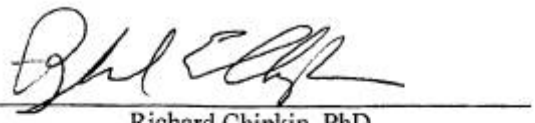
PROTOCOL SIGNATURE PAGE

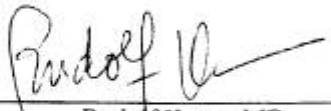
Amendment 3

SIGNATURES
Authors:



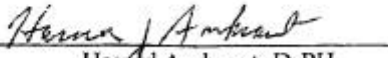
Richard Chipkin, PhD
Study Director
Psyadon Pharmaceuticals, Inc.

3/25/2015
Date



Rudolf Kwan, MD
Consultant, Medical Monitor
Psyadon Pharmaceuticals, Inc.

3/26/2015
Date



Harold Amkraut, DrPH
Consultant, Biostatistician
Psyadon Pharmaceuticals, Inc.

3/25/2015
Date

INVESTIGATORS SIGNATURE PAGE

Study Protocol Number:	PSY302 Amendment 3
Study Title:	Ecopipam Treatment of Tourette's Syndrome in Subjects 7-17 Years
Investigational Product:	PSYRX101 (ecopipam)

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation and all applicable local Good Clinical Practice guidelines, including the Declaration of Helsinki.

Investigator	**Signature**	**Date**

1. TITLE PAGE

Study Protocol Number:	PSY302
Study Title:	Ecopipam Treatment of Tourette's Syndrome in Subjects 7-17 Years
Sponsor:	Psyadon Pharmaceuticals Inc. 20451 Seneca Meadows Parkway Germantown, MD 20876
Medical Monitor:	Rudolf Kwan, MD Telephone: 908-522-3208 Mobile: 908-787-7847 E-mail: Rudolf.Kwan@gmail.com
Investigational Product:	PSYRX101 (ecopipam)
Indication:	Tourette's Syndrome
Phase:	Phase 2b
Approval Date:	7 January 2014 – Original Protocol.1 7 April 2014 – Amendment 1 14 August 2014 – Amendment 2 20 March 2015 – Amendment 3
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Psyadon Pharmaceuticals Inc. (Psyadon). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

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3. CLINICAL PROTOCOL SYNOPSIS

Compound No.	PSYRX101	
Name of Active Ingredient	Ecopipam	
Title of Study	Ecopipam Treatment of Tourette's Syndrome in Subjects 7-17 Years	
Investigators (Others to be named later)	Principal Investigator: Donald L Gilbert, MD, MS Director, Movement Disorder and Tourette Syndrome Clinics Cincinnati Children's Hospital Medical Center, ML No. 7018 3333 Burnet Avenue Cincinnati, OH 45229-3039	Roger Kurlan, MD Director, Movement Disorders program Atlantic Neuroscience Institute Overlook Hospital 99 Beauvoir Avenue Summit, NJ 07902
	Cathy Budman, MD Dept. of Psychiatry North Shore University Hospital 400 Community Drive Manhasset, NY 11030	Harvey Singer, MD The Johns Hopkins University Dept. of Neurology The David M. Rubenstein Child Health Bldg., Suite 2158 200 North Wolfe Street Baltimore, MD 21287
	Dr. Joseph Jankovic Baylor College of Medicine Department of Neurology The Smith Tower, Suite 1801 6550 Fannin Houston, Texas 77030	Dr. Justin Mohatt Weill Cornell Medical College and New York-Presbyterian Hospital 525 E. 68th Street Rm. F-1109; Box 140 New York, NY 10065
	Dr. Jorge Juncos Emory University Wesley Woods Health Center 1841 Clifton Road, NE, Third Floor Atlanta, GA 30329	Dr. Tanya Murphy Rothman Center for Neuropsychiatry 880 Sixth Street South Suite 460, Box 7523 Saint Petersburg, Florida 33701
Study Centers	Up to 10 investigational sites	
Study Period and Phase of Development	Approximately 30-40 (subject to accrual and treatment completion) Phase 2b	
Objectives	**Primary objective** The primary objective of this study is to evaluate the efficacy of ecopipam in children ages 7-17 with Tourette's Syndrome (TS). **Secondary objectives** The secondary objective of this study is to evaluate the safety of ecopipam in children ages 7-17 with TS.	
Study Design	The protocol is a multicenter, double-blind, placebo-controlled, randomized, cross-over study in 30 to 40 subjects conducted to assess the efficacy and safety of ecopipam in children ages 7 - 17 with TS. Eligible subjects will be started on the 74-day treatment period comprised of the following three phases. During the first thirty-day phase, the subjects will be treated with ecopipam or placebo. During the second 14-day phase, subjects will down-titrate from Period 1 for the first four days and then receive no treatment for ten days (wash-out). During the third 30-day phase, subjects will be treated with placebo or ecopipam. During the first 1-4 days of Follow-Up phase, subjects will down-titrate study medication by reducing the number of tablets.	

<table>
<tr><td>Compound No.</td><td>PSYRX101</td></tr>
<tr><td>Name of Active Ingredient</td><td>Ecopipam</td></tr>
<tr><td></td><td>Following initiation of treatment, subjects will be seen in the clinic on days 16, 30, 44, 60 and 74 with telephone contacts on days 3, 7, 23, 47, 51 and 67. Assessments will be performed at each clinic visit. Subjects will have a follow-up visit at Day 88 to record any adverse events (AEs). A data safety monitoring board (DSMB) will be established to monitor safety.</td></tr>
<tr><td>Dosing</td><td>Ecopipam will be provided as 12.5 or 50 mg tablets. Placebo will be provided as identical inert tablets. Since ecopipam is provided at 12.5 and 50 mg tablets, the dose range for this study will be a minimum of 12.5 mg/day and a maximum of 100 mg/day (see tables below). During the treatment phases (i.e., Periods 1 and 3), subjects will be instructed to take study medication as follows:
<table>
<tr><td colspan="4">IF 75LBS OR LESS AT BASELINE</td></tr>
<tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr>
<tr><td>Days 1-3 of Period 1 and 3</td><td>1 tablet orally each day at bedtime</td><td>Either 12.5 mg tablet of ecopipam or placebo</td><td>12.5 mg/day</td></tr>
<tr><td>Days 4-7 of Period 1 and 3</td><td>2 tablets orally each day at bedtime</td><td>Either 12.5 mg tablet of ecopipam or placebo</td><td>25 mg/day</td></tr>
<tr><td>Days 8-30 of Period 1 and 3</td><td>1 tablets orally each day at bedtime</td><td>Either 50 mg tablet of ecopipam or placebo</td><td>50 mg/day</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td colspan="4">IF 76LBS OR MORE AT BASELINE</td></tr>
<tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr>
<tr><td>Days 1-7 of Period 1 and 3</td><td>2 tablet orally each day at bedtime</td><td>Either 12.5 mg tablet of ecopipam or placebo</td><td>25 mg/day</td></tr>
<tr><td>Days 8-14 of Period 1 and 3</td><td>1 tablet orally each day at bedtime</td><td>Either 50 mg tablet of ecopipam or placebo</td><td>50 mg/day</td></tr>
<tr><td>Days 15-30 of Period 1 and 3</td><td>2 tablets orally each day at bedtime</td><td>Either 50 mg tablet of ecopipam or placebo</td><td>100 mg/day</td></tr>
<tr><td colspan="4"></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Compound No.</td><td>PSYRX101</td></tr>
<tr><td>Name of Active Ingredient</td><td>Ecopipam</td></tr>
<tr><td>Dosing (cont.)</td><td>
At the end of Periods 1 and 3, Subjects will be instructed to decrease their dose according to the following schedule
<table>
<tr><td colspan="4">IF 75LBS OR LESS AT BASELINE</td></tr>
<tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr>
<tr><td>Day 1 of Period 2 Or Follow-Up</td><td>3 tablets orally each day at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>37.5 mg/day</td></tr>
<tr><td>Day 2 of Period 2 Or Follow-Up</td><td>2 tablets orally each day at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>25 mg/day</td></tr>
<tr><td>Day 3 of Period 2 Or Follow-Up</td><td>1 tablet orally each day at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>12.5 mg/day</td></tr>
<tr><td>Day 4 of Period 2</td><td>Stop</td><td>None</td><td>None</td></tr>
<tr><td colspan="4">Down titration only occurs if subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.</td></tr>
</table>
<table>
<tr><td colspan="4">IF 76LBS OR MORE AT BASELINE</td></tr>
<tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr>
<tr><td>Day 1 of Period 2 Or Follow-Up</td><td>6 tablets orally at bedtime</td><td>Either 12.5 mg ecopipam or placebo</td><td>75 mg/day</td></tr>
<tr><td>Day 2 of Period 2 Or Follow-Up</td><td>4 tablets orally at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>50 mg/day</td></tr>
<tr><td>Day 3 of Period 2 Or Follow-Up</td><td>2 tablet orally at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>25 mg/day</td></tr>
<tr><td>Day 4 of Period 2 Or Follow-Up</td><td>1 tablet orally at bedtime</td><td>Either 12.5 mg ecopipam tablet or placebo</td><td>12.5 mg/day</td></tr>
<tr><td>Day 5 of Period 2</td><td>Stop</td><td>None</td><td>None</td></tr>
<tr><td colspan="4">Down titration only occurs if subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.</td></tr>
</table>
After stopping, Subjects should not be taking any study medication except under the supervision of the Investigator.
</td></tr>
</table>

Compound No.	PSYRX101
Name of Active Ingredient	Ecopipam
Number/Type of Subjects	30 – 40 male or female subjects ages 7-17 (i.e., ≥ 7 to < 18 years) with a diagnosis of TS based on the DSM-IV criteria for the disease.
Inclusion Criteria	• Subjects must have TS based on the clinician-administered DCI for TS. • Subjects must exhibit both motor and vocal tics. • Subjects must have a minimum score of 20 at both Screening and Baseline (just prior to the first treatment) on the YGTSS. • Subjects must be age (≥ 7 to < 18 years of age) • Subjects must weigh ≥ 20 kg (45 lbs) • Adolescent females of childbearing potential who are sexually active must be using effective contraception (i.e., oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for the duration of their participation in the study. They must also agree to use contraception for 30 days after their last dose of study drug. • Sexually active male subjects must use a barrier method of contraception during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug. • Subject's parent or legal guardian must execute a written informed consent. • Subject must execute a written informed assent.
Exclusion Criteria	• Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening. • Subjects with a major depressive episode in the past 2 years • Subjects with a history of attempted suicide • Subjects with clinically significant suicidality (based on C-SSRS scale) • Subjects with a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization, or attempted/ completed suicide with the exception of a hospitalization for post-partum depression. • Subjects with a history of seizures (excluding febrile seizures that occurred >2 years in the past) • Subjects with a myocardial infarction within 6 months. • Girls who are currently pregnant or lactating. • Subjects who have a need for medication (other than ecopipam) with possible effects on TS symptoms (i.e., lithium, psychostimulants) • Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., dopamine antagonists or agonists [including buproprion], tetrabenazine, or monoamine oxidase inhibitors. • Subjects with a lifetime history of significant psychiatric disorder(s) as rated using the American Psychiatric Association DSM-5 Cross-Cutting Symptom Measures rating scale. • Subjects with current or recent (past 3 months) DSM-IV substance abuse or dependence (with the exception of nicotine). • Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), opiates) at Screening. Subjects with urine positive only for benzodiazepines and/or marijuana (i.e., a user but not an abuser as based on DSM-IV criteria) may be eligible. • Subjects who have had previous treatment with ecopipam. • Subjects who have had treatment with: - investigational medication within 3 months of starting study - depot neuroleptics within 3 months of starting study - other psychotropics with possible effects on TS symptoms (i.e., lithium, tetrabenazine) within 2 weeks prior to Screening. - oral neuroleptics within 4 weeks - selective serotonin reuptake inhibitors unless the dosage has been stable for a

Compound No.	PSYRX101
Name of Active Ingredient	Ecopipam
	minimum of 4 weeks prior to study start and not prescribed to relieve the neurological signs of TS
Study Treatment	**Investigational drug:** Ecopipam Subjects who have a YGTSS of ≥ 20 at both the Screening and Baseline visits will begin the study of 74 days duration. Treatment Phase 1: On Day 1 of Phase 1, the first dose of study drug will be given in the clinic followed by a 4-hour observation period. Starting on the evening of day 2, the subject will take the tablet(s) before bedtime as instructed. Treatment Phase 1 will last for 30 days. The dose of study medication may be decreased for intolerable adverse events. Washout/ Phase 2: This is a wash-out period. During Days 1-4 of this period the Subjects will decrease the number of tablets taken as instructed. During the next ten days, no study medication should be taken. Subjects should be instructed not to change their concomitant medications. Treatment Phase 3: On Day 1 of Phase 3, the first dose of study drug will be given in the clinic followed by a 4-hour observation period. Starting on the evening of day 35 (i.e., day 2 of treatment Phase 3), the subject will take the tablet(s) before bedtime as instructed. Treatment Phase 3 will last for 30 days. The dose of study medication may be decreased for intolerable adverse events. Follow-Up Phase: During Days 1-4 of the Follow-Up Phase, subjects will down-titrate from their final dose of the Treatment Phase 3 as instructed, after which no study medication should be taken. A Follow-Up visit will take place 10 days later to assess compliance to the down-titration and to record any adverse events.
Duration of Treatment	Pretreatment Phase: up to 28 days Treatment Phase 1: 30 days (ecopipam or placebo) Washout Phase 2: 14 days (down-titration days 1-4 and then wash-out/ no study medication) Treatment Phase 3: 30 days (ecopipam or placebo) Follow-up Phase: 14 days (down-titration days 1-4 and then no study drug medication)
Criteria for Evaluation	**Efficacy assessments** • The total Yale Global Tic Severity Score (YGTSS) score is the primary efficacy parameter **Safety:** Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs), regular monitoring of hematology, blood chemistry, and urine values, regular measurement of vital signs and the performance of a physical examination and an ECG. A DSMB will be established to monitor safety. **Pharmacokinetic, Pharmacodynamic, and/or Pharmacogenomic Measurements** Not applicable.
Other Criteria for Evaluation	• Attention deficit/hyperactivity disorder (ADHD) using the DuPaul ADHD rating scale-IV, home version • Child Yale-Brown Obsessive Compulsive Scale (C-YBOCS) • Children's Depression Inventory (CDI), 2nd Edition Clinician • Global Impression – Improvement and Severity Scales (CGI-I; CGI-S) • Columbia-Suicide Severity Rating Scale (C-SSRS)
Bioanalytical Methods	Not applicable.

