ET visit is to obtain critical information about the patient's participation and should be scheduled preferably before there has been a substantial lapse in study drug usage. However, even if there has been a drug lapse, the patient should be encouraged to return to the clinic for this visit and should be instructed to return all study drug. NOTE: These visit procedures are not intended for patients who fail to qualify for randomization or for any other reason withdraw from the study prior to receipt of a dose of double-blind study drug.

<u>If the patient withdraws from the study, the following assessments and procedures are to be completed at this visit in the following general order:</u>

- Document reason for ET. The Investigator should carefully assess the role of AEs and/or lack of efficacy when determining the most accurate reason for the patient's early termination.
- Collect study drug and assess compliance and accountability
- Assess occurrence of AEs
- Update concomitant medications
- Obtain information on current use of alcohol, nicotine/tobacco (smoking, vaping and/or chewing), and marijuana
- Perform physical examination, including a brief neurological examination
- Obtain vital signs and weight

- Review placebo response training with patient
- Administer MADRS
- Conduct urine pregnancy test (for women of child-baring potential). Serum pregnancy test may be done at Investigator's discretion.
- Draw samples, fasting or non-fasting, for clinical laboratory tests for:
    - Chemistry and hematology
    - PK
- Conduct 12-lead ECG
- Have the patient complete the following outcome scales (in order):
    - SDS
    - PGIS, PGIC
    - CSFQ-14
- Administer the HARS
- Administer C-SSRS-Since Last Visit Version
- Administer SOWS and train the patient on how to report the SOWS at Day +1, +2, +3, +6, +9 and +12 days via the IWRS
- Administer MADDERS® only if any pre-defined AEs suspect for misuse, abuse, or diversion event is identified, or any drug accountability issues above the pre-defined threshold is identified
- Physician to assess CGI-S and CGI-I (needs to be completed once all other assessments are available for Investigator to review)
- Schedule the Post Study Follow-up (Visit 6)

Once these assessments have been completed, it should be impressed upon all early terminating patients that it is important for safety reasons that they complete the SOWS assessments over the next two weeks and return for the Week 8 Post-Study Follow-up visit.

10.4.2. Unscheduled Visits

Patients may need to be seen at other times than the scheduled study visits for additional safety assessments or to follow-up, as medically necessary, on clinical laboratory results, physical examination, or other findings. If an additional study visit is warranted, or occurs, the date and nature of the visit will be documented in the CRF and in the source documents.

10.5. Visit 6 (Week 8)

Post Study Follow-up (Visit 6) should occur after 2 weeks from the end of double-blind study drug treatment, scheduled at Day 57 + 7 days. The following assessments and procedures are to be completed in the following general order:

- Assess occurrence of AEs
- Obtain vital signs and weight
- Conduct urine pregnancy test (for women of child-bearing potential)
- Administer the C-SSRS- Since Last Visit Version
- Administer SOWS
    - Review the patient responses to the SOWS in the foregoing two weeks
- Administer MADDERS® Medication Use Survey

Between discontinuation of study drug and the Post Study Follow-up (Visit 6), potential withdrawal effects will be assessed at home using the SOWS at +1 day, +2 days, +3 days, +6 days, +9 days, and +12 days after the end of Treatment (Visit 5/ET). This includes patients who are early terminated.

11. STUDY ASSESSMENTS

11.1. Screening Assessments

11.1.1. Psychiatric and Medical History

A psychiatric interview using the MINI 7.0.2 (Sheehan et al, 1998), a self-assessed MSI-BPD and a comprehensive medical history will be obtained at screening in order to determine whether the patient is eligible for enrollment. The MINI 7.0.2 will assess for a lifetime look-back for opioid and sedative-hypnotic use disorder rather than the standard 12 months look-back.

While patients with mild TBI are eligible to participate in the study, moderate and severe TBI are excluded. Common traumatic brain injuries result from falls, motor vehicle accidents, assaults, and sports injuries. A *history of TBI* is defined as any traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

1. Any period of loss of or a decreased level of consciousness;
2. Any loss of memory for events immediately before or after the injury;
3. Any alteration in mental state at the time of the injury (eg, confusion, disorientation, slowed thinking);
4. Neurological deficits (eg, weakness, balance disturbance, praxis, paresis/plegia, change in vision, other sensory alterations, aphasia) that may or may not be transient;
5. Intracranial lesion.

Although *severity of TBI* depends in part on patient assessment in the days after a traumatic head injury, for the purposes of this protocol, mild TBI is defined as:

6. Normal structural brain imaging findings

7. Loss of consciousness not greater than 30 minutes after injury
8. Alteration of consciousness not greater than 24 hours after injury
9. Posttraumatic amnesia not more than 24 hours after injury
10. No ongoing neurological deficits (Note: tinnitus, headaches, or sleep disturbances that appeared to result from the head trauma would *not* be considered as ongoing neurological deficits and therefore should *not* be interpreted as meaning the person has a greater severity than mild TBI.)

Each incidence of traumatic brain injury in a patient's lifetime history should be assessed using these five rule outs for *greater than* mild TBI, which is exclusionary for the protocol.

In addition, the past medication history will be reviewed. Any psychiatric medication or MDD therapies utilized during the patient's lifetime should be collected. Responses from the MINI and MSI-BPD will serve to document the presence or suspicion of other psychiatric conditions. The diagnosis and severity of MDD will be based on the MINI 7.0.2 and MADRS, respectively (Section 11.2.1).

11.2. Efficacy Assessments

The primary efficacy endpoint and many of the secondary and exploratory efficacy endpoints in this study are derived from clinician-administered assessments which must be administered by qualified and trained individuals at each clinical site. Study specific training will be required before staff is allowed to administer these scales. In an attempt to minimize variability in responses of a given patient over time, it is important that the same rater administer the scales to a given patient throughout the study unless absolutely unavoidable due to the rater's absence from the clinic. It is also important that the assessments, including those that are patient-completed, be conducted in the specified order, according to specific instructions, and in a setting where the patient has minimal distractions, appropriate privacy, and sufficient time to complete them.

11.2.1. MADRS

The MADRS is a validated, 10-item, clinician-administered depression scale that has been used in clinical research since 1979 (Montgomery & Åsberg, 1979). This study will use a structured interview version of the MADRS (Structured Interview Guide for the MADRS, SIGMA), which was shown to have high interrater reliability (Williams & Kobak, 2008).

The MADRS will be completed at Screening (Visit 1), Baseline (Visit 2) and after Weeks 2,4, and 6 of treatment (Visits 3, 4, and 5, respectively). The 10 items measure the core symptoms and cognitive features of clinical depression. This scale has historically been used in drug-treatment trials due to its particular sensitivity to detect treatment effects.

Patients with a Screening (Visit 1) MADRS score of ≥28, ≥25 at Baseline (Visit 2), and a ≤25% decrease or increase in MADRS score from Screening (Visit 1) to Baseline (Visit 2) are eligible to be randomized.

11.2.2. Clinical Global Impression of Severity (CGI-S)

The CGI-S will be completed by an Investigator to assess overall patient severity at the time of the assessment. The CGI-S will be completed at Visits 2, 3, 4, and 5 (Baseline, Week 2, 4, and 6, respectively). The CGI-S should be completed toward the end of each visit once all assessments are available for the Investigator's review. The Investigator will answer the following question:

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

11.2.3. Clinical Global Impression of Improvement (CGI-I)

The CGI-I will be completed by an Investigator to assess the overall change in the patient's status since Baseline (Visit 2). The CGI-I will be completed at Visits 3, 4, and 5 (Week 2, 4, and 6, respectively). The CGI-I should be completed toward the end of each visit once all assessments are available for the Investigator's review. The Investigator will answer the following question:

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at Baseline (Visit 2) of TNX-TI-M201, how much has patient changed?

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

11.2.4. Patient Global Impression of Severity (PGIS)

The PGIS assesses the patients' overall perception of their condition. This form will be completed by the patient at Visits 2, 3, 4, and 5 (Baseline, Week 2, 4, and 6, respectively). The patient will answer a single question:

Please rate the severity of your depression right now:

1 = Not present

2 = Very mild

3 = Mild

4 = Moderate

5 = Moderately severe

6 = Severe

7 = Extremely severe

11.2.5. Patient Global Impression of Change (PGIC)

The PGIC is a validated, self-report instrument to gauge the patient's assessment of change in condition. This form will be completed by the patient after Week 2, 4 and 6 of treatment (Visits 3, 4, and 5, respectively). The patient will answer a single question:

Since the initiation of study drug, overall, my depression symptoms are:

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

11.2.6. Sheehan Disability Scale (SDS)

The SDS scale is a self-report questionnaire that was designed to assess the patient's view of the degree to which symptoms have disrupted work, social life/ leisure activities, and family life/home responsibilities during the past 2 weeks (Sheehan & Sheehan, 2008). In addition, the SDS asks the patient to provide the number of days or work lost as well as unproductive days in the past 2 weeks. The SDS scale will be completed by the patient at Baseline (Visit 2), and after 2, 4, and 6 weeks of treatment (Visits 3, 4, and 5 respectively).

11.2.7. Hamilton Anxiety Rating Scale (HARS)

The HARS is a widely used and well-validated 14-item clinician-administered scale for assessing the severity of symptoms of anxiety (Hamilton, 1959). The scale measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The HARS will be completed at Baseline (Visit 2) and after 2, 4, and 6 weeks of treatment (Visits 3, 4, and 5, respectively).

11.3. Safety Parameters

Safety will be assessed by evaluation of AEs; responses on the C-SSRS, and CSFQ-14; clinical laboratory test results, physical examination findings, ECG parameters, vital signs, and weight. AEs associated with abuse liability of the study drug will be evaluated using the MADDERS®. Withdrawal symptoms associated with the study drug after the End of Treatment (Visit 5/ET) will be evaluated using the SOWS.