Compound No.	PSYRX101
Name of Active Ingredient	Ecopipam
Statistical Methods and Data Safety Monitoring Board	**Sample Size Rationale:** Assuming a standard deviation of 10 for total YGTSS scores with 80%, a two-tailed alpha level of 0.05, with approximately 30 completed subjects a difference of 5 points can be detected. A 5 point change is considered clinically significant. **Analysis Sets:** All subjects who received study drug and have at least 1 post-dose safety assessment will be included in the analysis (intent-to-treat). Primary efficacy population is the set of patients who complete all three phases of the study i.e., Treatment Phase 1, Washout Phase 2 and Treatment Phase 3). The primary efficacy measure will be the YGTSS total score. The YGTSS will be analyzed using a two-way analysis of variance extracting the effects of group, subject (within group), period and treatment, with group compared with subject (within group) as the error term and period and treatment using the residual error. Scales will be listed and actual and changes tabulated. Primary analysis will use an intent-to-treat population with last observation carried forward; a completer analysis will also be done. Secondary parameters such as the ADHD scale and C-YBOCS will be analyzed using the model specified above for YGTSS. The Wilcoxon signed rank test will be used for comparisons of categorical variables such as the CGI. Changes from each treatment's baseline and endpoint (i.e., last treatment value) will be compared. Each treatment's baseline will be compared for comparability. The data from Period 1 will also be analyzed using a one-way ANOVA extracting treatment. **Interim analyses** Interim analyses will be done in coordination with the DSMB meetings to primarily assess safety and preliminary efficacy. An interim analysis will be conducted after the first 15 subjects have enrolled and completed all three treatment Phases (Treatment 1, Wash-Out Phase 2, and Treatment 3). **Pharmacokinetic, Pharmacodynamic, and/or Pharmacogenomic Analyses** Not applicable. **Safety Analyses** Evaluation of safety will be performed for all subjects. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, physical examination, and ECGs. Adverse events will be listed and tabulated; no statistical analysis will be performed. **Data Safety Monitoring Board** An independent data safety and monitoring board (DSMB) consisting of a physician experienced in the conduct of clinical trials (Chairman), an ethicist, and two clinicians experienced in Tourette's syndrome will review the data at the interim analysis. The data will be cleaned by the data management group, and the analysis and reporting of the interim data to the DSMB will be the responsibility of an independent statistical group (who will not be directly involved in the conduct of the study). The DSMB will meet after the data presentation and issue a set of minutes as to the safety and viability (i.e., statistical power) of the study to reach its goals at study completion. The minutes of the DSMB will be appended to the final study report.

Compound No.	PSYRX101
Name of Active Ingredient	Ecopipam
Long Term Safety Option	Subjects who successfully complete PSY302 are eligible to enter an optional long term treatment safety protocol (see Appendix 2 and labeled PSY302A). Treatment will be initiated following the request of the subject (or their parent/legal guardian) and with the agreement of the treating physician. The treating physician will keep a record of the subject's recent medical history, including their previous response to ecopipam (efficacy/safety), documented history of previous treatments, and why the treating physician has determined that the potential benefit justifies the potential risks of the treatment use as documented in the Investigator Brochure. The treating physician will also evaluate why the potential risks are not unreasonable in the context of the disease /condition of the subject to be treated. The subject will visit the clinic at the Investigator's site to close out their participation in Study PSY 302. The subject will subsequently have in-clinic evaluations at Baseline and at 3, 6, 9 and 12 months after starting this Open Label Safety protocol. At each visit, the subject will have their vital signs checked, will have blood tests per protocol, will be evaluated using the following rating scales: CDI, C-SSRS, YGTSS, and CGI-S. At the end of a 12-month dosing period, the subject will be evaluated for continued dosing for another 12 months. Details may be found in Appendix 2.

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADHD	Attention Deficit/Hyperactivity Disorder
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	area under the plasma-concentration time course profile
$AUC_{(0\text{-}24\ hr)}$	area under the plasma-concentration time course profile from time 0 (dosing) to 24 hours after dosing
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CDI	Children's Depression Inventory
CGI	Clinical Global Impression
C_{max}	maximum observed concentration
CNS	Central nervous system
CRA	Clinical research associate
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CV	coefficient of variation
C-YBOCS	Child Yale-Brown Obsessive Compulsive Scale
DCI	Diagnostic Confidence Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
DSM-V CC-SM	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition Cross-Cutting Symptom Measures
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCl	Hydrochloride
^{123}I-β-CIT SPECT	(2β-carbomethoxy-3β-[4-iodophenyl]tropane) single photon emission computed tomography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular

Abbreviation	Term
IRB	Institutional Review Board
IV	Intravenous
K_i	Inhibition constant
LDH	lactate dehydrogenase
LFT	Liver function test(s)
LND	Lesch-Nyhan Disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OCD	Obsessive-Compulsive Disorder
PCP	Phencyclidine
PET	Positron emission tomography
PO	Oral (*per os*)
PSYRX	Psyadon drug code indicator
QD	Once daily
SAE	serious adverse event
SC	Subcutaneous
SCH	Schering-Plough drug code indicator
THC	Tetrahydrocannabinol
t_{max}	time from dosing to the maximum observed concentration
TS	Tourette's Syndrome
US	United States
YGTSS	Yale Global Tic Severity Score

5. ETHICS

5.1 INSTITUTIONAL REVIEW BOARDS / INDEPENDENT ETHICS COMMITTEES

The protocol, any protocol amendments, and the informed consent form (ICF) will be reviewed and approved by the study center's Institutional Review Board/Independent Ethics Committee (IRB/IEC) before subjects are screened for entry. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/ICE for review and approval. Verification of the IRB/IEC unconditional approval of the protocol will be transmitted to Psyadon prior to the shipment of drug supplies to the investigational site. The Investigators or Psyadon will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per International Conference on Harmonisation (ICH) guidelines and local IRB/IEC standards of practice.

5.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with standard operating practices of Psyadon (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- In accordance to the principle of World Medical Association Declaration of Helsinki, 1996;
- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use; and
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations).

See Section 11 for administrative details.

5.3 SUBJECT INFORMATION AND CONSENT

All subjects (and/or their guardians/legally authorized representatives) will be provided with verbal and written information describing the nature and duration of the study and the procedures to be performed. Each subject will be given a copy of the ICF and written information, as applicable. The subject (or legal guardian) will be asked to sign an ICF at the Screening Visit and all authorizations required by local law (e.g., Protected Health Information in North America) must be obtained prior to performing any tests or assessments under this protocol. The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented. Sample subject ICFs will be included in the clinical study report for this protocol.

6. INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by a qualified Investigator under the sponsorship of Psyadon at up to 10 investigational sites in the US.

The name of the Medical Monitor along with the telephone and FAX numbers of the other contact persons at Psyadon or a designated Contract Research Organization (CRO) are listed in the Regulatory Binder provided to the site.

7. INTRODUCTION

7.1 BACKGROUND

7.1.1 Tourette's Syndrome

7.1.1.1 General

Several excellent reviews on Tourette's Syndrome (TS) have been published, and the reader is referred to these for details.[1,2,3,4,5] Briefly, TS is a neurological disorder characterized by motor or vocal tics that begin in childhood and persist over time (see box below with the Diagnostic and Statistical Manual for Mental Disorders – 4th Edition [DSM-IV] diagnostic criteria). The tics are brief in duration, occur spontaneously, and do not show a regular temporal pattern. Further the tics are not caused by medications, other medical reasons, or confirmed tissue damage. They can be consciously suppressible and are exacerbated by stress. Males are more susceptible than females with a ratio of about 3 to 4:1.

Motor tics can include such things as eye-blinking, facial grimacing, mouth movements, head jerks, shoulder shrugs and arm/leg jerks. In more severe cases gyrating, bending, pivoting and dystonic movements are possible. Vocal tics are fast meaningless sounds or noises, and include such things as sniffing, throat clearing, grunting, barks and squealing. Complex vocal tics can include shouting out of single words, whole sentences or repeating words (echolalia). In small numbers of patients, explosive obscenities (coprolalia) are possible.[4,6]

DSM-IV Diagnostic Criteria For Tourette's Syndrome

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A *tic* is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)

B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

Diagnosis of TS is complicated because it often co-exists with other psychiatric illnesses. Common co-morbid conditions include attention deficit/hyperactivity disorder (ADHD),

obsessive-compulsive disorder (OCD), anxiety, and depression.[7] These symptoms often mask TS and make diagnosis difficult.

Tic severity can range from mild to severe according to its frequency and intensity. The tics have a variable course, with severe bouts interspersed with complete absence of symptoms. Onset of tics is seen early in childhood (average approximately 7 years) and peaks in the teenage years. However, as patients mature, the vast majority of tics will disappear permanently. Severe tics are thought to occur only in about 10% of the cases. [6]

7.1.1.2 Disrupted Dopamine Systems in Tourette's Syndrome

The underlying mechanism responsible for TS is unknown. Although the disease tends to run in families, there have been no definitive genetic mutations identified.[8] Research to date has indicated that dopamine circuits in the central nervous system (CNS) are intimately involved based on the following observations[9,10,11]:

- Dopamine-rich areas of the brain (e.g.,, striatum) are believed to control motor tics
- Clinical neuroimaging studies of TS patients implicate dopamine-rich brain areas
- Dopamine antagonists can ameliorate tics
- Catecholamine depletors (e.g., tetrabenazine) can ameliorate tics

7.1.1.3 Nonclinical Data

There are no nonclinical models of TS that fully recapitulate the disease. Experimental work has focused on dopamine-containing neurons because of an extensive literature showing their involvement in movement disorders and tics.[10]

To evaluate novel treatments, nonclinical researchers have relied on surrogate models in which repetitive spontaneous or drug-induced behaviors are used. An example of this is apomorphine-induced stereotypy. In this model, rodents (usually mice) are injected with the dopamine agonist apomorphine, and the incidence of biting/gnawing on the wire-mesh cage wall is scored. Orally administered ecopipam (labeled as SCH 39166 in the figure below) potently blocks this behavior.[12]

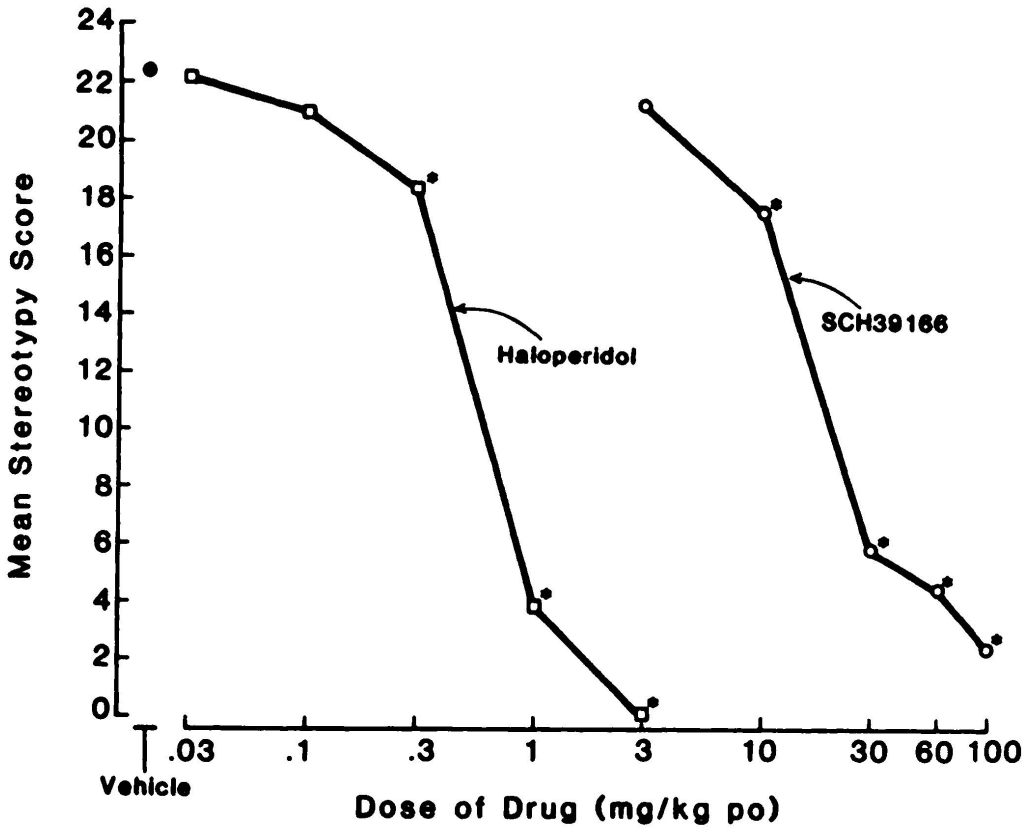


Figure 1 Effect of SCH39166, Haloperidol or Vehicle on Apomorphine-induced Stereotypy in Rats

SCH39166 (○), haloperidol (□), or vehicle (●). Each point is the mean of six rats. *Significantly different from vehicle, $P < 0.05$, Mann-Whitney *U* test. Chipkin et al[12]

Apomorphine is a mixed D1/D2 agonist. Selective agonists of the D1 receptor have been shown to induce repetitive oral movements in either rodents[13] or primates;[14,15] correspondingly, selective antagonists of the D1 receptor like ecopipam block these drug-induced behaviors. Berridge et al. have proposed that the "super-stereotypy" seen in dopamine transporter-knockdown mutant mice may be a model of TS.[16] This is based on the similarities between the rigid sequential actions seen in these mice and in patients with TS. Based on their previous work these behaviors are exclusively mediated by D1 receptors.[17,18] If these models are predictive of clinical activity, then a D1 antagonist like ecopipam should be efficacious.

7.1.1.4 Clinical Data

Several clinical reports have linked dopamine-containing neurons to TS. For example, dopamine antagonists (primarily mixed or D2-preferring) have been shown to ameliorate tics.[5,19,20] In addition, dopamine depleting drugs such as tetrabenazine have also been shown to have some efficacy against tics.[21,22,23]

A variety of neuroimaging studies have shown abnormalities in dopamine-rich brain areas in patients with TS. Using magnetic resonance imaging, Davila et al.[24] have shown that patients with TS have increased numbers of expanded perivascular spaces in the brain area where dopamine neurons arise from (i.e., substantia nigra); and Peterson et al. reported reduced volumes an areas where those neurons terminate (i.e., caudate nucleus).[24,25] Using positron emission tomography (PET), Frey and Albin report increased numbers of striatal monoamine-type 2 transporters.[26] Likewise, using (2β-carbomethoxy-3β-[4-iodophenyl]tropane) single photon emission computed tomography (^{123}I-β-CIT SPECT) imaging, Malison et al. reported higher levels of striatal dopamine transporters.[27] And, using PET, Singer et al. reported that TS patients have greater levels of intrasynaptic dopamine following amphetamine than normals.[28] Collectively these data suggest that dopamine systems are disrupted in TS, although the exact nature of the problem is not clear.

There are few clinical data specifically linking D1 receptors and TS. Neither Gelernter et al. nor Chou et al. found any linkage between the D1 receptor gene and pathology in TS patients.[29,30] However, Singer et al. have reported that brain levels of cyclic adenosine monophosphate (AMP) are decreased in TS patients relative to controls. D1 receptors (and not D2) use cyclic-AMP as its second messenger, suggesting a potential relationship.[31,32] Likewise, Singer et al. reported an increase in dopamine uptake sites in post-mortem cortical tissue, and this was confirmed using SPECT by Muller-Vahl et al.[33,34] One interpretation of these data is that increased dopamine reuptake induces a supersensitive postsynaptic D1 receptor with a subsequent depletion of its second messenger, cyclic-AMP. Demonstrating clinical efficacy of a selective dopamine D1 antagonist in patients with TS would go a long way to clarifying the situation.

Recently, Ferrari et al. reported that dopamine D5 mRNA was increased in peripheral lymphocytes taken from TS patients; further, there was a highly positive correlation between the levels and the severity of compulsive symptoms.[35] Interestingly, both Ricci et al. and Kirillova et al. demonstrated that only dopamine D5, and not D1, receptors are expressed on circulating human lymphocytes.[36,37] Although speculative, it is therefore reasonable to assert that the D5 receptor up-regulation observed by Ferrari et al. may be a surrogate marker for a similarly up-regulated brain D1 receptor. Regardless, since ecopipam blocks the D5 receptor with equal efficacy as the D1 receptor, the data suggest that if the peripheral lymphocytic D5 receptor is reflecting a role for the brain, ecopipam would still be effective.

7.1.2 Current Therapies

Treatment of TS has focused on two goals: control of the tics and control of the co-morbid psychiatric disturbances. The following section briefly summarizes current therapies. For a more complete description, the reader is referred to several recent reviews.[20,38,39]

7.1.2.1 Control of Tics

The literature on treatments for TS has been reviewed by the Tourette Syndrome Association Medical Advisory Board, and summarized as follows by Swain et al. (Table 1).[20,40]

Table 1 Drugs Used in the Treatment of Tics: Empiric Support and Dosing Guidelines

Medication	Empiric Support	Starting Dose, mg	Usual Dose Range, mg/day
Non-Antipsychotics			
Clonidine	B	0.025 – 0.05	0.2 – 0.4
Guanfacine	B	0.5 – 1	2 – 4
Pergolide	B	0.025 every 2 days	0.15 – 0.45
Botulinum Toxin A	B	Motor tics: 50 – 75 U	75 – 250
		Vocal tics: 1 – 2.5 U	1 – 2.5
Antipsychotics			
Haloperidol	A	0.25 – 0.5	1.0 – 4.0
Pimozide	A	0.5 - 1	2 – 8
Risperidone	A	0.25 – 0.5	1.0 – 3.5
Fluphenazine	B	0.5 – 1.0	1.5 – 10.0
Tiapride	B	50 – 150	150 – 500
Ziprasidone	B	5 – 10	10 – 80

Note: To guide clinical practice, the medications used for TS are classified according to the level of empirical support. The above criteria from the International Psychopharmacology Algorithm Project were selected (Scahill et al., 2006): category A reflects treatments with good short-term evidence of safety and efficacy derived from at least two randomized placebo-controlled trials with positive results; category B corresponds to treatments with fair supportive data as evidenced by at least one positive placebo-controlled study.

For children requiring pharmacotherapy, alpha-2A-adrenergic receptor agonists such as clonidine and guanfacine are recommended as first-line treatment of tics. These agents have limited efficacy and have a variety of adverse side effects including sedation and cardiovascular problems. Dopamine antagonists are recommended as second-line treatment; however, they are poorly efficacious, and have multiple limiting side effects including extra-pyramidal movement disorders, hyperprolactinemia, obesity and sedation. Low doses of the mixed dopamine agonist pergolide (thought to act by inhibiting dopamine release via activation of presynaptic D2/D3 receptors) have also been reported to be effective (see Gilbert et al.).[41] Injections of botulinum toxin can also be used, but are restricted to localized sites.[42]

Other pharmacotherapies that have been tried include (a) dopamine depletors such as tetrabenazine; (b) gamma-aminobutyric acid agonists such as baclofen; (c) anti-epileptic drugs and others.[9,40]

Overall, the treatment of tics with the most commonly used drugs has been inadequate (see Table 2 from Scahill et al.).[20] Non-pharmacological approaches include behavioral techniques, which require motivation and is time-consuming, or deep brain stimulation, a costly neurosurgical intervention which is not FDA approved for TS. [43,44] There is therefore a need for new therapeutic options.

Table 2 Percent Improvement for Medications Showing Superiority to Placebo for the Treatment of Tics

Drug	Improvement[a] (%)
Clonidine	35
Guanfacine	30 – 37
Pergolide	35
Botulinum Toxin	40
Ziprasidone	35
Risperidone	35 – 50
Haloperidol	66
Pimozide	39 – 58
Tiapride	44

a: Without adjustment for placebo.

7.1.2.2 Control of Comorbid Psychiatric Conditions

Because of the high incidence of comorbid psychiatric conditions in patients with TS, they are treated with a variety of other drugs. These include serotonin reuptake inhibitors for depression and obsessive-compulsive disorders, stimulants for ADHD, and benzodiazepines for anxiety. A review of all the drugs used to treat all the psychiatric comorbidities of patients with TS is outside the scope of this analysis.

7.1.3 Description of Drug

Ecopipam hydrochloride (HCl), a potent, selective antagonist of human D_1 and D_5 dopamine receptors, is being investigated for use in the treatment of TS.

The following is a summary of the experience with ecopipam in animals and humans. For details, refer to the Investigator's Brochure.

7.1.4 Nonclinical Profile

7.1.4.1 Basic Pharmacology

Ecopipam ([-]-Trans-6, 7, 7A, 8, 9,13B-hexahydro-3-chloro-2-hydroxy-N-Methyl-5H-benzodnaptho-[2, 1-b] -azepine, hydrochloride, also known as PSYRX101 and SCH 39166), is a selective antagonist of the D1-family of dopamine receptors (D1 and D5).[1]

7.1.4.2 Toxicology

The nonclinical development program for ecopipam comprised studies of bioavailability; acute and repeated-dose toxicity (including oral [PO] gavage, intramuscular [IM], intravenous [IV], and subcutaneous [SC] routes of administration); cardiovascular; neurological, behavioral, and autonomic nervous system toxicity; reproductive and endocrinological toxicity; and genetic

toxicity. Results from the extensive nonclinical studies demonstrate that ecopipam is well tolerated. Ecopipam did not cause any appreciable changes in cardiovascular function, any neurological disorders, or any enzyme induction or loss of efficacy or tolerance. Ecopipam is not considered embryotoxic, fetotoxic, or teratogenic in rats at doses up to 162 mg/kg. In rabbits, the no-observable-effect level for both maternal and developmental toxicity is > 150 mg/kg, but < 300 mg/kg. Ecopipam is not considered genotoxic or mutagenic. However, ecopipam was found to have a consistent sedative effect 2 hours after dosing in primates and to cause convulsions in mice, rats, and primates after high doses (≥10 mg/kg). Ecopipam did not cause any movement disorders in mice, rats, or primates.

Results of nonclinical pharmacokinetic and metabolism studies showed that ecopipam is rapidly absorbed after oral dosing and, in rodents and monkeys, is rapidly metabolized to the N-desmethyl analog (N-desmethyl-PSYRX101 or SCH 40853). Both ecopipam and N-desmethyl-PSYRX101 are extensively conjugated. There are no qualitative differences in metabolic profiles of ecopipam between species. For rodents and nonhuman primates, the estimated oral bioavailability of ecopipam (parent drug) was very limited (0.6% in rats and 1.5% in monkeys).

Based on nonclinical hormonal and toxicology studies conducted with ecopipam, there is no evidence that ecopipam will have endocrinological effects in humans similar to that of the D2 antagonists.

7.1.5 Clinical Profile

The previous clinical program for ecopipam investigated the safety and effectiveness of ecopipam for the treatment of obesity, cocaine addiction and schizophrenia. Ecopipam has been studied in over 2000 human subjects. These comprised three discontinued Phase 3 studies and one completed Phase 2 study in subjects with moderate to severe obesity, Phase 2 pilot studies for subjects with schizophrenia and cocaine addiction, and Phase 1 studies.

7.1.5.1 Pharmacokinetics in Humans

The Phase 1 studies included pharmacokinetic and safety/tolerance trials, PET studies, a food-effect study, and others. For greater detail, refer to the Investigator's Brochure.

In a rising, single-dose (25, 50, 100, 200, 400, 600, or 800 mg of ecopipam HCl, PO) study conducted in healthy, adult subjects, plasma concentrations of ecopipam reached maximum values (C_{max}) between 1.8 and 3.6 hours after dosing (T_{max}). Mean C_{max} and the area under the curve ($AUC_{[I]}$) values were generally dose proportional, indicating that the absorption of ecopipam HCl was independent of dose (Table 3). The terminal phase half-life of ecopipam HCl was 10 to 16 hours.

Table 3 Mean (n=6) Pharmacokinetic Variables of Unconjugated Ecopipam Following Single Oral Doses

Protocol No. C89-359

	Mean (% coefficient of variation [CV])				
Dose (mg)	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{(tf)}$ (ng•hr/mL)	$AUC_{(I)}$ (ng•hr/mL	t½ (hours)
25	10.9 (45)	1.9 (31)	71.7 (30)	91.1 (26)	9.9 (24)
50	20.8 (27)	1.8 (24)	164.0 (19)	190.1 (14)	10.7 (29)
100	76.2 (58)	2.3 (50)	615.7 (37)	634.4 (35)	12.4 (15)
200	66.5 (51)	1.9 (60)	578.7 (34)	592.0 (34)	11.0 (11)
400	119.1 (51)	2.3 (34)	1127.2 (37)	1167.4 (37)	14.8 (18)
600	172.9 (16)	3.6 (28)	2267.7 (30)	2338.9 (29)	14.2 (21)
800	380.7 (51)	2.0 (68)	4319.3 (64)	4546.9 (66)	15.6 (36)

In a rising multiple-dose study, 35 subjects initially received a single dose of 25, 50, 100, or 200 mg of ecopipam or placebo. Following a 2-day, drug-free interval, the same doses were administered every 12 hours (q12h) for 7 doses. The study did not progress to the 200 mg q12h dose level. Results show that ecopipam was well absorbed, attaining peak concentrations generally within 2 hours (Table 4). Plasma samples for pharmacokinetic evaluations were collected on Day 7. Plasma concentrations increased with increasing dose. The increases were dose proportional or slightly less than dose proportional. The mean $t_{1/2}$ of ecopipam after doses of 25 to 100 mg ranged from 11 to 20 hours, independent of dose frequency or magnitude. The AUCs within the respective dosage intervals (12 or 24 hours) increased after the first dose.

Table 4 Ecopipam HCl 25 mg, 50 mg, or 100 mg q12h: Mean Pharmacokinetic Data (%CV)

Protocol No. C90-857[a]

		25 mg q12h		50 mg q12h		100 mg q12h	
Parameter	Unit	Day 1	Day 6[b]	Day 1	Day 6[b]	Day 1	Day 6[b]
C_{max}	ng/mL	20 (44)	21 (28)	23 (27)	28 (36)	52 (31)	74 (33)
T_{max}	hr	1.3 (36)	1.6 (24)	1.8 (37)	2.6 (69)	1.9 (43)	2.2 (34)
$AUC_{(0\text{-}12\ hr)}$	ng•hr/mL	75.6 (27)	122 (25)	103 (25)	176 (26)	247 (33)	491 (20)
$AUC_{(I)}$	ng•hr/mL	132 (25)	—[c]	206 (24)	—[c]	477 (22)	—[c]
t½	hr	10.7 (29)	15.5 (34)	19.5 (50)	20.1 (39)	14.6 (16)	19.6 (31)

a: Study did not progress to 200 mg q12h dose level.

b: Data after the last (7th) q12h dose.

c: Not appropriate to calculate $AUC_{(I)}$ after multiple dosing.

In a second rising, multiple-dose study, a single 100 mg or 200 mg dose of ecopipam or placebo was given. After a 4-day, drug-free interval, the same doses were given every 12 hours for 9 days. Ecopipam was well absorbed, attaining peak concentrations generally within 2 hours (Table 5). Plasma concentrations increased with increasing dose. The increases were dose proportional or slightly less than dose proportional. The mean terminal phase half-life of ecopipam after doses of 100 to 200 mg ranged from 15 to 20 hours, independent of dose frequency or dose magnitude. The AUCs within the respective dosage intervals (after a single dose every 12 hours) increased after the first dose.

Table 5 Ecopipam HCl 100 mg or 200 mg q12h: Mean Pharmacokinetic Data (%CV)

Protocol No. C91-146

		100 mg q12h		200 mg q12h	
Parameter	**Unit**	**Day 1**	**Day 13[a]**	**Day 1**	**Day 13[a]**
C_{max}	ng/mL	54 (54)	71 (34)	75 (35)	90 (29)
T_{max}	hr	1.3 (33)	2.1 (94)	2.2 (35)	2.4 (94)
$AUC_{(0\text{-}12\ hr)}$	ng•hr/mL	316 (33)	452 (22)	396 (33)	607 (29)
$AUC_{(I)}$	ng•hr/mL	535 (30)	—[b]	748 (24)	—[b]
t½	hr	15.4 (46)	20.3 (25)	13.3 (8)	16.6 (38)

a: Data after the last (17th) q12h dose.

b: Not appropriate to calculate $AUC_{(I)}$ after multiple dosing.

In the third multiple-dose trial, 36 subjects received a single dose of 50, 100, 200, or 400 mg of ecopipam or placebo. Following a 4-day, drug-free interval, the same doses were given once daily (QD) for 9 consecutive doses. Results indicate that ecopipam was well absorbed, attaining peak concentrations generally within 2 hours (Table 6). Plasma concentrations increased with increasing dose. The increases were dose proportional or slightly less than dose proportional. The mean terminal phase half-life of ecopipam after single doses of 50 to 400 mg ranged from 13 to 22 hours, independent of dose frequency or dose magnitude. The AUCs within the respective dosage intervals (12 or 24 hours) increased after the first dose.