11.3.1. Adverse Events (AEs)

Patients will be monitored for the occurrence of AEs throughout the study from the time that the patient signs an informed consent to their last study visit. AEs that are spontaneously reported, elicited, or observed are to be recorded on the CRF with the date, time of onset, date and time of resolution, severity, seriousness, causality (relationship to study drug), actions required, and outcome.

To elicit AEs, non-leading, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. Examples of these questions can be:

- How have you felt since your last visit?
- Have you had any health problems since your last visit?

If an AE occurs, the Investigator will institute support and/or treatment as deemed appropriate. During the study, all AEs should be followed until resolution, stabilization, or until the subject is lost to follow-up. AEs (serious and non-serious) that are ongoing at the last study visit should be followed for up to 28 days following the last dose or until one of the above conditions (resolution, etc.) is (are) met.

There are many symptoms associated with MDD that can vary in intensity and frequency over time. Only symptoms that significantly worsen or become more frequent, in the opinion of the patient and outside of their normal experience, should be reported as an adverse event.

Additional information regarding definition and reporting requirements for AEs, SAEs, and pregnancies is provided in Section 12.2 , Section 12.3, and Section 12.4 respectively

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

The C-SSRS is a questionnaire developed by researchers at Columbia University to assess suicide risk and to track suicidal ideation and behavior during clinical trials. This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

There are multiple versions of this questionnaire. At Visit 1, the “Baseline/Screening” version will be administered, and the recall periods will be “lifetime” and “within the past 6 months” for suicidal ideation, and “within the past year” for suicidal behaviors. Patients whose responses are indicative of suicidal ideation with intent and/or plan (eg, Type 4-5 ideation) within the past 6 months or a history of prior suicidal behavior within the past year will be excluded from participation, with recommended referral for appropriate intervention.

At all subsequent visits (Visit 2 through 6), the "since last visit" version will be administered, and the recall period will be "since the last visit". Note that if there has been a significant change in responses indicative of increased suicide risk, appropriate intervention should be initiated.

11.3.3. Physical Examination

A complete physical examination, including a brief neurological examination, will be performed at Visit 1 (Screening) and End of Treatment (Visit 5/ET). At a minimum, the physical examination will include the following components: HEENT (head, eyes, ears, nose, and throat), neck, chest, and lungs, cardiovascular, abdomen, skin, and musculoskeletal in addition to the brief neurological examination. The physical examination may exclude rectal, genitourinary, and breast examinations.

11.3.4. Vital Signs, Height, and Weight

Vital signs including sitting or supine blood pressure, heart rate, temperature, and weight will be assessed at Visit 1 (Screening), Visit 2 (Baseline), and Visits 3, 4 and 5/ET (after 2, 4, and 6 weeks of treatment, respectively), as well as at Visit 6. Height will be measured without shoes at Screening (Visit 1) only. The BMI will be a derived variable, based on height and weight entries. A BMI of <18.0 or >40.0 kg/m^2 is an exclusion criterion. Blood pressure and heart rate should be measured after sitting or supine for five minutes at rest. Height will be measured without shoes at Screening (Visit 1) only. The BMI will be a derived variable, based on height and weight entries. A BMI of <18.0 or >40.0 kg/m^2 is an exclusion criterion.

11.3.5. Electrocardiogram (ECG)

A 12-lead ECG (supine after five minutes rest) will be performed at Screening (Visit 1), Baseline (Visit 2) and End of Treatment (Visit 5/ET). The purpose is to 1) exclude patients who have either a history of or current evidence of clinically significant and currently relevant cardiac disease (eg, significant arrhythmias or heart block, heart failure, or myocardial infarction within the past 2 years), a QTcF at Screening >450m/sec (males) or QTcF >470m/sec (females), and 2) to determine the effects of the study drug on cardiac intervals.

The ECG interpretation will be performed by the central reader and confirmed by the Investigator, recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. In addition, the standard ECG parameters including rhythm, heart rate, and intervals for PR (or PQ), QRS, and QTcF (Fridericia's) corrections for heart rate will be collected.

If the Investigator has any concerns about the eligibility of a patient or wishes to confirm his/her assessment, the Investigator should consult with the Medical Monitor for this study.

11.3.6. Clinical Laboratory Assessments

The clinical laboratory evaluations to be performed in this trial are listed in Table 2. Those marked as screening tests will be performed at screening only. All other tests will be performed at Week 4 (Visit 4) and after 6 weeks of treatment (Visit 5), or ET. Clinical laboratory values may be repeated prior to randomization in order to confirm exclusionary levels for ALT and/or

AST values. If these values remain persistently elevated upon repeat, the patient is not eligible for randomization.

With the exception of the urine pregnancy tests or the ad hoc urine drug test required at Baseline (Visit 2) for patients washing off excluded medications (eg, benzodiazepines, stimulants, opioids), all clinical laboratory evaluations will be analyzed via a central clinical laboratory, and information regarding appropriate sample volume, collection tubes, sample labeling and handling, and shipment will be provided in a study manual.

A urine drug screen for drugs of abuse (including marijuana) will be collected at Screening (Visit 1) and sent to the central laboratory for analysis, as well as an on-site urine drug test. If the patient has a positive drug screen at Screening (Visit 1) and/or Baseline (Visit 2) for anything other than marijuana, and the results cannot be explained by use of current allowable prescription medications, the patient should be excluded from the study. If the urine drug screen is positive at Screening (Visit 1) and the results can be explained by the use of current prescription medications (eg, benzodiazepines, stimulants, opioids) that will be discontinued during screening, the Investigator must repeat the drug screen and obtain a negative result using an in-clinic urine dipstick drug screen prior to randomization to confirm eligibility for the study. Patients with positive results for benzodiazepines at Screening (Visit 1) will need to come back to the clinic for repeat centralized urine drug screen following a minimum of one week off all benzodiazepines. And since the results of the repeat urine drug screen must be confirmed negative prior to randomization, the Baseline visit (Visit 2) should take place no sooner than 7 days after the patient's post-washout urine drug screen.

Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within a reasonable period, their etiology should be identified and Tonix or designee should be notified. Treatment-emergent clinically significant abnormalities in laboratory values will be recorded as AEs.

Table 2: Clinical Laboratory Assessments

Clinical chemistry	Hematology
Alanine aminotransferase (ALT)[a]	Hematocrit
Alkaline phosphatase	Hemoglobin
Aspartate aminotransferase (AST)[a]	MCH concentration (MCHC)
Bilirubin (total)[b]	Mean corpuscular hemoglobin (MCH)
Blood urea nitrogen (BUN)	Mean corpuscular volume (MCV)
Calcium	Platelet count
Chloride	Red blood cell (RBC) count
Cholesterol (total)	White blood cell (WBC) differential
Creatine kinase (CK)	Neutrophil count (absolute and %)
Creatinine	Lymphocyte count (absolute and %)
Glucose	Monocyte count (absolute and %)
Phosphorus	Eosinophil count (absolute and %)
Potassium	Basophil count (absolute and %)
Protein (albumin and total)	WBC count
Sodium	
Thyroid stimulating hormone (TSH)[c] at Screening (Visit 1)	Serum Pregnancy Test at Screening[d]
Estimated glomerular filtration rate (eGFR)	Urine Pregnancy Test (qualitative dipstick)[d]
Hemoglobin A1c at Screening (Visit 1)	Urine Drug Screen[e]
Pharmacokinetic (PK) testing	
Pharmacogenomic testing (optional; can be obtained at any visit post-Screening, including an early termination visit other than if the patient withdrew consent)	

a Level greater than 2 times the upper limit of normal is an exclusion (if persistent upon repeat).
b Level greater than 1.5 times the upper limit of normal is an exclusion (if persistent upon repeat), with the exception of patients with isolated Gilbert's syndrome.
c TSH level greater than 1.3 times higher than the upper limit of normal or less than 0.8 times the lower limit of normal is exclusionary at Visit 1.
d Pregnancy testing for females of child-bearing potential, including women who have had bilateral tubal ligation. A positive pregnancy test is exclusionary (Visit 1 or Visit 2) or mandates withdrawal from the study (all other visits).
e Urine drug screening will be conducted on all patients at Screening (Visit 1) and, if necessary, at Baseline (Visit 2) in patients with a positive result for excluded medications requiring washout (eg., benzodiazepines, stimulants, opioids) and who otherwise qualify for the study. For patients testing positive at the Screening visit (Visit 1) for an excluded medication that will be discontinued during the screening interval, an in-clinic urine dipstick drug screen will be performed at the Baseline (Visit 2) visit and must be negative in order for the patient to be eligible for randomization (this will primarily apply to opioids and amphetamines). Patients with positive results for benzodiazepines at Screening (Visit 1) will need to come into the clinic for a repeat centralized Urine drug screen following a one-week drug free interval, and the Baseline visit (Visit 2) may need to be delayed in order to ensure that the results from the repeat centralized UDS can be confirmed negative prior to randomization.

11.3.7. Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The CSFQ-14 (Keller et al. 2006) is a validated scale with internal reliability designed to allow a patient to self-evaluate his or her sexual behaviors or problems in a number of areas. The CSFQ-14 will be administered at Baseline (Visit 2) and Week 6 or ET. (Visit 5/ET). It yields a total score, 3 subscales corresponding to phases of the sexual response cycle (ie, desire, arousal, orgasm), and 5 subscales corresponding to important dimensions of sexual functioning. It is considered a useful scale for assessing sexual side effects of medications. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning

corresponds to greater frequency or enjoyment/pleasure (eg, 1 = never to 5 = every day). For 2 items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (eg, 1 = every day to 5 = never). Items 10 and 14 are included in the total score but not in any scale score.

Investigators will ensure that patient receives applicable male or female versions of the CSFQ-14.

11.3.8. Misuse, Abuse, Diversion Drug Event Reporting System (MADDERS®)

The MADDERS® is a structured method to:

- Identify potential abuse-related events associated with study drug
- Classify the events according to standardized definitions
- Identify potential abuse-related events not already classified as an adverse event of interest or drug accountability discrepancy.