Table 6 Ecopipam HCl: Mean Pharmacokinetic Data

Protocol No. C91-107[a]

		50 mg QD		100 mg QD		200 mg QD		400 mg QD	
Parameter	**Unit**	**Day 1**	**Day 13[b]**	**Day 1**	**Day 13**	**Day 1**	**Day 13**	**Day 1**	**Day 13**
C_{max}	ng/mL	24	19	64	54	85	76	184	160
T_{max}	hr	2.0	1.9	1.8	1.5	1.9	1.8	2.1	2.3
$AUC_{(0\text{-}24\ hr)}$	ng•hr/mL	168	192	359	411	623	692	1298	1366
$AUC_{(I)}$	ng•hr/mL	218	—[c]	487	—[c]	806	—[c]	1729	—[c]
t½	hr	12.7	22.3	13.6	14.1	13.1	15.7	14.6	20.5

a: %CV were within similar ranges as the previous 2 studies

b: Data after the last (9th) daily dose.

c: Not appropriate to calculate $AUC_{(I)}$ after multiple dosing.

Three PET studies evaluated the ability of ecopipam to bind with D_1 dopamine receptors in the CNS. Fifteen healthy subjects participated in these studies. In 1 study, 6 subjects received 1 IV tracer dose of ^{11}C-ecopipam. In the second study, 6 subjects received an IV tracer dose in combination with a low dose of nonradioactive ecopipam (1.5 mg IV). In the last study, 3 subjects received the IV tracer dose plus a single oral dose of 25, 100, or 400 mg 2 hours prior to the IV dose in a crossover study design; each subject received all 3 oral doses in an ascending sequence. The results indicated that ecopipam enters the CNS and binds in areas known to be enriched with D_1 dopamine receptors such as the caudate nucleus and putamen. Plasma concentrations of 1.2 to 3.1 ng/mL produce occupancy of D_1 receptors of 25% to 35% and plasma concentrations of 5.1 to 6.6 ng/mL produce D_1 receptor occupancy rates of 52% to 62%. D_1 receptor occupancy rates after oral ecopipam were estimated as: 49% to 60% for 25 mg; 65% to 78% for 100 mg; and 60% to 78% for 400 mg. Thus, a dose of 100 mg appeared to provide

maximal D_1/D_5 receptor occupancy.

Ecopipam is metabolized to a desmethyl metabolite, N-desmethyl-PSYRX101, and both ecopipam and N-desmethyl-PSYRX101 are rapidly glucuronidated. After single-dose and multiple-dose administration in humans, the ratio of parent to metabolite is approximately 9:1. N-desmethyl-PSYRX101 is also extensively bound to plasma proteins, with a ratio of total:unbound of 9:1. Radiolabeled ecopipam studies in rats showed a majority (92%) of ecopipam was eliminated fecally. Although there are no similar radiolabeled data in humans, extremely low urinary excretion of ecopipam or SCH 40853 (< 1%) was observed, suggesting that fecal excretion may also be the predominant route of elimination in humans.

A single-dose study in subjects showed that food intake did not affect the bioavailability of ecopipam.

PSYRX101 is a competitive inhibitor for CYP2D6 at nanomolar concentrations (inhibition constant [$K_{i]}$ approximately 20 nM) in vitro, and may influence the metabolic clearance of co-administered drugs that are primarily metabolized by this enzyme. One study examined the possible pharmacokinetic interactions between fluoxetine and ecopipam, since fluoxetine is metabolized by the cytochrome P450 enzyme CYP2D6. Results indicated that fluoxetine had no effect on C_{max} or $AUC_{(0\text{-}24\ hr)}$ values for ecopipam and N-desmethyl-PSYRX101; ecopipam caused a very small increase in C_{max} and $AUC_{(0\text{-}24\ hr)}$ values for fluoxetine.

7.1.5.2 Safety in Humans

The previous clinical program for ecopipam investigated the safety and effectiveness of ecopipam for the treatment of obesity, cocaine addiction and schizophrenia. These comprised three discontinued Phase 3 and 1 completed Phase 2 studies in patients with moderate to severe obesity, Phase 2 pilot studies for patients with schizophrenia and cocaine addiction, and Phase 1 studies.

The Phase 1 studies examined the pharmacokinetics, pharmacodynamics, bioavailability, tissue distribution, food effects, and drug interactions in healthy subjects. The results showed that ecopipam was well tolerated with no clinically significant changes in physical examinations, vital signs, electrocardiograms (ECGs), electroencephalograms (EEGs), laboratory tests (including liver function tests [LFTs]), or neurological examinations. Most of the reported AEs were mild to moderate in intensity. The most commonly reported AEs were somnolence (in Phase 1 clinical trials) and headache (in Phase 2 clinical trials). Frequently reported AEs in the three Phase 3 studies were insomnia, depression, somnolence, fatigue, and anxiety. Previous Phase 3 studies with ecopipam in obesity were discontinued because of psychiatric AEs. Other commonly reported AEs in all clinical trials were nausea, dizziness, anxiety, vomiting, insomnia, restlessness, and dyspepsia.

Over 279 subjects with cocaine dependence in 3 dose groups (10, 25, and 100 mg/day) were exposed to ecopipam HCl for 8 weeks in a placebo controlled trial. No differences in the reduction of cocaine use were demonstrated in favor of ecopipam HCl compared with placebo. The most common AEs reported among all subjects in the cocaine addiction trials were fatigue, headache, nausea, insomnia, and somnolence. Fatigue and somnolence were reported more often in subjects treated with ecopipam HCl than placebo. Somnolence occurred in a dose-related

fashion; 28%, 31%, and 43% in subjects treated with ecopipam HCl (10, 25, and 100 mg/day), respectively, and 20% in subjects treated with placebo.

Five open-label safety, tolerance, and pilot efficacy trials of ecopipam in 56 subjects with schizophrenia were conducted. Subjects diagnosed with acute schizophrenia, schizophreniform disorder, or bipolar schizoaffective disorder were treated with ecopipam up to a daily dose of 600 mg. The maximum duration of treatment was 6 weeks. Ecopipam, when administered to subjects with schizophrenia, did not demonstrate efficacy in these studies. The most commonly reported AEs were somnolence (21%), headache, nausea, vomiting and dizziness (each reported in 14%), insomnia (9%), dyspepsia (7%), and anxiety (7%).

In a Phase 2, double-blind, placebo-controlled study, 185 subjects with a primary diagnosis of moderate to severe obesity were treated with ecopipam (10, 30, or 100 mg PO, once per day) for 12 weeks. Subjects receiving ecopipam showed a dose-dependent weight loss. The most commonly reported AEs by subjects receiving ecopipam were headache (19%); viral infection (19%); somnolence (18%); insomnia (9%); and nausea (9%). Most AEs were mild to moderate in intensity and occurred in similar frequency in subjects receiving either ecopipam or placebo. There was very little difference in the incidence of changes in laboratory values for either treatment group. Adverse events associated with ecopipam were reversible, and there was no evidence of withdrawal after the end of treatment.

In three Phase 3, placebo-controlled, double-blind studies, 1482 subjects with obesity were treated with ecopipam (50 or 100 mg PO, QD for 52 weeks). Subjects had dose-dependent weight loss. Adverse events seen in these controlled studies were mainly in the CNS, consistent with its pharmacology property as a D1/D5 antagonist. Adverse events in other organ systems or laboratory test findings were generally similar to placebo. The most frequently reported AEs associated with ecopipam were insomnia (17%), depression (16%), somnolence (15%), fatigue (15%) and anxiety (14%). Insomnia, depression, somnolence, fatigue and anxiety were about 3 times as frequent in subjects receiving ecopipam than placebo. These Phase 3 studies in obesity were discontinued because of psychiatric AEs, including depression, anxiety, and suicidal ideation (2%, twice that of placebo-treated subjects).

An open label study evaluating ecopipam for the treatment of adults with TS has been completed. Ecopipam was given to 18 subjects at a dose of 50 mg/day po at bedtime for two weeks and 100 mg/day po at bedtime for six weeks. The results showed that there was a statistically significant reduction in YGTSS starting as early as one week after treatment initiation that persisted for the entire study. Ecopipam was generally well tolerated with primarily central nervous system (e.g., sedation, insomnia, fatigue, somnolence, headache, muscle twitching and anxiety) and gastrointestinal (e.g., nausea, abdominal pain) adverse events reported.

Three other clinical studies with ecopipam have recently been completed. The first (PSY101) was a multidose, rising, safety, and pilot activity study to assess the maximal tolerated dose of ecopipam in adults, adolescents, and juvenile children with Lesch-Nyhan Disease (LND) in an in-patient setting. Five male subjects aged from 9 to 52 years were enrolled and completed the study. Two unrelated SAEs were reported (pyelonephritis and viral respiratory infection/aspiration pneumonia). Both events resolved without sequelae. In general, ecopipam was well tolerated. The most commonly reported adverse events were sedation, dystonia, and

nausea. Pharmacokinetic data indicate that mean peak plasma concentrations of ecopipam were similar to those observed in normal healthy subjects given single oral doses of 25 or 50 mg, and were approximately 2-fold higher after single 100 or 200 mg doses; however, the high variability and small sample size precludes any rigorous comparisons. There were no apparent differences related to age and no markedly unexpected (i.e., >2 to 3 fold) accumulation occurred with repeated dosing. The second study (PSY201) was a Phase 2 open-label study of ecopipam for the treatment of pathological gambling. Twenty-eight patients were enrolled, and twenty-two completed the eight-week trial. Ecopipam was generally well-tolerated and side effects reported by subjects were mild to moderate in nature and resolved without sequelae. The most common adverse event reported was anxiety (n=4; 14.3%) There was one Serious Adverse Event (SAE) reported for one subject (abdominal pain requiring hospitalization), but this was deemed unrelated to the medication.

The third study (PSY401) was a rising, single dose safety and tolerability of a new controlled release capsule formulation of ecopipam versus the existing immediate-release tablet (100 mg) formulation (90, 180 and 270 mg). Sixteen normal volunteers were enrolled and no serious adverse events were reported. According to the investigator, of the five adverse events reported during the study (abdominal pain, feeling hot, headache, insomnia and erectile dysfunction), none were considered to be related to ecopipam.

There was an on-going Phase 3 outpatient study with ecopipam (≥ 6 years old) with Lesch-Nyhan Disease (LND) with moderate to severe self-injurious behavior (see Section 7.2.2 below). Protocol PSY102 is a multicenter, double-blind, randomized, placebo-controlled, 3-period crossover study with an open-label extension in 20 to 24 subjects to assess efficacy and the effect of withdrawal, maintenance, and safety of ecopipam in oral daily doses of 12.5 to 100 mg (based on body weight).

7.1.5.3 Activity in Subjects with TS

Ecopipam has been evaluated in only one clinical trial in patients with Tourette's. This was a Phase 2a, open-label, nonrandomized study (PSY301) designed to examine the safety and activity of ecopipam in adults. Subjects received ecopipam 50 mg for 2 weeks followed by 100 mg for 6 weeks. The most commonly reported adverse events (incidence ≥20%) were sedation (33%), insomnia (33%), fatigue (33%), somnolence (28%), headache (22%), muscle twitching (22%) and anxiety (22%). There were no Serious Adverse Events reported in this study.

The primary activity in this trial was the Yale Global Tic Severity Score (YGTSS). After ecopipam treatment, YGTSS total score, motor tics score, phonic tics score and overall impairment were all significantly decreased from baseline to endpoint, which indicated that the severity of tics was decreased (Table 7**).**

Table 7 YGTSS total score and subscale scores at baseline and endpoint in Intent to treat population

Protocol No. PSY301

	Baseline	Endpoint
YGTSS total score*		
N	18	18
Mean	30.61	25.28
SD	8.85	9.17
Median	29	25
Min-Max	20-50	12-48
YGTSS motor tics score*		
N	18	18
Mean	16.22	13.67
SD	4.49	4.24
Median	15.5	12.5
Min-Max	10-25	7-25
YGTSS phonic tics score*		
N	18	18
Mean	14.39	11.61
SD	5.90	6.84
Median	14	12
Min-Max	5-25	0-23
YGTSS impairment score*		
N	18	18
Mean	29.72	22.78
SD	10.91	13.74
Median	30	20
Min-Max	10-50	0-45

* Endpoint value compared to baseline value by T-test, all P <0.05.

7.2 ADVERSE EVENTS IN PEDIATRIC SUBJECTS

7.2.1 Phase 1b study on LND

An open-label, inpatient rising safety and tolerability of ecopipam HCl was conducted in Lesch-Nyhan patients to determine the drug's profile in these particular patients and in a non-adult population. Protocol PSY101 included 5 male subjects with LND, ranging in age from 9 to 53 years old, and in weight from approximately 19.6 to 70.5 kg. Subjects received a single, 12.5 mg oral dose of ecopipam on the morning of Day 1, and additional oral doses of ecopipam (12.5, 25, 50, 100, 200 mg, if tolerated) were then administered daily. The dosage could be increased every 1 to 3 days up to 200 mg, and was to remain at the highest dosage for 3 days.

In this study, 4 of 5 subjects enrolled in this study were children (ages 9, 10. 14 and 17 years). All four pediatric subjects experienced at least 1 TEAE during the study. The most commonly reported adverse events in the children were sedation (2 subjects), dystonia (2 subjects), and

nausea (2 subjects). Two children subjects developed SAEs. One 14 year old subject developed severe left sided flank pain which led to hospitalization; the SAE was likely due to a renal calculus which is common in these patients and was judged as unrelated to the study drug; the subject recovered without sequelae. Approximately two weeks following the end of the study, a 10 year old subject developed persistent cough, fatigue and progressing weakness and was hospitalized; the SAE was unrelated to the study drug, and the subject recovered with sequelae. No subject discontinued from treatment due to adverse events. No subject died during the study.

7.2.2 PSY102 Study In Lesch-Nyhan Disease Patients

PSY102 study was a Phase 3 study of ecopipam in Lesch-Nyhan Disease patients. A total of nine pediatric subjects were enrolled before the study was terminated for non-safety related reasons. Ecopipam was administered at either 50 mg/day (<20 kg body weight) or 100 mg/day (≥20 kg body weight). One subject aged 10 years old experienced dystonia, swallowing difficult and depressed mood which involved persistence or significant disability or incapacity. The same subject experienced renal calculus, dystonia and bronchospasm which involved persistence or significant disability or incapacity and the relationship to study drug was No Reasonable Possibility. Another subject aged 6 years old experienced dysphagia, somnolence and depressed mood which involved persistence or significant disability or incapacity and the relationship to study drug was Reasonable Possibility. Since dystonia and dysphagia have not been seen previously in other study populations and because Lesch-Nyhan patients have a genetic mutation known to impact dopaminergic systems, it is believed these adverse events are uniquely seen in this population and are unlikely to occur in subjects without this disorder.

8. STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of ecopipam in subjects with TS ages 7 to 17 years old.

8.2 SECONDARY OBJECTIVES

The secondary objective of this study is to evaluate the safety of ecopipam in individuals with TS ages 7 to 17 years old.

9. INVESTIGATIONAL PLAN

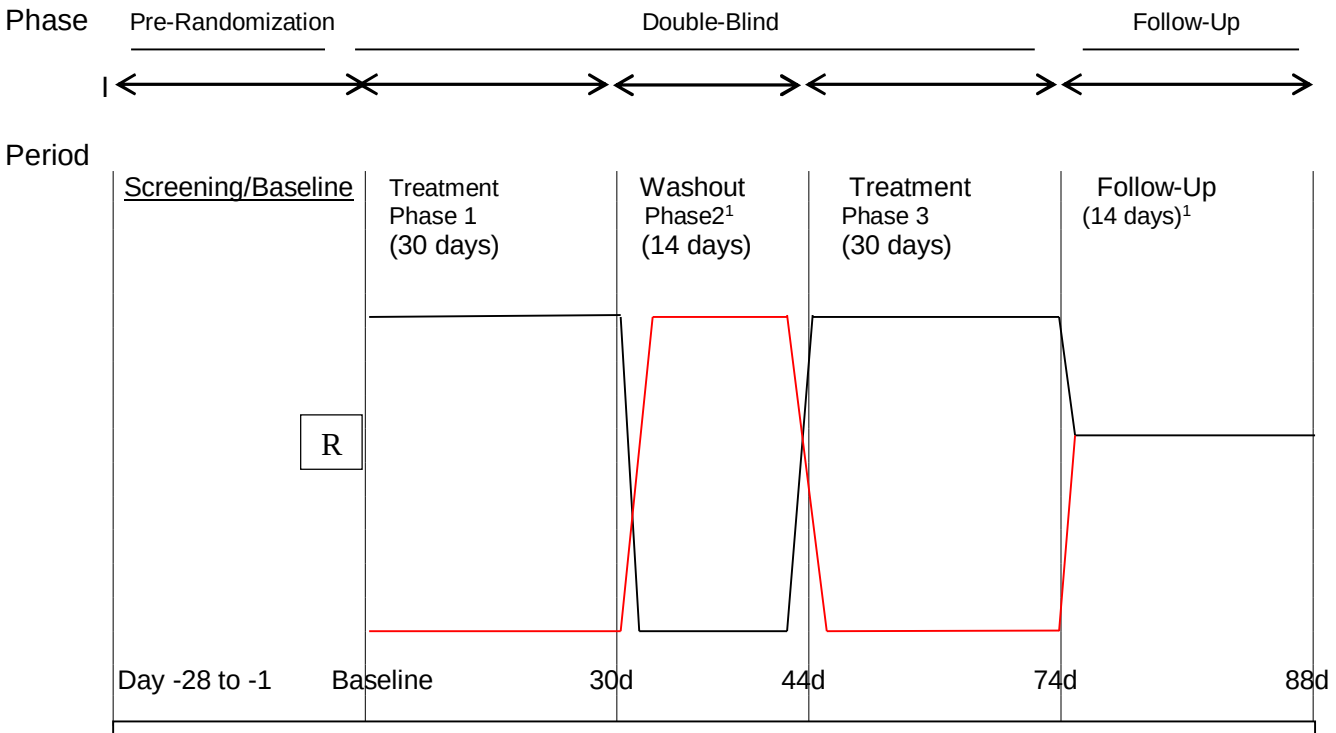
9.1 OVERALL STUDY DESIGN AND PLAN

Protocol PSY302 is a multicenter, double-blind, placebo-controlled, randomized cross-over study in approximately 30 – 40 subjects conducted to assess the efficacy and safety of ecopipam in children 7 to 17 years. On the first day of each dosing phase (Periods 1 and 3), subjects will take their study medication at the Investigator's office. Subjects will be instructed to take their next dose of study medication on the following evening at bedtime. Dosing of study medication will increase until either the maximal allowable level is reached or adverse events occur. In the event adverse events occur, the number of tables can be reduced until a tolerable level is reached. Subjects will be followed on an outpatient basis. A data safety monitoring board (DSMB) will be established to monitor safety (see Section 9.7.20).

Eligible subjects for this study will have a diagnosis of TS based on the Diagnostic Confidence

Index (DCI) for TS. The measurement of efficacy will be based on a series of self-reported and Investigator-reported validated instruments geared to the assessment of TS.

Figure 2 depicts the study design for this protocol.



Clinic Visits at Screening, Baseline (may be the same day), and days 16, 30, 44, 60 and 74

[1] During the first 1-4 days of Washout Phase 2 (Washout) and Follow-Up, the Subjects will discontinue study medication by reducing the number of tablets as instructed below.

Follow-up on day 88 will be at the investigator's office.

Since this is a crossover study, subjects receiving ecopipam during Treatment Phase 1 and washout will receive placebo during Treatment Phase 3 and Follow-Up. Similarly, subjects receiving placebo during Treatment Phase 1 and washout will receive ecopipam during Treatment Phase 3 and Follow-up.

Figure 2 Study Diagram

9.1.1 Screening Visit

Subjects will be screened and all safety evaluations as detailed in Table 8 and Section 9.5.5 will

be performed after the subject or parent/guardian provides informed consent and eligibility criteria are met.

9.1.2 Treatment Phase

9.1.2.1 Treatment Phases 1 and 3

Subjects who have a Yale Global Tic Severity Score (YGTSS) Total Tic Score of ≥ 20 at both the Screening and Baseline visits will begin Treatment Phase 1 of 30 days duration. Subjects who have a YGTSS score that is within 20% of their Baseline scores will be eligible to start Treatment Phase 3. If the Subject's YGTSS at the start of Treatment Phase 3 is >20% different than their Treatment Phase 1 Baseline value, the start of Treatment Phase 3 will be delayed until such time that their scores return to within 20% of the Treatment Phase 1 Baseline score.

On Day 1 of Treatment Phases 1 and 3, the first dose of study drug will be given in the clinic followed by a 4-hour observation period. Starting on the evening of day 2 of Treatment Phases 1 and 3, the subject will take study medication according to the following table:

IF 75LBS OR LESS AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-3 of Period 1 and 3	1 tablet orally each day at bedtime	Either 12.5 mg tablet of ecopipam or placebo	12.5 mg/day
Days 4-7 of Period 1 and 3	2 tablets orally each day at bedtime	Either 12.5 mg tablet of ecopipam or placebo	25 mg/day
Days 8-30 of Period 1 and 3	1 tablets orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	50 mg/day
• Subjects will receive three bottles during each Treatment Phase (1 and 3) of the study. o Bottle #1 will be for days 1-3 and will contain three tablets (either 12.5 mg active or placebo). The first dose is taken at the Investigator's office o Bottle #2 will be for days 4-7 and will contain 8 tablets (either 12.5 mg active or placebo) o Bottle 3 will for days 8-30 and will contain 23 tablets (either 50 mg active or placebo)			
IF 76LBS OR MORE AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-7 of Period 1	2 tablet orally each	Either 12.5 mg tablet of	25 mg/day

and 3	day at bedtime	ecopipam or placebo	
Days 8-14 of Period 1 and 3	1 tablet orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	50 mg/day
Days 15-30 of Period 1 and 3	2 tablets orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	100 mg/day
• Subjects will receive three bottles during each Treatment Phase (1 and 3) of the study. o Bottle #1 will be for days 1-7 and will contain 14 tablets (either 12.5 mg active or placebo). The first dose is taken at the Investigator's office. o Bottle #2 will be for days 8-14 and will contain 7 tablets (either 50 mg active or placebo) o Bottle 3 will for days 15-30 and will contain 32 tablets (either 50 mg active or placebo)			
If side effects occur, patient will be instructed to decrease dose to the previously tolerated number of tablets until side effects are resolved.			

During the dose titration phase of Treatment Phase 1 subjects will be called by the Study Nurse or Investigator every third day to monitor the Subject's progress and adverse events.

9.1.2.2 Washout Phase 2

Washout Phase 2 will last 14 days. During the first four days of this period, the Subject will discontinue study medication according to the following schedule. Thereafter, all subjects will stop all study medications until starting Treatment Phase 3.

IF 75LBS OR LESS AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1 of Period 2	3 tablets orally each day at bedtime	Either 12.5 mg ecopipam tablet or placebo	37.5 mg/day
Day 2 of Period 2	2 tablets orally each day at bedtime	Either 12.5 mg ecopipam tablet or placebo	25 mg/day
Day 3 of	1 tablet	Either 12.5 mg	12.5 mg/day

Period 2	orally each day at bedtime	ecopipam tablet or placebo	
Day 4 of Period 2	Stop	None	None
Down titration only occurs in subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			
IF 76LBS OR MORE AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1 of Period 2	6 tablets orally at bedtime	Either 12.5 mg ecopipam or placebo	75 mg/day
Day 2 of Period 2	4 tablets orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	50 mg/day
Day 3 of Period 2	2 tablet orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	25 mg/day
Day 4 of Period 2	1 tablet orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	12.5 mg/day
Day 5 of Period 2	Stop	None	None
Down titration only occurs in subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			

9.1.3 Follow-up Phase

During the first four days of this period, the Subject will discontinue study medication according to the following schedule until s/he is no longer taking any study medication. The Study Nurse or the Investigator will contact the Subject by phone on Day 6 to record any AEs. Subjects will have a final follow-up visit on Day 88 to assess compliance and record any AEs.

IF 75LBS OR LESS AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1 of Follow-Up	3 tablets orally each day at bedtime	Either 12.5 mg ecopipam tablet or placebo	37.5 mg/day
Day 2 of Follow-Up	2 tablets orally each day at bedtime	Either 12.5 mg ecopipam tablet or placebo	25 mg/day

Day 3 of Follow-Up	1 tablet orally each day at bedtime	Either 12.5 mg ecopipam tablet or placebo	12.5 mg/day
Day 4 of Follow-Up	Stop	None	None
Down titration only occurs in subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			
IF 76LBS OR MORE AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1 of Follow-Up	6 tablets orally at bedtime	Either 12.5 mg ecopipam or placebo	75 mg/day
Day 2 of Follow-Up	4 tablets orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	50 mg/day
Day 3 of Follow-Up	2 tablet orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	25 mg/day
Day 4 of Follow-Up	1 tablet orally at bedtime	Either 12.5 mg ecopipam tablet or placebo	12.5 mg/day
Day 5 of Follow-Up	Stop	None	None
Down titration only occurs in subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			

9.2 Discussion of Study Design, Including Choice of Control Groups

This study is designed as a double blind randomized cross over study for several reasons. First, in order to document by accepted scientific standards that a new treatment is effective, a double blind, randomized trial is the only acceptable design. Second, a cross over design was used to minimize the number of subjects exposed in the study and to allow each subject to act as their own control. This latter point is important since there may be significant intersubject variability. Allowing each patient to serve as their own control reduces the impact of this.

A DSMB will be established to allow for independent safety assessments during the study and to perform an interim analysis after 15 subjects have completed both blinded Treatment Phases.

9.3 Selection of Study Population

A previous open-label study demonstrated that ecopipam may be active for the treatment of TS in adults. However, the majority of patients afflicted with this disease are children. Therefore, we have selected a pediatric population since this will allow us to treat the largest eligible group.

Male or female children (≥ 7 to < 18 years of age) with a diagnosis of TS based on DSM-IV criteria will be eligible for this study. Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

9.3.1 Inclusion Criteria

Subjects who meet all of the following criteria will be included in the study. Any amendments to this protocol that change the inclusion criteria will be included in the clinical study report for this protocol.

1. Subjects must have TS based on the clinician-administered DCI for TS.
2. Subjects must exhibit both motor and vocal tics.
3. Subjects must have a minimum score of 20 at both Screening and Baseline (just prior to the first treatment) on the YGTSS.
4. Subjects must be age 7 to 17 years (≥ 7 to < 18 years of age)
5. Subjects must weigh ≥ 20 kg (45 lbs)
6. Females of childbearing potential (defined by menarche and not having undergone surgical sterilization/hysterectomy) must have a negative pregnancy test, must be practicing acceptable double-barrier methods of contraception (or can confirm abstinence at each scheduled visit), and must not be pregnant or lactating. Girls of childbearing potential and who are sexually active must be using effective contraception (i.e., oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for the duration of their participation in the study. They must also agree to use contraception for 30 days after their last dose of study drug.
7. Sexually active male subjects must use a barrier method of contraception during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.
8. Subject's parent or legal guardian must execute a written informed consent.
9. Subject must execute a written informed assent.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study. Any amendments to this protocol that change the study entry exclusion criteria will be included in the clinical study report for this protocol.

1. Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening.
2. Subjects with a major depressive episode in the past 2 years
3. Subjects with a history of attempted suicide
4. Subjects with clinically significant suicidality (as determined by the C-SSRS scale)
5. Subjects with a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization, or attempted/ completed suicide, with the exception of a hospitalization for post-partum depression.
6. Subjects with a history of seizures (excluding infantile febrile seizures that occurred >2 years in the past)
7. Subjects with a myocardial infarction within 6 months.
8. Girls who are currently pregnant or lactating.

9. Subjects who have a need for medication (other than ecopipam) with possible effects on TS symptoms (i.e., lithium, psychostimulants)
10. Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., dopamine antagonists or agonists [including buproprion], tetrabenazine, or monoamine oxidase inhibitors.
11. Subjects with a lifetime history of significant psychiatric disorder(s) as rated using the American Psychiatric Association DSM-V Cross-Cutting Symptom Measures rating scale[51].
12. Subjects with current or recent (past 3 months) DSM-IV substance abuse or dependence (with the exception of nicotine).
13. Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), opiates) at Screening. Subjects with urine positive only for benzodiazepines and/or marijuana (i.e., a user but not an abuser as based on DSM-IV criteria) may be eligible.
14. Subjects who have had previous treatment with ecopipam.
15. Subjects who have had treatment with:
    a. investigational medication within 3 months of starting study
    b. depot neuroleptics within 3 months of starting study
    c. other psychotropics with possible effects on TS symptoms (i.e., lithium, tetrabenazine) within 2 weeks prior to Screening.
    d. oral neuroleptics within 4 weeks
    e. selective serotonin reuptake inhibitors unless the dosage has been stable for a minimum of 4 weeks prior to study start and not prescribed to relieve the neurological signs of TS

9.3.3 Removal of Subjects from Therapy or Assessment

Any subject with a CDI assessment indicative of the onset of a new depressive episode at any visit will be discontinued from study participation.