The Investigator at each site will be trained to identify related adverse events and drug accountability discrepancy. This information is collected throughout the study in real time. If any of these events are identified during the study, the Investigator will determine if it matches a MADDERS® triggering event. If so, the MADDERS® Supplemental Adverse Event Form or the MADDERS® Supplemental Drug Accountability Form will be completed. These events are adjudicated by a MADDERS® Adjudication Committee after the patient exits the study.

In addition to, all participants (regardless of the occurrence of a MADDERS® triggering events) will complete the MADDERS® Medication Use Survey on Visit 6. If the participant is lost to follow-up prior to Visit 6, the Medication Use Survey should be completed based on the site's knowledge of the participant.

11.3.9. Subjective Opiate Withdrawal Scale (SOWS)

The SOWS is a self-administered 16-item scale for evaluating opioid withdrawal symptoms (Handelsman et al., 1987). The SOWS will be administered at End of Treatment (Visit 5/ET) (after 6 weeks of treatment/ET), then completed at home at +1 day, +2 days, +3 days, +6 days, +9 days, and +12 after Visit 5/ET, and lastly administered at the Post Study Follow-up (Visit 6).

The purpose of the first administration of the SOWS at End of Treatment (after 6 weeks of treatment or ET) is to establish a "baseline" for withdrawal symptoms. The SOWS is given over the next three days (+1, +2, and +3 days) because that is the estimated time for TNX-601 ER to be eliminated from the body (5 x 11-hour half-life of MC5, a major metabolite of TNX-601 ER). The additional days for the SOWS (+6, +9, +12 days) ensures that the SOWS is given at least twice a week between the End of Treatment (Visit 5/ET) and the Post Study Follow-up (Visit 6).

11.4. Optional Pharmacogenomic Assessment

Patients who meet all criteria for randomization will be eligible to participate in the pharmacogenomic assessment. A single blood draw will be collected in one 6mL K2 EDTA tube for each participating patient after they have signed a separate ICF for pharmacogenomic

assessment. The blood draw for this assessment can be done at any in-clinic visit post-Screening; however, it is preferred that the sample is collected at Baseline (Visit 2) whenever possible. The blood draw may only be performed after the patient has been confirmed to meet all criteria for randomization, and after the patient has reviewed and signed the separate pharmacogenomic testing ICF.

The purpose of this testing is to allow genetic sequencing and analysis for genetic variants related to treatment response to TNX-601 ER. It is presumed that unused sample will be stored up to 15 years, and potentially utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-601 ER. A decision not to participate in optional pharmacogenomic testing will not affect the patient's eligibility for the main study. Patients have the right to stop participating at any time during the study or during the time of sample storage, and, if a patient decides to withdraw from the pharmacogenomics portion of this study, any remaining sample will be destroyed and not used for further research. Data collected before a patient's withdrawal from the pharmacogenomics portion of this study will remain in the research database.

12. DEFINITIONS, RECORDING, AND REPORTING OF ADVERSE EVENTS

12.1. Definition of Adverse Events

According to International Conference on Harmonization (ICH) guidance E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which is not necessarily required to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

A treatment-emergent AE (TEAE) is an AE that either commenced following initiation of study drug or was present prior to study drug but increased in frequency or severity following initiation of study treatment.

12.2. Adverse Event Recording

12.2.1. Coding the Adverse Event

Standard medical terminology should be used in describing AEs. MedDRA® will be used as the standard coding dictionary for AEs and in describing the patient's medical history, and the World Health Organization (WHO) Drug Dictionary will be used to code concomitant medications. Informal descriptions should be avoided.

12.2.2. Severity of Adverse Event

AEs should be graded as mild, moderate, or severe using the following definitions.

- ***Mild:*** Awareness of signs or symptoms, but easily tolerated and of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- ***Severe:*** Events interrupt the patient's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, maybe of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

12.2.3. Relationship of Adverse Events (AEs) to Study Drug

The Investigator will assess the potential relationship of the AE to study drug using the following descriptions.

- ***Not Related:*** This category applies to an AE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of study drug and/or a causal relationship is considered biologically implausible.
- ***Unlikely Related:*** This category applies to an AE that could reasonably be considered caused by something else, and where there is no known or expected response pattern to the suspected study drug.
- ***Possibly Related:*** This category applies to an AE that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.

12.3. Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions

Any SAE that occurs at any time during the study, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported to Tonix or its designee(s) so that Tonix may comply with regulatory obligations. For these and all other SAEs, an SAE report form must be completed and sent by facsimile or email to Tonix or its designee(s) within 24 hours of the site's initial awareness of the event. These requirements apply equally to all patients, regardless of the study phase or the at-risk patient's treatment assignment or dosage.

A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose:

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

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A death occurring during the study, during the per-protocol follow-up period, or reported to the Investigator after study participation must be reported to Tonix or its designee(s) immediately, whether or not it is considered treatment-related.

SAEs report forms must be submitted to [redacted] within 24 hours of the site/investigator's awareness of the event via facsimile or email:

[redacted]

For questions pertaining to the reporting of SAEs or the completion of SAE documentation, site personnel should call the [redacted]

Initial SAE reports must be followed by detailed descriptions. These may include copies of hospital case records and other documents when requested. All facsimile and email submissions will be confirmed by Rho Product Safety within 1 business day of receipt.

As noted above, all SAEs need to be initially reported to Rho Pharmacovigilance. The study Medical Monitors are available to discuss any SAEs or other AEs of concern with sites and investigators as needed.

Contact information for the Medical Monitors is provided below:

Table 3: Medical Monitoring Contact Information

The Investigator, or the sponsor or designee in the case of a central Institutional Review Board (IRB), also must notify the Ethics Committee (EC)/IRB of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with local law. A copy of this notification must be provided to Tonix or its designee.

In the event of an SAE that meets the criteria for expedited reporting, an Investigational New Drug (IND) Safety Report will be prepared for submission to the Food and Drug Administration (FDA).

12.4. Pregnancy

All pregnancies occurring during the study (after exposure to study drug) or within 28 days after discontinuation of study drug must be followed until resolution (ie, birth or voluntary or spontaneous termination of the pregnancy) and reported within 24 hours of the site's awareness to Tonix and/or its designee. Any patient found to be pregnant at any time during the study will be withdrawn from the study immediately. Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

13. STATISTICS

A full description of the statistical analyses to be performed at study completion will be provided in a Statistical Analysis Plan (SAP) prior to unblinding.

Baseline (Visit 2) will be defined as those values recorded closest to, but prior to administration of the first dose of study drug.

Unless otherwise noted, significance tests of treatment differences will be tested at the two-sided 0.05 level.

13.1. Populations for Analysis

The following populations will be defined for use in analyzing the efficacy and safety data in the study (see SAP for more details):

- Safety Population (SAFETY): All patients who receive at least 1 dose of the investigational product. All safety analyses and demographic/baseline characterization will be performed using this population, analyzed as treated.
- Intention-to-Treat Population (ITT): All randomized patients who receive at least 1 dose of the investigational product. This is the primary population for efficacy analyses and patients will be analyzed based on their randomized treatment.

13.2. Estimate of Sample Size

The sample size will be approximately 300 patients with MDD. [redacted]

13.3. Assessment of Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, weight, BMI, education, employment status, and smoking history will be summarized by treatment group (TNX-601 ER and placebo) and overall using descriptive statistics.

Medical History will be coded using MedDRA and summarized by SOC and Preferred Term using frequency counts by treatment group.

13.4. Efficacy Analysis

13.4.1. Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint will be the change from baseline in the MADRS total score at Week 6.

Key Secondary Efficacy Endpoints: The efficacy endpoints listed below are considered key secondary endpoints.

- Change from Baseline (Visit 2) in the CGI-S score at Week 6
- Change from Baseline (Visit 2) in the SDS total score at Week 6

Exploratory Endpoints:

- Proportion of patients achieving response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score, assessed at Weeks 2, 4, and 6
- Proportion of patients in remission, defined as a MADRS total score <=10 at Weeks 2,4, and 6
- Proportion of patients achieving sustained response, defined as a ≥50% decrease from Baseline (Visit 2) in MADRS total score at Weeks 4 and 6
-
- Proportion of patients with a CGI-I rating of "very much improved" or "much improved" at Weeks 2, 4, and 6
- Mean CGI-I score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) in PGIS score at Weeks 2, 4, and 6
- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at Weeks 2, 4, and 6
- Mean PGIC score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) to Week 6 in the CSFQ-14 total score in females and in males (analyzed separately)
- Change from Baseline (Visit 2) in the MADRS total score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the CGI-S score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the SDS total score at Week 2 and Week 4
- Change from Baseline (Visit 2) in the HARS total score at Weeks 2, 4, and 6
- Change from Baseline (Visit 2) in each of the 3 domains (work/school; social life; home life or family responsibilities) using the SDS at Weeks 2, 4, and 6
- Proportion of patients with a CGI-S rating of "normal, not at all ill" or "borderline mentally ill" at Weeks 2, 4, and 6
- Proportion of patients with a PGIS rating of "not present", "very mild", or "mild" at Weeks 2, 4, and 6

13.4.2. Primary Efficacy Estimand

Population

The analysis population will be ITT patients with MDD as defined by the protocol inclusion/exclusion criteria.

Variable

The primary endpoint will be the change from Baseline (Visit 2) to Week 6 in the MADRS total score.

Intercurrent Events

Concomitant medications and all other intercurrent events other than discontinuation will use a treatment policy strategy; data will be analyzed as observed. A hypothetical strategy will be employed to handle intermittent missing data and discontinuation. Missing data will be imputed via MI, and details regarding the MI approach will be described in the SAP.

Population-Level Summary

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 6.

The primary efficacy analysis will use a mixed model repeated measures (MMRM) approach to estimate mean change from baseline to Week 6 in the MADRS total score visit in the TNX-601 ER and placebo arms. The model will include all patients in the ITT population, and the dependent variable will be the observed change from baseline in the MADRS total score at each post-randomization in-clinic visit. Covariates in the model will include the fixed categorical effects of treatment, site, visit, and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. Missing data will be imputed via MI, and details regarding the MI approach will be described in the SAP.

The primary analysis will be followed by several sensitivity analyses. Further details on sensitivity analyses can be found in the SAP.

13.4.3. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will apply estimands parallel with the primary estimand, adjusted for the endpoint in question, but with identical populations and handling of intercurrent events. MMRM methodology will be utilized for the continuous secondary endpoints, and analyses will be based on the ITT population. The dependent variable will be the observed change from baseline in the respective secondary endpoint at each post-randomization visit. Covariates in the model will include the fixed categorical effects of treatment, site, visit, and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction.

To adjust for multiplicity and to control for overall type I error, a sequential test procedure will be applied to the key secondary efficacy endpoints. If the primary analysis produces a result that is statistically significant, a nominal significance level will be used for comparing the secondary endpoints in an ordered fashion. If the analysis for a secondary endpoint does not produce a statistically significant result, then the remaining secondary endpoint analyses will automatically be considered non-significant regardless of the p-value produced. In the case of an increase in sample size, the same methodology/critical value used for the primary endpoint will be applied to the key secondary endpoints for the purposes of the sequential testing. The order in which the secondary endpoints are to be tested will be specified in the SAP.

No other adjustments for multiplicity will be made and other p-values displayed in the output will be considered for descriptive summary purposes only and will not be used for formal

inference. Full details regarding the statistical analyses for the listed endpoints will be provided in the SAP.

13.4.4. Exploratory Analyses

Exploratory efficacy analyses will be based on the ITT population. Details on exploratory efficacy analyses can be found in the SAP.

13.5. Safety Analyses

Safety analyses will be performed using the Safety Population. Safety and tolerability will be assessed by:

- Incidence of AEs and SAEs throughout the entire duration of the study
- Incidence of AEs associated with abuse liability using the MADDERS®
- Assessment of physical examination findings
- Changes from baseline (Visit 2) in ECG results
- Changes from baseline (Visit 2) in clinical laboratory test results
- Changes from baseline (Visit 2) in vital signs and weight
- Indications of increased suicidal ideation or behavior as assessed by the C-SSRS
- Changes from baseline (Visit 2) in patient-rated CSFQ-14 in males and in females, assessed separately
- Change from baseline Visit 5 or End of Treatment) in the SOWS at the safety follow-up visit

Adverse events will be coded using MedDRA and will be summarized overall and by preferred term and system organ class. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from baseline for responses on the CSFQ-14, and actual values and changes from baseline in clinical laboratory test results, ECG parameters, vital signs, and weight will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). AEs associated with abuse liability of the study drug will be evaluated using the MADDERS®. Withdrawal symptoms associated with the study drug after the End of Treatment (Visit 5/ET) will be evaluated using the SOWS.

The number of patients with suicidal behaviors, ideations and acts based on the C-SSRS will be tabulated by treatment group and listed. Physical examination data will be presented in data listings.

13.6. Interim Analyses

An interim analysis will be performed once approximately 50% of the planned patients have enrolled and those patients have either completed the study or discontinued early. The purpose of the interim will be to evaluate the study for futility and potentially increase the sample size to maintain statistical power conditioned on the results of the first 50% of patients. The study team

will only be informed of the recommendation to halt the study for futility, maintain the original sample size, or to increase the sample size (by a fixed, pre-specified amount). All recommendations by the statistical review committee are non-binding.

For the primary and key secondary outcomes, the results from before and after the interim will be combined with Cui, Hung, Wang (CHW) methodology (Cui, 1999). Full details of the interim analysis procedure and steps to maintain treatment blinding of the study team will be described in the SAP and the Interim Analysis Charter and finalized prior to execution of the interim analysis.

14. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

14.1. Protocol Modifications and Deviations

The Investigator will make all reasonable efforts to comply with the written protocol and protocol amendments. All protocol modifications must be reviewed and approved by the appropriate ethics committee (EC)/Institutional Review Board (IRB) before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to patients do not require preapproval by the EC/IRB. However, the EC/IRB must be notified, in writing, as soon as possible after the modification has been made. A copy of this communication must be forwarded to Tonix.

14.2. Study Termination

The study may be prematurely terminated at any time at the discretion of Tonix, its designee, or the Principal Investigator. Should premature termination be considered necessary, written notification documenting the reason for study termination will be provided, and specific procedures for termination will be arranged. Circumstances that may warrant premature study termination include, but are not limited to, the following.

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to the requirements of the protocol
- Insufficient provision of complete and evaluable data
- Plans to modify, suspend, or discontinue development of the study drug

In the event that the study is terminated prematurely, all study materials must be returned to Tonix or its designee.

15. ETHICAL CONSIDERATIONS

15.1. Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (World Medical Association, 2013) and amendments and clarifications adopted by subsequent General Assemblies. The Investigator will make sure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, International Council on Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (CFR title 21), any EC requirements relative to clinical studies. As required by the United States Food and Drug Administration (FDA), the study drug may not be shipped to any participating Investigator until the requisite study documentation has been submitted an investigational new drug (IND) application.

Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual patient. The Investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

15.2. Ethics Committee/Institutional Review Board (EC/IRB) Review

The EC/IRB must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "IRBs." This protocol, any protocol amendments, the associated ICFs, and the informed consent procedures must be submitted to the EC/IRB for review and approved before the enrollment of any patient into the trial.

All types of patient recruitment or advertising information must be submitted to Tonix or its designee and to the EC/IRB for review and approval prior to implementation. EC/IRB approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study patients. In such cases, the chair of the EC/IRB should be notified immediately, and the amendment forwarded to the EC/IRB for review and approval.

15.3. Written Informed Consent

It is the responsibility of the Investigator to obtain signed written informed consent from each potential study patient prior to the conduct of any screening or other study procedures. This written informed consent will be obtained after the methods, objectives, and potential risks of the study have been fully explained to the potential patient. The Investigator must explain to each patient that he or she is completely free to refuse to enter the study or to withdraw from it at any time.

The patient should also be asked in the ICF for permission for the Principal Investigator or their designee to contact the patient's other personal physicians, as appropriate, concerning participation in the study.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Patients," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. A properly executed written ICF shall be read, signed, and dated by each patient prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept on file at the study site. Patients will be given a copy of the signed ICF and will be informed of any new developments during the course of the study that might influence their continued participation in the study.

The Investigator or a qualified designee will be available to answer each patient's questions throughout the study, and all questions must be answered to the patient's satisfaction. If the protocol is amended and a revised ICF is introduced during the study, each patient's further consent must be obtained. The new version of the ICF must be approved by the EC, prior to subsequently obtaining each patient's consent.

Receipt of written informed consent will be documented in each patient's or potential patient's CRF. The signed ICF must remain in each patient's study file and must be available for verification by study monitors at all times.

Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment.

16. DATA HANDLING AND RECORDING KEEPING

16.1. Maintaining Privacy and Confidentiality

In order to maintain patient privacy, all CRFs, study drug accountability records, and other documents, including communications between the study site and Tonix, will identify patients only by their initials or their assigned study identification numbers. If required, the Investigator will grant monitors and auditors from Tonix or its designee and/or regulatory authority's access to patients' original medical records for verification of the data gathered on the CRFs and to audit the data collection process. Patients' confidentiality will be maintained and will not be made publicly available.

16.2. Maintaining Essential Clinical Documents

Study site files for the retention of regulatory documents will be established at the beginning of the study, maintained for the duration of the study, and retained according to FDA and ICH/GCP guidelines and applicable regulatory requirements. The records maintained must be adequate to fully document appropriate protection of study patients/patients, the validity of the study, the integrity of the data, and the manner in which the study was conducted.

The Investigator's site file, copies of protocols, CRFs, originals of test result reports, drug disposition logs, correspondence, records of written informed consent, and other documents pertaining to the conduct of the study must be kept on file by the Investigator and in readily accessible order for at least 2 years after the last approval of a marketing application, until at least 2 years have elapsed after formal discontinuation of the clinical development of the investigational product, or according to local regulatory requirements. No study document may

be destroyed without prior written consent from Tonix or its designee. Should the Investigator wish to withdraw from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Tonix must be notified in writing in advance if a custodial change is to occur. It is important that the Investigator remain ready to provide background information from the archived study records on request.

The sponsor or designee will maintain adequate study records for at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. After that period, the sponsor will be contacted to determine whether the study records will be forwarded to the sponsor, destroyed, or kept at the location of the designee or another facility for a longer period of time.

16.3. Data Handling

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the Standard Operating Procedures (SOPs) of the contract research organization (CRO). The Investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data. All data will be verified for quality control and will also be subject to audits from Tonix or designee to ensure quality.

All laboratory results will be analyzed by an accredited and licensed clinical laboratory facility. Clinical laboratory data will be transferred from the central laboratory to the clinical database maintained by the CRO using systems which are validated and Part 11-compliant.

The responsible clinical study monitor(s) will check data at the monitoring visits to the clinical study site. The Investigator will ensure that the data collected are accurate, complete, and legible. Any changes made to the clinical data will be documented with a full audit trail.

Aspects of the clinical and statistical phases of the study, including all associated documentation may be reviewed by the Quality Assurance Unit of the CRO using a risk-assessment approach. The final clinical and statistical report will be audited to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.

16.4. Case Report Forms (CRFs)

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Data must be recorded on CRFs approved by Tonix or its designee. Data (including AEs) will be recorded on raw data sheets and/or electronic or paper source documents.

If selected data is collected via paper (patient questionnaires, etc.), the data must be entered into the electronic case report form (eCRF) and verified that it has been transcribed correctly.

16.5. Screening Records

A record generated by IWRS must be kept of all patients considered for the study who sign informed consent and who began any screening procedures. The information should include the patient’s sex at birth, age at Screening (Visit 1), and unique patient identification numbers, whether they passed or failed screening, and, if they failed, the reason for SF.