The Investigator or subject themselves may stop study treatment at any time for safety or personal reasons.

Where possible, a subject who discontinues treatment will undergo protocol-specified end-of-study procedures (i.e., Day 74 assessments) at the time of discontinuation (see Section 9.5.1.2). Date and reason(s) of premature discontinuation will be described on the case report form (CRF). In addition, the date of last dose of study treatment will be recorded on the Study Treatment Dosing CRF.

Subjects who discontinue treatment for any reason, other than a serious adverse event (SAE) (even if the SAE is not treatment related) or an AE (unless the AE can be determined to be unrelated to treatment), may be replaced only after consultation with Psyadon.

9.4 TREATMENTS

9.4.1 Treatments Administered

The treatments administered in the study are presented below:

Formulation: Ecopipam will be supplied as 12.5 or 50 mg tablets
Placebo will supplied as matching tablets

Dosing Schedule:

- The first dose of study medication will be taken in the clinic to allow for the initial assessment of response.
- Beginning with the following evening, subjects will take a single tablet by mouth of study medication at bedtime

During the treatment phases (i.e., Periods 1 and 3), subjects will be instructed to take study medication as follows:

IF 75LBS OR LESS AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-3 of Period 1 and 3	1 tablet orally each day at bedtime	Either 12.5 mg tablet of ecopipam or placebo	12.5 mg/day
Days 4-7 of Period 1 and 3	2 tablets orally each day at bedtime	Either 12.5 mg tablet of ecopipam or placebo	25 mg/day
Days 8-30 of Period 1 and 3	1 tablets orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	50 mg/day
• Subjects will receive three bottles during each Treatment Phase (1 and 3) of the study. o Bottle #1 will be for days 1-3 and will contain three tablets (either 12.5 mg active or placebo). The first dose is taken at the Investigator's office o Bottle #2 will be for days 4-7 and will contain 8 tablets (either 12.5 mg active or placebo) o Bottle 3 will for days 8-30 and will contain 23 tablets (either 50 mg active or placebo)			
IF 76LBS OR MORE AT BASELINE			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-7 of Period 1 and 3	2 tablet orally each day at bedtime	Either 12.5 mg tablet of ecopipam or placebo	25 mg/day
Days 8-14 of Period 1 and 3	1 tablet orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	50 mg/day

Days 15-30 of Period 1 and 3	2 tablets orally each day at bedtime	Either 50 mg tablet of ecopipam or placebo	100 mg/day
• Subjects will receive three bottles during each Treatment Phase (1 and 3) of the study. o Bottle #1 will be for days 1-7 and will contain 14 tablets (either 12.5 mg active or placebo). The first dose is taken at the Investigator's office. o Bottle #2 will be for days 8-14 and will contain 7 tablets (either 50 mg active or placebo) o Bottle 3 will for days 15-30 and will contain 32 tablets (either 50 mg active or placebo)			
If side effects occur, patient will be instructed to decrease dose to the previously tolerated number of tablets until side effects are resolved.			

Since ecopipam is provided at 12.5 mg tablets, the dose range for this study will be a minimum of 12.5 mg/day and a maximum of 100 mg/day.

9.4.2 Identity of Investigational Products

Study drug will be supplied in labeled containers by the Sponsor. The product release certificates for ecopipam will be included in the clinical study report for this protocol. Any special storage conditions will be noted on the label and should be followed by the study site.

The labels will be produced by Psyadon**.** Minimally, the labels will contain the following information:

1. Name, address and telephone number of the Sponsor
2. Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and dose strength
3. Lot number
4. Protocol Number
5. Study identifier
6. Trial subject identification number
7. Directions of use
8. "Caution: New Drug - Limited by Federal (US) law to investigational use"
9. "Keep out of reach of children"
10. Storage Conditions
11. Expiration Date

Drug supplies will be sent to the Investigator after the following documentation has been received by Psyadon:

- A signed Confidentiality Agreement
- A copy of the final signature page, signed and dated by both the Investigator
- Written proof of approval of both the protocol and its consent form by the Institutional Review Board (IRB) of the institution where the study is to be conducted
- A copy of the IRB-approved Subject Information and Consent Form to be used in the study
- The IRB membership list or Health and Human Services Assurance number
- A copy of the certification for the reference laboratory conducting the clinical laboratory tests required by this protocol
- A signed and dated Food and Drug Administration (FDA) Form 1572
- A signed and dated Curriculum Vitae of the Principal Investigator
- A copy of the Principal Investigator's medical license
- A signed Clinical Trial Agreement
- A signed and dated Financial Disclosure Form for Principal and Subinvestigators listed on the FDA 1572 (if applicable)

Study drug must be stored as instructed on the study drug label. All relevant site-specific guidelines and country-specific labeling requirements must be followed. Study drug must be kept in a secure location and carefully stored at the study site within its original container and protected from light. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the Sponsor. Total study site accountability will be conducted at the end of the study and the Investigator must explain all discrepancies.

A Drug Dispensing Log must be kept current and should contain the following information:

- Identification (subject number and initials) of subject to whom the study drug was dispensed
- The dates and lot numbers for the study drug dispensed
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the Clinical Research Associate (CRA).

On close-out of the site, all used and unused investigational product must be shipped to the Psyadon-designated location. The Drug Dispensing Log must be available for monitoring, auditing, or inspection.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is a randomized study. All eligible subjects will take study drug to reduce the tics associated with TS.

9.4.4 Selection of Doses in the Study

The dose rationale for this study (up to 100 mg/day) is based on previous experience with ecopipam ranging from 25 to 800 mg (single doses), 25 to 400 mg per day (multiple doses for up to 9 days), PET studies, long-term studies in obesity, studies in children with Lesch-Nyhan Disease and in adults with Tourette's Syndrome. Subjects will be monitored throughout for toxicities of interest which is defined as an AE with a National Cancer Institute (NCI) severity of Grade 3 or above and that is at least possibly related to study medication. Particular AEs that will be monitored closely because of the pharmacology of the drug are sedation, psychiatric events of depression/anxiety/agitation, seizure, and weight loss. The NCI criteria for these events are listed below:

Table 8 Toxicities of Interest

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sedation/ Somnolence	—	Interfering with function, but not interfering with activities of daily living (ADL)	Obtundation or stupor, difficult to arouse; interfering with ADL	Coma	Death
Depression	Mild - not interfering with function	Moderate – interfering with function, but not interfering with ADL	Severe – interfering with ADL	Suicidal ideation; danger to self or others	Death
Anxiety	Mild - not interfering with function	Moderate – interfering with function, but not interfering with ADL	Severe – interfering with ADL	Suicidal ideation; danger to self or others	Death
Agitation	Mild - not interfering with function	Moderate – interfering with function, but not interfering with ADL	Severe – interfering with ADL	Suicidal ideation; danger to self or others	Death
Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered, poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death
Weight loss	5 - <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	20% or more from baseline; tube feeding or total parenteral nutrition indicated	—	—

9.4.5 Selection and Timing of Dose for each Subject

The initial dose of study medication for Period 1 and Period 3 will be taken in the clinic. Beginning with the following evening, subjects will take study medication orally at bedtime. The doses were selected based on the previous open-label trial of ecopipam for the treatment of TS in adults.

9.4.6 Blinding

Throughout the study, subjects and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (e.g., Safety) until the time of unblinding.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor and by the sponsor. In addition, master code breaker reports identifying the treatment group of each subject number will be provided to the site and to the sponsor in sealed envelopes. These code breaker reports are not to be opened unless an emergency occurs and knowledge of the subject's randomization code may affect his/her medical treatment. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. The investigator is to record the date and time of opening the code breaker report and the reason for breaking the code. At the conclusion of the study, all master code breaker reports at the site are to be returned to Psyadon for final reconciliation.

9.4.7 Prior and Concomitant Medications

For subjects who receive study treatment, any medication (including over-the-counter medications) administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication CRF. Nonpharmacologic therapies/procedures will also be captured on the CRF. The Investigator will record any AE on the Adverse Events CRF for which the concomitant medication was administered.

9.4.8 Treatment Compliance

During the study period, subject compliance will be monitored by review of the tablet counts at the study site visits. Any violation of compliance will require evaluation by the Investigator and Sponsor to determine if the subject may continue the study.

9.4.9 Drug Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following Psyadon's instructions and adhere to GCP guidelines as well as local and/or regional requirements.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not

enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of study drug to the subject; collection of unused supplies returned by the subject; and subsequent return of unused study drug to the Sponsor must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, and (d) all shipping service receipts. All forms will be provided by Psyadon. Any comparable forms that the investigational site wishes to use may be subject to approval by Psyadon.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Psyadon, a representative of the FDA, or a representative of a non-US health authority. All unused study drug, including empty containers, are to be returned to Psyadon at the conclusion of the study, unless provision is made by Psyadon for destruction of supplies and containers at the investigational site. On completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Psyadon personnel, study drug that is to be returned to Psyadon must be sealed with tamper-evident seals and shipped back to Psyadon following all local regulatory requirements.

Records of study drug and doses administered will be kept during the study. The CRA will review drug accountability during investigational site visits and at the completion of the study.

9.5 STUDY METHODS

9.5.1 Schedule of Procedures and Assessments

Table 9 presents the Time and Events Schedule for the study.

Table 9: Schedule of Procedures and Treatments

	Pretreatment		**Treatment Phase 1**		**Washout Phase 2 (Wash-out)**		**Treatment Phase 3**		**Follow-up**
Study Site Visit Number	**1 (Screening)**	**2 (Baseline)**	**3[a]**	**4[a]**	**5[a]**	**6[a]**	**7[a]**	**8[a]**	**9[b]**
Study Day	**-28 to -1**	**0**	**16**	**30**	**30**	**44**	**60**	**74**	**88**
Procedure									
Informed Consent	X								
Review Inclusion/Exclusion Criteria	X	X							
Medication History	X	X							
Medical/Psychiatric History and Complete Physical Exam	X								
ECG	X			X				X	
Vital Signs	X	X	X	X		X	X	X	X
Laboratory tests (Hematology and Chemistry)	X			X				X	
Urine Drug Screen	X								
Urine Pregnancy Test	X	X				X			X
DCI for Tourette's	X	X							
YGTSS Score	X	X	X	X		X	X	X	
DuPaul ADHD	X	X	X	X		X	X	X	

Table 9 (cont.): Schedule of Procedures and Treatments

	Pretreatment		**Treatment Phase 1**		**Washout Phase 2 (Wash-out)**		**Treatment Phase 3**		**Follow-up**
Study Site Visit Number	**1 (Screening)**	**2 (Baseline)**	**3[a]**	**4[a]**	**5[a]**	**6[a]**	**7[a]**	**8[a]**	**9[a]**
Study Day[b]			**16**	**30**	**30**	**44**	**60**	**74**	**88**
Procedure									
Child YBOCS	X	X	X	X		X	X	X	
Child Depression Inventory	X	X	X	X		X	X	X	
Columbia Suicide Severity Rating Scale	X	X	X	X		X	X	X	X
Clinical Global Impression Severity Score	X	X	X	X		X	X	X	
Clinical Global Impression Improvement Score			X	X			X	X	
Record Adverse Events		X	X	X		X	X	X	X
Assess Concomitant Medications	X	X	X	X		X	X	X	X
Dispense Study Drug		X			X	X		X	
Administer Study Drug		X				X			
Collect Unused Study Drug			X	X		X	X	X	X
Assess Study Drug Compliance			X	X		X	X	X	X

[a] Visit will be at clinic [b] Visit days may vary by up to 72 hours to account for scheduling.

9.5.1.1 Screening Procedures

Screening - Visit 1 (Day –28 to Day -1)

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent obtained. Once informed consent has been obtained, the following screening procedures will be performed.

Screening Procedures:

- Inclusion/exclusion criteria
- Demography
- Medication history (within the past 30 days)
- Medical/psychiatric (using the DSM-V-CC-SM) history and complete physical examination
- ECG
- Vital signs (sitting or supine systolic and diastolic blood pressure, radial pulse, respiration, oral body temperature, weight, and height)
- Clinical laboratory tests (hematology and biochemistry, including LFTs)
- Urine drug screen
- Urine pregnancy test (for women of childbearing potential only)
- Perform DCI for TS
- YGTSS (must be ≥ 20 to qualify)
- DuPaul ADHD rating scale-IV, home version
- Yale-Brown Obsessive Compulsive Scale (C-YBOCS)
- Clinical Global Impression - Severity Scale
- CDI
- Columbia-Suicide Severity Rating Scale (C-SSRS) (Baseline Screening Scale) Record concomitant medication use
- Schedule return visit

9.5.1.2 Treatment Phase

Subjects will return to the clinic within 28 days of the Screening visit.

Baseline - Visit 2 (Day 0)

- Review of Inclusion/Exclusion criteria
- Vital signs (sitting or supine systolic and diastolic blood pressure, radial pulse, respiration, oral body temperature, weight, and height)
- Urine pregnancy test (for women of childbearing potential only)
- Perform DCI for TS
- YGTSS (must be ≥ 20 to qualify)
- DuPaul ADHD rating scale-IV, home version
- C-YBOCS
- Clinical Global Impression - Severity Scale

- CDI
- C-SSRS (Baseline Scale)
- Administer the first dose of ecopipam in the clinic
- Record any adverse events
- Record concomitant medication use
- Dispense ecopipam tablets to be taken at home
- Schedule return visit

Clinic visits -Days 16, 30, 44, 60, and 74

- Vital signs (sitting or supine systolic and diastolic blood pressure, radial pulse, respiration, oral body temperature, weight.
- Clinical laboratory tests (hematology and biochemistry, including LFTs) (Visit 4 and 8 only)
- ECG (Visits 4 and 8 only)
- Urine pregnancy test (for women of childbearing potential only) (Visits 6 and 9 only)
- YGTSS
- DuPaul ADHD rating scale-IV, home version
- C-YBOCS
- Clinical Global Impression - Severity Scale
- Clinical Global Impression - Improvement Scale
- CDI
- C-SSRS ("Since Last Visit" Scale)
- Administer study medication (visits 6)
- Record adverse events
- Record concomitant medication use
- Dispense ecopipam tablets (Visit 2, 5, 6, 8)
- Assess study drug compliance
- Collect unused study drug (Visit 3, 4, 6 7, 8 and 9(if necessary))
- Schedule return visit (except Visit 8)

Phone Contacts on Days 3, 7, 23, 47, 51 and 67

- The Investigator, Study Nurse or their Designee will contact the Subject by phone to record any adverse events, to monitor compliance and answer any questions.