16.6. Clinical Laboratory Certification

A central clinical laboratory will be used to analyze all samples in this study, with the exception of the urine pregnancy test and ad hoc urine drug screens. The Investigator must maintain, on file, written evidence that the central clinical laboratory to be used is certified under the Clinical Laboratory Improvement Act or equivalent certification (depending on local regulations). Further, the Investigator will maintain a copy of the certification, the range of normal values, the effective dates for the ranges, and the units of measurement for all laboratory tests requested in the protocol. If any of the laboratory measurements will be transformed and/or categorized in any way, a description of the procedures(s) used should be included. The Investigator is expected to receive these documents before the shipment of clinical supplies.

16.7. Site Monitoring and Tonix's Right to Review Records

Monitoring and auditing procedures developed by Tonix and/or its designee will be implemented to ensure compliance with FDA and ICH GCP and GLP guidelines.

Tonix's designated representative (the monitor or auditor) will contact the Investigator and conduct regular visits to the clinical site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of EC/IRB review, with the stipulation that patient confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other patient records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The monitor/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and difficulties detected by the monitor.

16.8. Audits and Inspections

The Investigator understands that regulatory authorities, the EC/IRB, and/or Tonix or their designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

17. CONFIDENTIALITY

17.1. Protection of Patient Anonymity

The Investigator must make sure that each patient's anonymity is maintained. On CRFs or other documents submitted to Tonix or its agent, patient should not be identified by their names or initials, but only by their sex at birth and age at Screening (Visit 1), and the assigned study identification numbers. The Investigator should keep a separate record of the patient initials, names, address, and contact information. Documents that contain the names associated with these initials and codes are not for submission to Tonix or its agents (eg, written ICFs). These records should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, Tonix, or its agents. These records should be kept in compliance with HIPAA regulations.

17.2. Confidentiality of Study Information

All information relevant to this study, whether supplied by Tonix or its agents to the Investigator or collected by the Investigator in support of this study, is privileged and confidential. The Investigator agrees to use this information to carry out the study and will not use it for other purposes without written consent from Tonix. It is understood that the Investigator is under obligation to provide Tonix with all data obtained during the study. The information obtained from this study will be used by Tonix towards the clinical development of the indicated investigational drug and may be disclosed by Tonix to regulatory authorities, other Investigators, corporate partners, or consultants as required.

17.3. Publication of Data and Protection of Trade Secrets

No presentations, abstracts (including meeting abstracts), or other publications based on the conduct or results of this study will be permitted without the express written permission of Tonix or its designated agent. All such presentations or publications will proceed only as collaborations between Tonix and the Investigators.

If the Investigator wishes to publish the results of this study, a copy of the proposed manuscript or abstract (including meeting abstracts) will be provided to Tonix or its designee for review, revision, and approval at least 60 days before the expected date of submission for publication, unless otherwise arranged with Tonix in writing. This will enable Tonix to protect its proprietary information and augment the publication with insights or information of which the Investigator may not be aware.

Patient names and other identifiers, such as photographs or audio or video recordings, may not be disclosed in any publication or public forum without prior written authorization from the patients involved or their legal guardians. Tonix retains authority to delete any of its confidential information from such disclosures.

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19. APPENDICES

APPENDIX 1 – STABLON SUMMARY OF PRODUCT CHARACTERISTICS (MARCH 2018)

1 Stablon Summary of Product Characteristics (Original)

1. DENOMINATION DU MEDICAMENT

STABLON 12,5 mg, comprimé enrobé.

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Tianeptine (sel de sodium) 12,5 mg

Pour un comprimé enrobé.

Excipients à effet notoire : saccharose.

Pour la liste complète des excipients, voir rubrique 6.1.

3. FORME PHARMACEUTIQUE

Comprimé enrobé.

4. DONNEES CLINIQUES

4.1. Indications thérapeutiques

Episodes dépressifs majeurs (c'est-à-dire caractérisés).

4.2. Posologie et mode d'administration

Posologie

La posologie recommandée est de 1 comprimé dosé à 12,5 mg trois fois par jour, matin, midi et soir, au début des principaux repas.

Populations particulières

Sujets âgés

L'efficacité et la sécurité de la tianeptine ont été établies chez les patients âgés dépressifs (≥ 65 ans) (voir rubrique 5.1). Aucune adaptation posologique en rapport avec l'âge n'est nécessaire.

Chez les patients âgés fragiles (< 55 kg), limiter la posologie à 2 comprimés par jour (voir rubrique 5.2).

Insuffisance rénale

Chez les patients insuffisants rénaux sévères (ClCr < 19ml/min), limiter la posologie à 2 comprimés par jour (voir rubrique 5.2).

Insuffisance hépatique

Chez les patients atteints de cirrhose sévère (Classe C, Score de Child Pugh), limiter la posologie à 2 comprimés par jour (voir rubrique 5.2).

Chez les patients alcooliques chroniques, qu'ils soient exempts de cirrhose ou atteints de cirrhose légère ou modérée, aucune adaptation posologique n'est nécessaire (voir rubrique 5.2).

Population pédiatrique

La sécurité et l'efficacité de la tianeptine chez les enfants et les adolescents de moins de 18 ans n'ont pas été établies. Aucune donnée n'est disponible (voir rubrique 4.4).

La tianeptine est contre-indiquée chez les enfants et adolescents de moins de 15 ans (voir rubrique 4.3).

Mode d'administration

Voie orale. Mentions légales complètes

4.3. Contre-indications

- Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1.
- Enfants et adolescents de moins de 15 ans.

4.4. Mises en garde spéciales et précautions d'emploi

Suicides/idées suicidaires ou aggravation clinique

La dépression est associée à un risque accru d'idées suicidaires, d'auto-agression et de suicide (comportement de type suicidaire). Ce risque persiste jusqu'à obtention d'une rémission significative. L'amélioration clinique pouvant ne pas survenir avant plusieurs semaines de traitement, les patients devront être surveillés étroitement jusqu'à obtention de cette amélioration. L'expérience clinique montre que le risque suicidaire peut augmenter en tout début de rétablissement.

Les patients ayant des antécédents de comportement de type suicidaire ou ceux exprimant des idées suicidaires significatives avant de débuter le traitement présentent un risque plus élevé de survenue d'idées suicidaires ou de comportements de type suicidaire, et doivent faire l'objet d'une surveillance étroite pendant le traitement. Une méta-analyse d'essais cliniques contrôlés versus placebo sur l'utilisation d'antidépresseurs chez l'adulte présentant des troubles psychiatriques a montré une augmentation du risque de comportement de type suicidaire chez les patients de moins de 25 ans traités par antidépresseurs par rapport à ceux recevant un placebo. Une surveillance étroite des patients, et en particulier de ceux à haut risque, devra accompagner le traitement médicamenteux, particulièrement au début du traitement et lors des changements de dose.

Les patients (et leur entourage) devront être avertis de la nécessité de surveiller la survenue d'une aggravation clinique, l'apparition d'idées/comportements suicidaires et tout changement anormal du comportement et de prendre immédiatement un avis médical si ces symptômes survenaient.

En cas d'anesthésie générale, il convient d'avertir l'anesthésiste réanimateur et d'arrêter le traitement 24 ou 48 heures avant l'intervention.

En cas d'urgence, l'intervention pourra être néanmoins réalisée sans interruption préalable, sous surveillance peropératoire.

Comme avec tout traitement psychotrope, la prise de ce médicament avec des boissons alcoolisées ou médicaments contenant de l'alcool est déconseillée.

A l'arrêt du traitement, il est recommandé, comme avec tous les psychotropes, de réduire la posologie pendant 7 à 14 jours.

En cas d'antécédents de pharmacodépendance ou de dépendance à l'alcool, les malades doivent être surveillés tout particulièrement pour éviter l'augmentation de la posologie.

Ne pas dépasser les doses recommandées.

L'association avec les I.M.A.O. est déconseillée (voir rubrique 4.5). Il est nécessaire de laisser un intervalle libre :

- de deux semaines lorsque la tianeptine est utilisé en relais d'un I.M.A.O.,
- de 24 heures lorsque un I.M.A.O. est utilisé en relais de la tianeptine.

Ce médicament contient du saccharose. Son utilisation est déconseillée chez les patients présentant une intolérance au fructose, un syndrome de malabsorption du glucose et du galactose ou un déficit en sucrase-isomaltase (maladies héréditaires rares).

Teneur en sodium

STABLON contient moins de 1 mmol de sodium (23 mg) par comprimé enrobé et peut donc être considéré comme dépourvu de sodium. Mentions légales complètes

Population pédiatrique

STABLON est contre-indiqué chez les enfants et adolescents de moins de 15 ans (voir rubrique 4.3) et ne devrait pas être utilisé chez les adolescents âgés de 15 à 18 ans. Des comportements de type suicidaire (tentatives de suicide et idées suicidaires) et de type hostile (principalement agressivité, comportement d'opposition et colère) ont été plus fréquemment observés au cours des études cliniques chez les enfants et adolescents traités par antidépresseurs par rapport à ceux traités par placebo. Si, en cas de nécessité clinique, la décision de traiter est néanmoins prise, le patient devra faire l'objet d'une surveillance attentive pour détecter l'apparition de symptômes suicidaires. De plus, il n'y a pas de données de tolérance à long terme chez l'enfant et l'adolescent, concernant les effets sur la croissance, la maturation sexuelle, et le développement cognitif et comportemental.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

Associations déconseillées

- **I.M.A.O irréversibles (iproniazide) :** en raison des risques de collapsus ou hypertension paroxystique, hyperthermie, convulsions, décès.

4.6. Fertilité, grossesse et allaitement

Grossesse

Dans une étude péri- et post-natale, une augmentation des pertes post-implantatoires et post-natales ont été observées chez les rats à dose maternotoxique (voir rubrique 5.3).

Il n'existe pas de données ou il existe des données limitées (moins de 300 grossesses) sur l'utilisation de la tianeptine chez la femme enceinte.