9.5.1.3 Follow-up Phase Procedures

Visit 9

- On Day 6 of Follow Up Phase, a phone contact will be arranged to record any adverse events. On Study Day 88, subject will return to the investigator's clinic to check vital signs, assess study drug compliance, collect unused study drug, record adverse events and concomitant medications, complete a final C-SSRS, and (if patient is female and of child bearing potential) do a urine pregnancy test.

9.5.1.4 Study Restrictions

There are no special restrictions needed for this study.

9.5.2 Appropriateness of Measurements

This is a Phase 2b study to determine the efficacy and safety/tolerability of ecopipam administrated orally. Collection of safety information is consistent with the known pharmacologic effects of ecopipam.

9.5.3 Efficacy and Clinical Assessments

9.5.3.1 Yale Global Tic Severity Score

The primary outcome measure will be the YGTSS.[45] The YGTSS is a clinician-completed rating scale used to quantify overall tic severity as well as specific subdomains of tic number, frequency, duration, intensity, and complexity. Each of these subdomains is scored, on a 5-point scale, separately for motor and vocal tics and then summed across both motor and vocal tics to yield a tic severity score ranging from 0 to 50. The YGTSS also provides for an overall impairment rating (0 = ‘‘none’’ to 50 = ‘‘severe’’). The YGTSS has demonstrated acceptable internal consistency, good interrater reliability, and acceptable convergent and divergent validity.

9.5.3.2 DuPaul ADHD Rating Scale-IV, Home Version

The DuPaul ADHD rating scale-IV, home version is a validated instrument consisting of 18 behavioral criteria[46].

9.5.3.3 Child Yale Brown Obsessive Compulsive Scale

The C-YBOCS is a reliable and valid scale to both determine severity of OCD and to monitor improvement during treatment [47] The scale is a clinician-rated, 10-item scale that includes questions about the amount of spent on obsessions/compulsions, level of impairment or distress, and how much resistance and control subjects have over these thoughts.

9.5.3.4 Clinical Global Impression - Severity and Improvement Scales

The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms.[48] The improvement scale will be used at every visit after the Screening and Baseline Visits. The scale ranges from 1 = “very much improved” to 7 = very much worse.” The CGI severity scale will be used at each study site visit and ranges from 1 = “not ill at all” to 7 = “among the most extremely ill.”

9.5.3.5 DSM-V-CC-SM

The DSM-V-CC-SM is a rating scale that has been validated[51] in children and is used to assess current psychiatric symptoms and for this protocol it is only utilized to exclude ineligible subjects. The scoring rubric that will be used to exclude subjects is as follows:

Instructions to Investigators

The DSM-5 Parent/Guardian-Rated Level 1 Cross-Cutting Symptom Measure assesses mental health domains that are important across psychiatric diagnoses. It is intended to help investigators identify subjects who are eligible for participation in PSY302.

The measure consists of 25 questions that assess 12 psychiatric domains, including depression, anger, irritability, mania, anxiety, somatic symptoms, inattention, suicidal ideation/attempt, psychosis, sleep disturbance, repetitive thoughts and behaviors, and substance use. Each item asks the parent or guardian to rate how much (or how often) his or her child has been bothered by the specific symptom during the past 2 weeks. The measure was found to be clinically useful and had good test-retest reliability in the DSM-5 Field Trials in pediatric clinical samples across the United States.

Scoring and Interpretation

1. Any score greater than Level 2 in Sections 1, 2, 5, 6, 7 and 8 will exclude the subject
a. The only exception being if the Somatic scores in Section 1 have a well-diagnosed and on-going physical basis (e.g., GI problems due to GERD controlled by H2 blockers or proton-pump inhibitors)
2. Any score greater than Level 1 for Section 4 (Depression) will exclude the subject
3. Any score greater than 0/None in Section 9 (Psychosis) will exclude the subject
4. Since Sections 3 (Inattention) and 10 (Repetitive Thoughts) are symptoms of ADHD or OCD and since these are typical co-morbidities of patients with Tourette's, any score here is acceptable. (The severity of these symptoms and any changes will be captured more thoroughly with the DuPaul and YBOCS scales.)
5. Any positive answer to Section 11 (Substance Abuse) can be verified using the urine drug screen. If positive, the subject will need to be evaluated to see if they meet DSM criteria for being a user or an abuser (with the exception of cigarette smoking). Per the protocol, abusers are excluded while users can be enrolled. This evaluation is separate and not covered by either scale.
6. Any positive answer in Section 12 (Suicide) will exclude the subject

9.5.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Measurements

Not applicable to this study.

9.5.5 Safety Assessments

9.5.5.1 General

Safety assessments (sitting or supine blood pressure, heart rate, AEs, and concomitant medications) will be documented at each study site visit. Subjects who endorse suicidal thoughts at any time during the study will be removed from the study and appropriate clinical intervention (e.g., hospitalization) will be arranged. The investigator will record use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use. Laboratory assessments (e.g., clinical chemistry, hematology) and ECG will be performed at Screening, Visit 4 and the Final Visit (i.e., either the last visit scheduled per the protocol or the final visit if the

subject terminates the study early). Urine pregnancy tests will be performed at Screening, Baseline, Visit 6, and the Final Visit (i.e., either the last visit scheduled per the protocol or the final visit if the subject terminates the study early).

Safety assessments will consist of monitoring and recording all AEs and SAEs; monitoring hematology, blood chemistry, and ECG; periodic measurement of vital signs, and the performance of physical examinations. An independent DSMB will also be instituted in order to ensure the safety of the subjects.

9.5.5.2 Safety Rating Scales

9.5.5.3 Columbia-Suicide Severity Rating Scale

The C-SSRS is a low burden (approximately 5 minutes for completion) instrument to assess both suicidal behavior and ideation[49]. The scale is appropriate for subjects from age 6 through to an elderly population. There are 3 scales to be used at various points in the study: Screening/Baseline, Baseline, and Since Last Visit.

9.5.5.4 Child Depression Inventory

The Child Depression Inventory is a clinically validated rating scale designed to assess psychiatric signs and symptoms of depressions[50].

9.5.5.5 Adverse Events, Serious Adverse Events and Reporting

ADVERSE EVENTS, SEVERITY, AND RELATIONSHIP

Adverse Event (AE): Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study the medicinal product is ecopipam.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline.

An abnormal laboratory test result may be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study treatment
- results in withholding of study treatment pending some investigational outcome
- medical evaluation that results in the initiation of an intervention (e.g., potassium supplementation for hypokalemia)
- any out of range laboratory value that the Investigator's judgment, fulfils the definitions of an AE with regards to subject's medical profile
- increases in severity compared to Baseline by ≥ 2 NCI grades (see Appendix 1 in Section 12 for modified NCI common toxicity criteria [CTC]), with the exception of lymphocytes, albumin, cholesterol, glucose and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the Investigator to determine if they are of clinical significance and, if so, will be considered an AE.
- any subject reporting an AE which is rated as ≥3 will be discontinued from the study.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. All laboratory abnormalities considered to constitute an AE should be reported on the Adverse Event CRF.

It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

REPORTING OF ADVERSE EVENTS

All AEs encountered during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent. Adverse events in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.

Subjects with AEs that are ongoing at the subject's last study visit (including any telephone visits) must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. Adverse events that are reported during the 7 days following the subject's last study visit will be recorded on the Adverse Events CRF and followed until resolution or for up to the 30 days after the subject's last study visit, whichever comes first, with the exception that SAEs will be followed until the event resolves or the event or sequelae stabilize.

Every effort must be made by the Investigator to categorize each adverse event according to its severity and its relationship to the study treatment.

ASSESSING SEVERITY OF ADVERSE EVENTS

Adverse events will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

MILD:	Discomfort noticed, but no disruption of normal daily activity
MODERATE:	Discomfort sufficient to reduce or affect normal daily activity
SEVERE:	Incapacitating, with inability to work or to perform normal daily activity.

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.5.2 for the definition of a SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment, or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy treatment-related factors which are known to be associated with the occurrence of the event.

CLASSIFICATION OF CAUSALITY

Not Related: A causal relationship between the study treatment and the AEs not a reasonable possibility.

Related: A causal relationship between the study treatment and the AEs a reasonable possibility. The Investigator must further qualify the degree of certainty as "**possible**" or "**probable**."

9.5.5.6 Serious Adverse Events

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

- results in death;
- is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situation.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug.

In addition to the above, other events of interest which includes treatment-emergent significant laboratory abnormality and "overdose" are to be captured using the SAE procedures but are to be considered as SAEs only if they met 1 of the above criteria. All events of these types are to be reported on CRF whether or not they meet the criteria for SAEs. Consideration for other protocol specified events can be those identified by safety from previous clinical studies, preclinical studies or therapeutic findings such as those identified by toxicology.

All SAEs, other important medical events and other events of interest, including those occurring up to 30 days following the subject's last study treatment, and those made known to the Investigator at any time that are suspected of being related to study drug, will be recorded on the Adverse Events CRF. In addition, SAEs must be reported in an expedited fashion following the procedures detailed in "Reporting of SAEs". Subjects with SAEs must be followed until the event resolves or the event or sequelae stabilize.

REPORTING OF SAEs

Deaths and life-threatening events should be reported immediately by telephone to:

Richard Chipkin, PhD
301-919-2020

The immediate report should be followed-up within 1 business day by faxing or emailing the completed SAE form to:

Richard Chipkin, PhD
RChipkin@Psyadonrx.com
Fax Number: 301-556-1659

For Urgent Safety Issues call: 301-919-2020

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality.

All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization. Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the termination visit and for 30 days following study drug discontinuation. Any SAE that occurred within 7 days of treatment termination must be entered in the CRF.

Any SAE event judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents requested by the Sponsor.

The Investigator should notify the IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to Psyadon.

REPORTING OF PREGNANCY

Initial information on a pregnancy (during or after the study) must be reported immediately to Psyadon and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Psyadon according to SAE reporting procedures described above.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the

pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of their partner's pregnancy, including perinatal and neonatal outcome should be reported where possible.

REPORTING OF OVERDOSE

Any study drug overdose during the study, should be noted on the Study Medication CRF.

All AEs associated with an overdose should both be entered on the Adverse Event CRF and reported using the procedures detailed in "Reporting of SAEs", even if the events do not meet serious criteria. If the AE associated with an overdose does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner, but should be noted as being not serious on the SAE form and the Adverse Event CRF.

REPORTING A SIGNIFICANT LABORATORY ABNORMALITY

Any significant treatment-emergent laboratory abnormality observed during treatment or observed 7 days after last study treatment should be entered on the Adverse Event CRF and reported using the procedures detailed in "Reporting of SAEs", even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner, but should be noted as being not serious on the SAE form and the Adverse Event CRF. A laboratory result should be considered a treatment-emergent significant abnormality if the result.

- is within normal limits at baseline and has increased in severity to meet modified NCI – CTC Version 3 criteria of Grade 3 or above;

- is outside of normal limits at baseline and increased in severity to modified NCI-CTC Version 3 criteria of Grade 4 or above-these abnormalities are automatically considered to be serious; and/or

- is otherwise considered by the Investigator to meet serious criteria as defined in Section 9.5.5.2.

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

EXPEDITED REPORTING

Psyadon must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

BREAKING THE BLIND

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the Investigator may break the randomization code for

an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.5.7 Laboratory Measurements

Clinical laboratory tests during the study will be performed by a local laboratory. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow for a repeat analysis.

Laboratory certification as available will be included in the clinical study report for this protocol.

Table 10 presents the clinical laboratory tests to be performed.

Table 10 Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, and white blood cell count with differential (neutrophils, bands lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine
Other	Glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin
Pregnancy Test	Urine test (for women of childbearing potential only)

A laboratory abnormality may meet the criteria to qualify as an AEs described in this protocol (see Section 9.5.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

For laboratory abnormalities meeting criteria as SAE (see Section 9.5.5.2), the study site must fax the SAE report including the laboratory report to the Psyadon Drug Safety Department using the SAE Form (see “Reporting of SAEs”).

9.5.5.8 Vital Sign and Weight Measurements

Vital sign measurements (e.g., blood pressure [systolic/diastolic blood pressure in mm Hg], heart rate [beats per minute], respiratory rate [per minute], weight [kg], height [cm, first visit only] and oral body temperature [in degrees centigrade]) will be obtained at the visits designated on the Schedule of Procedures/Assessments by a validated method. Blood pressure and pulse will be measured with the subject seated or supine.

9.5.5.9 Medical History and Physical Examinations

Medical history and complete physical examinations will be taken as designated on the Schedule of Procedures/Assessments. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to the start of study drug will be recorded on the Medical History CRF. Only changes from Screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Complete Physical Examination

A complete physical examination will be performed and will include evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, skin, and neurological status.

9.5.5.10 Psychiatric History

Psychiatric history will be assessed using the DSM-V-CC-SM.

9.5.5.11 Other Special Tests

Not applicable.

9.5.6 Completion/Discontinuation of Subjects

A subject may elect to discontinue from the study at any time for safety or personal reasons. All subjects who discontinue from the study are to complete the early study discontinuation procedures.

Any subject with an adverse event with a "Toxicities of Interest Grade 3 or More" (as per Table 8 above) will be discontinued from the study.

Any subject with a new positive response on the Columbia Suicide Severity Scale will be immediately discontinued and evaluated for risk. Dosing may be re-started at the discretion of the Investigator following consultation with the Sponsor.

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, and Administrative/other. In addition to the primary reason, the subject may have indicated one or more of these reasons as secondary reasons for discontinuation. Study disposition information will be collected on the CRF.

Subjects who discontinue treatment for any reason, other than a SAE (even if the SAE is not treatment related) or an AE (unless the AE can be determined to be unrelated to treatment), may be replaced only after consultation with Psyadon.

9.5.7 Pharmacologic Effects of Special Interest

Not applicable.

9.6 DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site visit audits will be made periodically by Psyadon's or a designated CRO's qualified compliance auditing team, which is an independent function from the study conduct team.

9.6.1 Data Collection

Investigators will enter the information required by the protocol onto the CRFs in accordance with the CRF Completion guidelines that are provided with the CRFs. CRAs will visit each investigational site as frequently as documented in the monitoring plan to review the CRFs for completeness and accuracy against the source documents. CRAs will highlight any discrepancies found in the documentation of study conduct and ensure that appropriate site personnel address the discrepancies.