Pour cette raison, il est préférable d'éviter d'utiliser la tianeptine au cours de la grossesse quel qu'en soit le terme.

Le maintien d'un bon équilibre psychique maternel est souhaitable tout au long de la grossesse. Si une prise en charge médicamenteuse par tianeptine est nécessaire pour assurer cet équilibre, le traitement doit être initié ou poursuivi à dose efficace tout au long de la grossesse et si possible en monothérapie et le profil pharmacologique de la molécule doit être pris en compte lors de la surveillance du nouveau-né.

Allaitement

Une dysfonction de la sécrétion lactique a été observée chez le rat à dose maternotoxique (voir rubrique 5.3).

Les antidépresseurs tricycliques sont excrétés dans le lait maternel, l'allaitement est donc déconseillé pendant la durée du traitement.

Fertilité

Chez le rat, une étude a montré une diminution des performances reproductives (augmentation des pertes pré-implantatoires), à dose maternotoxique. (voir rubrique 5.3).

L'impact clinique n'est pas connu.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Chez certains patients une baisse de la vigilance est susceptible de se manifester. L'attention est donc attirée sur les risques de somnolence attachés à l'emploi de ce médicament notamment chez les conducteurs de véhicules et les utilisateurs de machines.

4.8. Effets indésirables

Résumé du profil de sécurité :

Les effets indésirables constatés avec la tianeptine au cours des essais cliniques sont d'intensité modérée. Ils consistent principalement en des nausées, constipation, douleurs abdominales, somnolence, céphalées, bouche sèche et vertiges. Mentions légales complètes

Tableau des effets indésirables

Les effets indésirables suivants ont été observés lors des essais cliniques et/ou de l'utilisation post-AMM de la tianeptine et sont classés en fonction de leur fréquence :

Très fréquent (>1/10); fréquent (>1/100, <1/10); peu fréquent (>1/1000, <1/100); rare (>1/10000, <1/1000); très rare (<1/10000), indéterminée (ne pouvant être estimée à partir des données disponibles).

Système Organe-Classe (SOC)	Fréquence	Effets indésirables
	Fréquent	Anorexie

Système Organe-Classe (SOC)	**Fréquence**	**Effets indésirables**
Troubles du métabolisme et de la nutrition	Indéterminée*	Hyponatrémie
Affections psychiatriques	Fréquent	Cauchemars
	Peu fréquent	Abus, dépendance, en particulier chez les sujets de moins de 50 ans ayant des antécédents de pharmacodépendance ou de dépendance à l'alcool
	Indéterminée*	Des cas d'idées et de comportements suicidaires ont été rapportés durant le traitement avec la tianeptine ou peu après son arrêt (voir rubrique 4.4.) Etat confusionnel, hallucinations
Affections du système nerveux	Fréquent	Insomnie Somnolence Sensations vertigineuses Céphalées Présyncope Tremblements
	Indéterminée*	Troubles extrapyramidaux Dyskinésie
Affections cardiaques	Fréquent	Tachycardie Extrasystoles Douleur thoracique
Affections vasculaires	Fréquent	Bouffées de chaleur
Affections respiratoires, thoraciques et médiastinales	Fréquent	Dyspnée
Affections gastro-intestinales	Fréquent	Gastralgies Douleurs abdominals Bouche sèche Nausées Vomissements Constipation Flatulences
Affections de la peau et du tissu sous cutané	Peu fréquent	Eruption maculo-papuleuse ou érythémateuse Prurit

Système Organe-Classe (SOC)	Fréquence	Effets indésirables
		Urticaire
	Indéterminée*	Acné Réactions bulleuses exceptionnelles
Affections musculo-squelettiques et systémiques	Fréquent	Myalgie Lombalgies
Troubles généraux et anomalies au site d'administration	Fréquent	Asthénie Sensation de gêne au niveau de la gorge
Affections hépato-biliaires	Indéterminée*	Augmentation des enzymes hépatiques Hépatites pouvant être exceptionnellement sévères

**Données post-commercialisation*

Déclaration des effets indésirables suspectés

La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : www.ansm.sante.fr.

4.9. Surdosage

Symptômes

L'expérience relative aux cas d'intoxication aiguë par la tianeptine (quantité maximale: 2250mg, ingérée en une seule prise) met principalement en évidence des troubles de la vigilance pouvant aller jusqu'au coma, particulièrement en cas d'intoxications multiples.

Conduite à tenir

La tianeptine n'a aucun antidote spécifique connu. En cas d'intoxication aiguë, un traitement symptomatique et une surveillance de routine doivent être mis en place. Un suivi médical en milieu spécialisé est recommandé.

5. PROPRIETES PHARMACOLOGIQUES

5.1. Propriétés pharmacodynamiques

Classe pharmacothérapeutique : AUTRES ANTI-DEPRESSEURS, code ATC : N06AX14.
Mécanisme d'action

La tianeptine est un antidépresseur :

Chez l'animal, la tianeptine possède les caractéristiques suivantes :

- la tianeptine augmente l'activité spontanée des cellules pyramidales de l'hippocampe et en accélère la récupération après leur inhibition fonctionnelle,

- la tianeptine augmente le taux de recapture de la sérotonine par les neurones du cortex et de l'hippocampe.

In vitro, la tianeptine n'a pas d'affinité pour les récepteurs monoaminergiques et n'inhibe pas la recapture de la sérotonine (5-HT), de la noradrénaline (NA) ou de la dopamine (DA). La tianeptine peut moduler la neuro-transmission glutamatergique synaptique. Mentions légales complètes

La contribution précise de chaque effet à l'activité antidépressive est inconnue.

Efficacité et sécurité clinique

Quatre essais en double aveugle, contrôlés, versus placebo, ont été réalisés pour évaluer l'efficacité à court terme de la tianeptine dans le traitement des épisodes dépressifs majeurs chez l'adulte : un à doses fixes (37,5 mg, 75 mg), deux avec possibilité d'adaptation posologique à une dose supérieure ou inférieure (dose initiale 37,5 mg, puis 25, 37,5 ou 50 mg) et un chez le patient âgé (311 patients âgés de 65 ans et plus ; ~100 patients par bras, incluant ~20 patients de plus de 75 ans dans chaque bras) avec possibilité d'adaptation posologique à une dose supérieure en fonction de l'amélioration après 2 semaines de traitement (dose initiale 25 mg puis 25 mg ou 50 mg). Dans les essais chez l'adulte, le critère principal a été l'évolution du score total MADRS par rapport au score initial pour les essais à dose fixe ou flexible.

A la fin du traitement (6 semaines), l'efficacité de la tianeptine était significative dans les deux essais à doses flexibles mais pas dans l'essai à doses fixes. Dans un essai, l'imipramine, utilisée comme comparateur actif, a permis de démontrer la sensibilité de l'essai.

Dans l'étude réalisée chez le sujet âgé (étude avec possibilité d'augmenter la posologie), après 8 semaines de traitement, une efficacité significative de la tianeptine a été démontrée sur le critère principal (évolution du score total HAMD par rapport au score initial). Dans cette étude, l'escitalopram utilisé comme comparateur actif, a permis de démontrer la sensibilité de l'essai.

Le maintien de l'efficacité antidépressive a été évalué dans un essai de prévention des rechutes et des récidives. Les patients considérés comme répondeurs au traitement par l'investigateur (6 semaines de traitement « en ouvert » avec la tianeptine à la posologie journalière de 2 à 4 comprimés soit 25 à 50mg par jour) ont été randomisés à tianeptine ou placebo pour une durée supplémentaire de 16,5 mois. La tianeptine a montré une supériorité d'efficacité statistiquement significative par rapport au placebo ($p < 0,001$) sur le critère principal de l'essai : la prévention des rechutes ou des récidives mesurée par le délai d'apparition de celles-ci. L'incidence des rechutes après 6 mois de suivi en double aveugle a été de 6% pour la tianeptine et de 22% pour le placebo. L'incidence des rechutes ou des récidives après 18 mois de suivi en double aveugle a été de 16% pour la tianeptine et 36% pour le placebo.

5.2. Propriétés pharmacocinétiques

Absorption

L'absorption gastro-intestinale est rapide et complète.

Distribution

La distribution est rapide et est associée à une fixation protéique proche de 94 %, principalement à l'albumine.

Biotransformation

La tianeptine est fortement métabolisée par le foie, principalement par bêta-oxydation, sans implication des CYP450. Son métabolite principal, l'acide pentanoïque (MC5), est actif et moins puissant que la tianeptine.

Élimination

L'élimination de la tianeptine est caractérisée par une demi-vie terminale courte de 3 h avec la plupart des métabolites excrétés dans les urines.

Patients âgés, très âgés et patients fragiles

Chez les patients âgés, les concentrations plasmatiques de tianeptine ont été augmentées de 30% et celles de MC5 ont été environ doublées après administration unique ou répétée, en comparaison de celles de patients plus jeunes (voir rubrique 4.2).

Chez les patients très âgés (87 ± 5 ans) ou fragiles (45 ± 9 kg), une augmentation significative du Cmax et de l'exposition (aire sous la courbe, ASC) à la tianeptine et au MC5 a été observée après administration unique (voir rubrique 4.2).

Patients insuffisants rénaux sévères (CLCR < 19ml/min)

La pharmacocinétique de la tianeptine reste inchangée mais l'exposition au MC5 est approximativement doublée après administration unique et répétée (voir rubrique 4.2).

Patients atteints de cirrhose hépatique sévère (Classe C, Score de Child-Pugh)

Les expositions à la tianeptine et au MC5, après l'administration d'une dose de 12,5mg, sont augmentées par rapport à celles de patients adultes dépressifs (voir rubrique 4.2).

En cas de cirrhose plus légère, comme les alcooliques chroniques, les effets sur les paramètres pharmacocinétiques sont négligeables (voir section 4.2).

5.3. Données de sécurité préclinique

Les données non cliniques issues des études conventionnelles de génotoxicité et de cancérogenèse n'ont pas révélé de risque particulier pour l'homme.

Dans l'étude de fertilité, une augmentation des pertes pré-implantatoires a été observée à la dose maternotoxique de 45 mg/kg/jour (soit 12 fois la dose humaine déterminée selon la surface corporelle).

La tianeptine n'est pas tératogène chez les rats et les lapins.

Dans l'étude péri- et post-natale, une dysfonction de la sécrétion lactique et une augmentation des pertes post-implantatoires et post-natales ont été observées chez les rats à la dose maternotoxique de 45 mg/kg/jour (soit 12 fois la dose humaine déterminée selon la surface corporelle).

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Mannitol, amidon de maïs, talc, stéarate de magnésium.

Enrobage: éthylcellulose, mono-oléate de glycerol, SEPIFILM SE 700 Blanc (polyvidone, carmellose sodique, silice colloïdale anhydre, talc, saccharose, polysorbate 80, dioxyde de titane, bicarbonate de sodium), cire d'abeille blanche.

6.2. Incompatibilités

Sans objet.

6.3. Durée de conservation

36 mois.

6.4. Précautions particulières de conservation

Pas de précautions particulières de conservation (zones climatiques I et II).

A conserver à une température ne dépassant pas 30°C (zones climatiques III et IV).

6.5. Nature et contenu de l'emballage extérieur

28 ou 100 comprimés sous plaquettes thermoformées (Aluminium/P.V.C.) (zones climatiques I et II).

28 ou 100 comprimés sous plaquettes thermoformées (Aluminium/P.V.C.) suremballées en sachet (zones climatiques III et IV).

6.6. Précautions particulières d'élimination et de manipulation

Pas d'exigences particulières.

7. TITULAIRE/EXPLOITANT DE L'AUTORISATION DE MISE SUR LE MARCHE

LES LABORATOIRES SERVIER

50 RUE CARNOT

92284 SURESNES

FRANCE

8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE

- 34009 267 223 5 7 : 28 comprimés sous plaquettes (Aluminium/P.V.C.)
- 34009 558 336.0 4 : 100 comprimés sous plaquettes (Aluminium/P.V.C.)
- 34009 267 224 1 8 :28 comprimés sous plaquettes (Aluminium/P.V.C.) suremballées en sachet
- 34009 579 827 3 7 : 100 comprimés sous plaquettes (Aluminium/P.V.C.) suremballées en sachet.

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

AMM validée en date du 06/02/1987.

Renouvellement en date du 06/02/2012.

Version 2.0, 02 March 2023

10. DATE DE MISE A JOUR DU TEXTE

Mars 2018

11. CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I.

Durée de prescription limitée à 28 jours.

Prescription en toutes lettres sur ordonnance sécurisée.

Chevauchement interdit sauf mention expresse du prescripteur portée sur l'ordonnance.

Conservation d'une copie de l'ordonnance par le pharmacien pendant 3 ans.

Boîte de 28 : Remboursé Sécurité sociale à 65%. Agréé Collectivités.

Boîte de 100 : Agréé Collectivités.

Prix (hors honoraire de dispensation) :

7,10 €

(Boîte de 28 comprimés sous plaquettes thermoformées (Aluminium/PVC).

CTJ : **0,51 € A 0,76 €.**

Au travers des engagements écrits de sa Direction, Servier s'inscrit dans une démarche Qualité d'amélioration continue de ses pratiques d'information par démarchage ou prospection visant à la promotion des médicaments conformément à la Charte signée par le LEEM et le CEPS et à son référentiel de certification émis par la Haute Autorité de Santé (HAS).

Le collaborateur qui vous a remis le présent document exerce ces missions dans le respect des règles de déontologie d'organisation des rencontres avec les professionnels de santé qu'il est à même de vous présenter. Ces règles sont également à votre disposition sur notre site internet http://servier.fr rubrique « médicaments ».

Information Médicale et Pharmacovigilance : Servier Affaires Médicales - 35 rue de Verdun, 92284 Suresnes Cedex- Tel. 01 55 72 60 00

Appréciation de la qualité des pratiques d'information promotionnelle de nos délégués médicaux : qualiteVM@servier.com

Dans le cadre des activités d'information par démarchage ou prospection visant à la promotion des médicaments LES LABORATOIRES SERVIER, situés au 50 rue Carnot, 92284 Suresnes cedex, sont amenés à recueillir des données à caractère personnel vous concernant. En application des articles 38 et suivants de la loi n° 78-17 du 6 janvier 1978 modifiée, vous pouvez demander à accéder, rectifier ou vous opposer au traitement

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2 Stablon Summary of Product Characteristics (English Translation)

1. NAME OF THE MEDICINAL PRODUCT

STABLON 12.5 mg coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tianeptine (sodium salt) 12.5 mg

Per coated tablet.

Excipients with a known effect: sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Major depressive episodes.

4.2. Posology and method of administration

Posology

The recommended posology is 1 tablet (12.5 mg) three times a day, morning, noon and evening, before main meals.

Special populations

Elderly patients

The efficacy and safety of tianeptine have not been established in elderly patients (>65 years) with depression (see section 5.1). No age-related dose adjustment is required.

In fragile elderly patients (<55 kg), limit the dose to 2 tablets a day (see section 5.2).

Renal impairment

In patients with severe renal impairment (CrCl <19 ml/min), limit the dose to 2 tablets a day (see section 5.2).

Hepatic impairment

In patients with severe cirrhosis (Child Pugh score Class C), limit the dose to 2 tablets a day (see section 5.2).

In patients with chronic alcoholism, whether they do not have cirrhosis or have mild or moderate cirrhosis, no dose adjustment is necessary (see section 5.2).

Paediatric population

The safety and efficacy of tianeptine have not been established in children and adolescents under 18 years of age. No data are available (see section 4.4).

Tianeptine is contraindicated in children and adolescents under 15 years of age (see section 4.3).

Method of administration

Oral use.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Children and adolescents under 15 years of age.

4.4. Special warnings and precautions for use

Suicide/suicidal ideation or clinical worsening

Depression is associated with an increased risk of suicidal ideation, self-harm and suicide (suicidal behaviour). This risk persists until significant remission is obtained. As clinical improvement may not be obtained until after several weeks of treatment, patients should be closely monitored until this improvement is achieved. Clinical experience shows that suicide risk may increase in the very early stages of recovery.

Patients with a history of suicidal behaviour or those expressing significant suicidal thoughts prior to treatment present a higher risk of suicidal ideation or suicidal behaviour and should therefore be monitored closely during treatment. A meta-analysis of placebo-controlled clinical trials of the use of antidepressants in adults with psychiatric disorders has shown an increased risk of suicidal behaviour in patients under 25 years of age treated with antidepressants compared to those receiving placebo. Close monitoring of patients, particularly those at high risk, should accompany medication, particularly at the start of treatment and when adjusting the dose.

Patients (and their friends and family) should be advised to monitor for clinical worsening, the onset of suicidal ideation/behaviour and abnormal changes in behaviour and to seek medical advice immediately if these symptoms occur.

If the patient requires general anaesthesia, the anaesthetist should be informed and the treatment should be withdrawn 24 or 48 hours before the procedure.

In the event of an emergency, the procedure may however be carried out without prior washout, under intraoperative monitoring.

As with any psychotropic treatment, taking this medicinal product with alcoholic beverages or medicinal products containing alcohol is not recommended.

When discontinuing the treatment, as with all psychotropic medicinal products, it is recommended to reduce the dose over 7 to 14 days.

Patients with a history of drug dependence or alcohol dependence should be monitored particularly closely in order to prevent an increase in the posology.

Do not exceed the recommended doses.

Treatment in combination with MAOIs is not recommended (see section 4.5). It is necessary to leave a washout period:

- of two weeks when switching from an MAOI to tianeptine,
- of 24 hours when switching from tianeptine to an MAOI.

This medicine contains sucrose. Use in patients with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency (rare hereditary disorders) is not recommended.

Sodium content

STABLON contains less than 1 mmol sodium (23 mg) per coated tablet and can therefore be considered sodium-free.

Paediatric population

STABLON is contraindicated in children and adolescents under 15 years of age (see section 4.3) and should not be used in adolescents aged 15 to 18 years. Suicidal behaviour (attempted suicide and suicidal ideation) and hostility (primarily aggression, oppositional behaviour and anger) have been more frequently observed in clinical studies in children and adolescents treated with antidepressants compared to those treated with placebo. If clinical circumstances lead to treatment being initiated, the patient should be carefully monitored for the onset of suicidal symptoms. In addition, there are no long-term safety data in children and adolescents regarding effects on growth, sexual maturity and cognitive and behavioural development.

4.5. Interactions with other medicinal products and other forms of interaction

Combinations to avoid

- **Irreversible MAOIs (iproniazid):** due to the risk of collapse or paroxysmal hypertension, hyperthermia, convulsions and death.

4.6. Fertility, pregnancy and lactation

Pregnancy

In a peri- and postnatal study, an increase in postimplantation and postnatal loss was observed in rats at maternally toxic doses (see section 5.3).

There are no data or limited data (fewer than 300 pregnancies) on the use of tianeptine in pregnant women.

It is therefore preferable to avoid using tianeptine in pregnancy whatever the term.

Maintaining good maternal psychological stability is desirable throughout pregnancy. If pharmaceutical management with tianeptine is necessary to ensure this stability, the treatment must be initiated or continued at an effective dose throughout pregnancy and if possible as monotherapy, and the pharmacological profile of the drug must be considered during neonatal monitoring.

Breastfeeding

Dysfunction in milk secretion has been observed in rats at maternally toxic doses (see section 5.3).

As tricyclic antidepressants are excreted into breast milk, breastfeeding is not recommended during treatment.

Fertility

In rats, a study has shown decreased reproductive performance (increased preimplantation loss) at a maternally toxic dose. (see section 5.3).

The clinical impact is unknown.

4.7. Effects on ability to drive and use machines

Some patients may experience decreased alertness. Attention is therefore drawn to the risks of somnolence associated with the use of this medicinal product, particularly for individuals driving vehicles and using machinery.

4.8. Undesirable effects

Summary of safety profile:

The undesirable effects observed with tianeptine during clinical trials are of moderate severity. They primarily consist of nausea, constipation, abdominal pain, somnolence, headaches, dry mouth and dizziness.

Table of side effects

The following side effects have been observed in clinical trials and/or post-marketing use of tianeptine and are listed according to their frequency:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class (SOC)	Frequency	Undesirable effects
Metabolism and nutrition disorders	Common	Anorexia
	Not known*	Hyponatraemia
Psychiatric disorders	Common	Nightmares
	Uncommon	Abuse, dependence, especially in individuals under 50 years of age with a history of alcohol dependence or drug dependence
	Not known*	Cases of suicidal ideation and suicidal behaviour have been reported during treatment with tianeptine or shortly after its discontinuation (see section 4.4).
		Confusional state, hallucinations
Nervous system disorders	Common	Insomnia
		Somnolence
		Dizziness
		Headache
		Presyncope
		Tremors
	Not known*	Extrapyramidal disorder

System Organ Class (SOC)	Frequency	Undesirable effects
		Dyskinesia
Cardiac disorders	Common	Tachycardia
		Extrasystoles
		Chest pain
Vascular disorders	Common	Hot flushes
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Gastralgia
		Abdominal pain
		Dry mouth
		Nausea
		Vomiting
		Constipation
		Flatulence
Skin and subcutaneous tissue disorders	Uncommon	Maculopapular or erythematous rash
		Pruritus
		Urticaria
	Not known*	Acne
		Dermatitis bullous in exceptional cases
Musculoskeletal and connective tissue disorders	Common	Myalgia
		Lower back pain
General disorders and administration site conditions	Common	Asthenia
		Lump in the throat sensation
Hepato-biliary disorders	Not known*	Increased liver enzymes
		Hepatitis that may be severe in exceptional cases

**Post-marketing data*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: Agence nationale de sécurité du médicament et des produits de santé (ANSM) and network of Regional Pharmacovigilance Centres - Website: www.ansm.sante.fr.

4.9. Overdose

Symptoms

Experience of cases of acute tianeptine poisoning (maximum quantity: 2,250 mg, taken in a single dose) has primarily shown impaired alertness that may develop into coma, particularly in cases of multiple poisoning.

Action to take

Tianeptine has no known specific antidote. In cases of acute poisoning, symptomatic treatment and routine monitoring should be initiated. Medical monitoring in a specialist setting is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANTI-DEPRESSANTS, ATC code: N06AX14.

Mechanism of action

Tianeptine is an antidepressant:

In animals, tianeptine has the following characteristics:

- tianeptine increases the spontaneous activity of pyramidal neurons in the hippocampus and speeds up their recovery after functional inhibition,
- tianeptine increases the rate of serotonin reuptake by neurons in the cerebral cortex and hippocampus.

In vitro, tianeptine has no affinity for monoamine receptors and does not inhibit the reuptake of serotonin (5-HT), noradrenaline (NA) or dopamine (DA). Tianeptine may modulate synaptic glutamate neurotransmission. The precise contribution of each effect to antidepressant activity is unknown.

Efficacy and clinical safety

Four double-blind, placebo-controlled trials were conducted to assess the short-term efficacy of tianeptine in the treatment of major depressive episodes in adults: one at fixed doses (37.5 mg, 75 mg), two with the ability to adapt to a higher or lower dose (starting dose 37.5 mg, then 25, 37.5 or 50 mg) and one in elderly patients (311 patients aged 65 years and over; ~100 patients per arm, including ~20 patients over 75 years of age in each arm) with the ability to increase the dose depending on improvement after 2 weeks of treatment (initial dose of 25 mg then 25 mg or 50 mg). In the clinical trials in adults, the primary endpoint was the change from baseline in the total MADRS score for the fixed or flexible dose trials.

At the end of treatment (6 weeks), the efficacy of tianeptine was significant in both the flexible dose trials but not in the fixed dose trial. In one trial, imipramine was used as an active comparator, making it possible to demonstrate the sensitivity of the trial.

In the study carried out in elderly patients (with the ability to increase the dose), after 8 weeks of treatment, tianeptine was shown to have significant efficacy in relation to the primary endpoint (change from baseline in the total HAM-D score). In this study, escitalopram was used as an active comparator, making it possible to demonstrate the sensitivity of the trial.

Maintenance of antidepressant efficacy was assessed in a trial to prevent relapse and recurrence. Patients considered by the Investigator to be treatment responders (6 weeks of "open-label" tianeptine treatment at a daily posology of 2 to 4 tablets ie 25-50 mg per day) were randomised to tianeptine or placebo for an additional 16.5 months. Tianeptine was shown to have statistically significant superiority in efficacy over placebo ($p < 0.001$) for the primary endpoint of the trial: prevention of relapse or recurrence as measured by time to onset. The incidence of relapse after 6 months of double-blind follow-up was 6% for tianeptine and 22% for placebo. The incidence of relapse or recurrence after 18 months of double-blind follow-up was 16% for tianeptine and 36% for placebo.

5.2 Pharmacokinetic properties

Absorption

Gastrointestinal absorption is rapid and complete.

Distribution

Distribution is rapid and is associated with a level of protein binding close to 94%, primarily to albumin.

Biotransformation

Tianeptine is extensively metabolised in the liver, primarily by beta-oxidation, without CYP450 involvement. Its primary metabolite, pentanoic acid (MC5), is active and less potent than tianeptine.

Elimination

The elimination of tianeptine is characterised by a short terminal half-life of 3 h with most metabolites excreted in the urine.

Elderly, very elderly and fragile patients

In elderly patients, plasma concentrations of tianeptine were increased by 30% and those of MC5 approximately doubled after single or repeated administration, in comparison with younger patients (see section 4.2).

In very elderly (87±5 years) or fragile (45±9 kg) patients, a significant increase in Cmax and exposure (area under the curve, AUC) to tianeptine and MC5 was observed after single administration (see section 4.2).

Patients with severe renal impairment (CRCL <19 ml/min)

The pharmacokinetics of tianeptine remain unchanged but exposure to MC5 is approximately doubled after single and repeated administration (see section 4.2).

Patients with severe cirrhosis (Child-Pugh score Class C)

Exposure to tianeptine and to MC5 after the administration of a single dose of 12.5 mg is increased compared to adult patients with depression (see section 4.2).

In cases of milder cirrhosis, such as patients with chronic alcoholism, the effects on pharmacokinetic parameters are negligible (see section 4.2).

5.3 Preclinical safety data

Non-clinical data from conventional genotoxicity and carcinogenicity studies have identified no specific risks for humans.

In the fertility study, an increase in preimplantation loss was observed at the maternally toxic dose of 45 mg/kg/day (12 times the human dose determined by body surface area).

Tianeptine is not teratogenic in rats and rabbits.

In the peri- and postnatal study, dysfunction in milk secretion and increased postimplantation and postnatal loss were observed in rats at the maternally toxic dose of 45 mg/kg/day (12 times the human dose determined by body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, corn starch, talc, magnesium stearate.

Coating: ethylcellulose, glycerol monooleate, SEPIFILM SE 700 White (polyvidone, carmellose sodium, colloidal anhydrous silica, talc, sucrose, polysorbate 80, titanium dioxide, sodium bicarbonate), white beeswax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

No special precautions for storage (climate zones I and II).

Do not store at a temperature above 30°C (climate zones III and IV).

6.5 Nature and contents of container

28 or 100 tablets in blister packs (Aluminium/PVC) (climate zones I and II).

28 or 100 tablets in blister packs (Aluminium/PVC) overwrapped in sachets (climate zones III and IV).

6.6 Special precautions for disposal and handling

No specific requirements.

7. MARKETING AUTHORISATION HOLDER / EXPLOITANT

LES LABORATOIRES SERVIER

50 RUE CARNOT

92284 SURESNES

FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 267 223 5 7: 28 tablets in blister packs (Aluminium/PVC)
- 34009 558 336.0 4: 100 tablets in blister packs (Aluminium/PVC)
- 34009 267 224 1 8: 28 tablets in blister packs (Aluminium/PVC) overwrapped in sachets
- 34009 579 827 3 7: 100 tablets in blister packs (Aluminium/PVC), overwrapped in sachets.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MA approved on 06/02/1987.

Renewed on 06/02/2012.

10. DATE OF REVISION OF THE TEXT

March 2018

11. GENERAL CLASSIFICATION FOR SUPPLY

List I.

Duration of prescription limited to 28 days.

The prescription must be written in full on a secure prescription pad.

Overlapping prohibited unless expressly stated by the prescriber on the prescription.

A copy of the prescription must be retained by the pharmacist for a period of 3 years.

Box of 28: 65% social security reimbursement. Approved for hospital use.

Box of 100: Approved for hospital use.

Price (excluding dispensing fee):

€7.10 (Box of 28 tablets in blister packs (Aluminium/PVC).

Daily cost of treatment: €0.51 to €0.76

Through the written commitments made by its Management team, Servier is committed to continuous quality improvement in the information it provides for solicitation or business development purposes for the promotion of medicinal products in accordance with the Charter signed by LEEM and CEPS and the certification guidelines issued by the French National Authority for Health (HAS).

The employee who has provided you with this document exercises his/her role in accordance with the ethics guidelines for organising meetings with health professionals, a copy of which (s)he can also provide. These regulations are also available on our website http://servier.fr in the "medicinal products" section.

Medical Information and Pharmacovigilance: Servier Medical Affairs - 35 rue de Verdun, 92284 Suresnes Cedex- Tel. 01 55 72 60 00

Version 2.0, 02 March 2023

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3 Stablon Summary of Product Characteristics Certificate of Translation

[ubiqus]

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TRANSLATION CERTIFICATE

31/01/2019

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Translation Sales Manager

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