When a discrepancy results in corrected CRF data, the data that is corrected will be struck through with a single line, initialed, and dated by site personnel. Uniform procedures will be discussed at the Investigator meetings and/or at site initiation.

The CRFs will be forwarded to Psyadon with a copy retained at the investigational site. The original, completed CRF will be kept by Psyadon in its central document repository.

9.6.2 Clinical Data Management

Data from CRFs and other external data (e.g., laboratory data) will be entered into a clinical database as specified in the Psyadon or a designated CRO's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

9.6.3 Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

9.6.4 Bioanalytical Data Management and Quality Control

Not applicable.

9.7 STATISTICAL METHODS

All data analyses will be performed by Psyadon or a designated CRO after the study is completed and the database is finalized and released. Statistical programming and analyses will be performed using SAS and/or other validated statistical software as required.

9.7.1 Statistical and Analytical Plans

The statistical analyses described in this section will be performed for the study.

9.7.1.1 Analysis Sets

All subjects who received ≥ 1 dose of ecopipam and have at least 1 safety assessment (after taking ecopipam) will be included (intent-to-treat).

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

For continuous demographic variables, results will be summarized and presented as N, mean, standard deviation, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of subjects will be used. No statistical test will be performed.

PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

9.7.1.2 Efficacy Analyses

The primary efficacy measure will be the YGTSS total score. The YGTSS will be analyzed using a two-way analysis of variance extracting the effects of group, subject (within group), period and treatment, with group compared with subject (within group) as the error term and period and treatment using the residual error. Scales will be listed and actual and changes tabulated. Primary analysis will use an intent-to-treat population with last observation carried forward; a completer analysis will also be done.

Secondary parameters such as the ADHD scale and YBOC-C will be analyzed using the model specified above for YGTSS. The Wilcoxon signed rank test will be used for comparisons of categorical variables such as the CGI.

Changes from each treatment's baseline and endpoint (i.e., last treatment value) will be compared. Each treatment's baseline will be compared for comparability. The data from Period 1 will also be analyzed using a one-way ANOVA extracting treatment.

9.7.1.3 Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Analyses

Not applicable to this study.

9.7.1.4 Safety Analyses

Assessment of safety will be performed for all subjects. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and other results.

Adverse events will be coded to a standard set of System Organ Class and preferred term as defined in the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Incidence of treatment-emergent adverse events will be tabulated by system organ class and preferred term.

Concomitant medication will be presented coded with WHO dictionary and tabulated by ATC

and preferred drug name.

EXTENT OF EXPOSURE

The actual number of doses will be summarized.

ADVERSE EVENTS

Adverse events will be classified into standardized medical terminology from the verbatim description (Investigator term) using the MedDRA. Adverse events will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the clinical study report for this protocol. Adverse events will be summarized by presenting, for each cohort, the incidence of AEs. The incidence of AEs will be based on the numbers and percentages of subjects with AEs. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only 1 time in the incidence count for that MedDRA term.

Treatment-emergent adverse events will be analyzed. Adverse events that are not treatment emergent will be listed. Treatment-emergent adverse events are defined as AEs that emerge during treatment, having been absent at pretreatment (Baseline) or

- Reemerge during treatment, having been present at Baseline but stopped prior to treatment, or
- Worsen in severity during treatment relative to the pretreatment state, when the AE is continuous.

LABORATORY VALUES

Clinical laboratory results after baseline will be evaluated for markedly abnormal values. Appendix 1 presents the modified NCI CTC criteria that will be used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

VITAL SIGNS

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

OTHER SPECIAL TESTS

Not applicable.

9.7.2 Determination of Sample Size

Assuming a standard deviation of 10 for total YGTSS scores with 80%, a two-tailed alpha level of 0.05, with approximately 30 completed subjects a difference of 5 points can be detected. A 5 point change is considered clinically significant.

Interim Analysis

Interim analyses will be done in coordination with the Data Safety Monitoring Board (DSMB) meetings to primarily assess safety and preliminary efficacy. An interim analysis will be conducted after the first 15 subjects have enrolled and completed all three study phases (Treatment 1, Wash-Out, and Treatment 2).These interim analyses will be performed by a statistician and governed by an external DSMB. To maintain the credibility and integrity of the study, procedures will be implemented to ensure the DSMB and statistician have sole access to evolving information from the clinical study regarding comparative safety data. Full details of the DSMB procedures including primary responsibilities of the DSMB, its relationship with other study components, its membership, and the purpose and timings of its meetings will be documented in a DSMB charter. These details will also include procedures to ensure confidentiality and proper communication, the guidelines to be implemented by the DSMB and an outline of the content of the closed reports (unblinded) and open reports (blinded) that will be provided to the DSMB.

Data Safety Monitoring Board

An independent data safety and monitoring board (DSMB) consisting of a physician experienced in the conduct of clinical trials (Chairman), an ethicist, and two clinicians experienced in Tourette's syndrome will review the data at the interim analysis. The data will be cleaned by the data management group, and the analysis and reporting of the interim data to the DSMB will be the responsibility of an independent statistical group (who will not be directly involved in the conduct of the study). The DSMB will meet after the data presentation and issue a set of minutes as to the safety and viability (i.e., statistical power) of the study to reach its goals at study completion. The minutes of the DSMB will be appended to the final study report.

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11. PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 ETHICS AND GOOD CLINICAL PRACTICE

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH GCPs to which the protocol conforms as well as all governing local regulations and principles for medical research.

The protocol, informed consent, and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations, e.g., Federal Regulations, Title 21 CFR Part 56. Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. SAEs should be reported to the IRB/IEC in accord with local regulatory requirements.

11.1.1 Subject Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. Subjects will be given time to read the consent either in the research center of each site and have the opportunity to take the consent home for further consideration. They will also be given time to ask as many questions about the study protocol and other treatment options available to them prior to signing the consent form. Furthermore, each subject will be given a copy of the signed document. Only subjects with the ability to provide written informed consent will be included in this clinical trial. No subject can enter the study before his informed consent has been obtained.

An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 3, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the Sponsor. Each subject/legal guardian must sign an approved informed consent prior to study participation. The form must be signed

and dated by the appropriate parties. The original signed ICF for each subject will be verified by the Sponsor and kept in the study center's investigational site files; a signed copy will be given to the subject.

11.2 ADMINISTRATIVE PROCEDURES

11.2.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's Medical Monitor must be notified promptly and the IRB/IEC for the site must be informed within 5 working days.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB/IEC detailing such changes.

11.2.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with ICH E6, Section 4, "Investigator Guideline for Good Clinical Practices."

11.2.3 Monitoring Procedures

The Sponsor's or CRO's CRA will maintain contact with the Investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCPs and Good Laboratory Practices. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with federal regulations. All records at the investigational site are subject to inspection by the FDA.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as Interactive Voice-response Systems, x-rays, and other imaging reports, e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives)

- Pain, quality of life, medical history questionnaires completed by subjects

- Records of telephone contacts

- Diaries or evaluation checklists

- Drug distribution and accountability logs maintained in pharmacies or by research personnel

- Laboratory results and other laboratory test outputs, e.g., urine pregnancy test result documentation and urine dip-sticks

- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs

- CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source

11.2.4 **Recording of Data**

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained:

- All entries are to be typed or printed using a black ink ballpoint pen.(for paper CRF)

- There are to be no erasures, write-overs, use of correction fluid or tape, and the original entry must remain legible.

- Errors are to be corrected by placing 1 line through the error. The correct entry should appear next to the error, dated, and initialed by the responsible person making the change. The name of anyone making corrections must appear on the Site Signature Log collected at the beginning of the study and as study assignments change throughout the conduct of the study. Each error is to be corrected separately.

- The Investigator must sign and date the CRF where noted. A signature stamp may not be used.

- Changes to a CRF that has been previously signed by the Investigator must be initialed and dated by the Investigator after the change is made. Changes made to CRFs via data clarification forms issued by the Sponsor must likewise be signed by the Investigator.

- Neither a subject's name nor initials are to appear on documents transmitted to the Sponsor in order to maintain confidentiality.

11.2.5 **Retention of Records**

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of CRFs, Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence. The investigational site should plan on retaining study documents for approximately 15 years after completion of the study.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

11.2.6 **Auditing Procedures**

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH GCPs and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

11.2.7 **Handling of Study Drug**

All study drug will be supplied to the Principal Investigator by the Sponsor. Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the drug labels. The Investigator must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The assigned CRA will review these documents along with all other study conduct documents at each and every visit to the investigational site once study drug has been received by the investigational site.

All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator must not destroy any drug labels or any partly used or unused drug supply. At the conclusion of the study and as appropriate during the course of the study, the Investigator will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor's CRA and to the Sponsor's address provided in the Investigator folder at each site.

11.2.8 **Publication of Results**

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Psyadon, in advance of submission. The review is aimed at protecting Psyadon's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between the Investigators and Psyadon.

11.2.9 **Disclosure and Confidentiality**

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and Institutional Review Board and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor (provided by the Sponsor).

11.2.10 **Discontinuation of Study**

The Sponsor reserves the right to discontinue the study for medical reasons or by sponsor at any time for any reason. Reimbursement for expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees will be made. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. In such an event, final settlement of the grant-in-aid will be adjusted pro rata, and the Investigator will refund the excess of payments made in advance. The Investigator will notify the IRB/IEC in case of study discontinuation. Study records must be retained as noted above.

12. APPENDICES

Appendix 1 Modified NCI Toxicity Grade

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	< LLN - 10.0 g/dL < LLN - 100 g/L < LLN - 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 - 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 – 6.5 g/dL < 80 - 65 g/L < 4.9 - 4.0 mmol/L	< 6.5 g/dL < 65 g/L < 4.0 mmol/L
Leukocytes (total white blood cell count)[d]	< LLN - 3.0 x 10^9 /L or < LLN - 3000/mm^3	< 3.0 – 2.0 x 10^9 /L < 3000 - 2000/mm^3	< 2.0 – 1.0 x 10^9 /L < 2000 - 1000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	<800/ - 500mm^3 <0.8 – 0.5 x 10^9 /L	<500 - 200/mm^3 <0.5 – 0.2 x 10^9 /L	< 200/mm^3 <0.2 x 10^9/L
Neutrophils/granulocytes (ANC/AGC)	< LLN - 1.5 x 10^9 /L < LLN - 1500/mm^3	<1.5 – 1.0 x 10^9 /L <1500 - 1000/mm^3	<1.0 – 0.5 x 10^9/L <1000 - 500/mm^3	< 0.5 x 10^9 /L < 500/mm^3
Platelets[c]	< LLN - 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9 /L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9 /L < 50,000 – 25,000/mm^3	< 25.0 x 10^9 /L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dl <LLN – 30 g/L	2 - < 3 g/dl 20 – 30 g /L	< 2 g/dl < 20 g /L	—
Alkaline phosphatase	> ULN – 3.0 x ULN[b]	> 3.0 - 5.0 x ULN [b]	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT, SGPT (serum glutamic pyruvic transaminase)[c,e]	> ULN - 3.0 x ULN[b]	> 3.0 - 5.0 x ULN[b]	> 5.0 - 20.0 x ULN	> 20.0 x ULN
AST, SGOT (serum glutamic oxaloacetic transaminase) [c,e]	> ULN – 3.0 x ULN[b]	> 3.0 - 5.0 x ULN[b]	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
Bilirubin (hyperbilirubinemia)[c,e]	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Creatinine[c]	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN[b]	> 3.0 - 5.0 x ULN[b]	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	2.0 - <2.5 mg/dl 0.6 - <0.8 mmol/L	1.0 - <2.0 mg/dl 0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Potassium, serum-high (hyperkalemia)	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	—	2.5 - <3.0 mmol/L	<2.5 mmol/L
Sodium, serum-high (hypernatremia)	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Sodium, serum-low (hyponatremia)	<LLN - 130 mmol/L	—	120 - <130 mmol/L	<120 mmol/L
Triglyceride, serum-high (hypertriglyceridemia)	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Uric acid, serum-high (hyperuricemia)	> ULN - 10 mg/dl <= 0.59 mmol/L without physiologic consequences	—	> ULN - 10 mg/dl <=0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L

13. APPENDIX 2

Protocol Number:	PSY 302A (PSY302 Appendix)
Title of Protocol:	Open Label Safety Protocol in Children 7-17 Years with Tourette's Syndrome
Sponsor:	Psyadon Pharmaceuticals Inc. 20451 Seneca Meadows Parkway Germantown, MD 20876
Medical Monitor:	Rudolf Kwan, MD Telephone: 908-522-3208 Mobile: 908-787-7847 E-mail: Rudolf.Kwan@gmail.com
Investigational Product:	PSYRX101 (ecopipam) Tablets, 12.5, 50 mg & 100 mg
Indication:	Treatment of Tourette's Syndrome in Children 7-17 Years
Phase:	Phase 2: Open Label Safety Protocol
GCP Statement:	This protocol is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and Open Label Safety regulations. All required treatment documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Psyadon Pharmaceuticals Inc. (Psyadon). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this open access protocol.

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<table>
<tr><td>Compound No.</td><td colspan="2">PSYRX101</td></tr>
<tr><td>Name of Active Ingredient</td><td colspan="2">Ecopipam Hydrochloride</td></tr>
<tr><td>Title of Open Label Safety Protocol Amendment to PSY302</td><td colspan="2">PSY302A - Open Label Safety Protocol in Children 7-17 Years with Tourette’s Syndrome</td></tr>
<tr><td rowspan="5">Investigator</td><td>Principal Investigator:
Donald L Gilbert, MD, MS
Director, Movement Disorder and Tourette Syndrome Clinics
Cincinnati Children’s Hospital Medical Center, ML No. 7018
3333 Burnet Avenue
Cincinnati, OH 45229-3039</td><td>Dr. Joseph Jankovic
Baylor College of Medicine
Department of Neurology
The Smith Tower, Suite 1801
6550 Fannin
Houston, Texas 77030</td></tr>
<tr><td>Roger Kurlan, MD
Director, Movement Disorders program
Atlantic Neuroscience Institute
Overlook Hospital
99 Beauvoir Avenue
Summit, NJ 07902</td><td>Cathy Budman, MD
Dept. of Psychiatry
North Shore University Hospital
400 Community Drive
Manhasset, NY 11030</td></tr>
<tr><td>Dr. Tanya Murphy
Rothman Center for Neuropsychiatry
880 Sixth Street South
Suite 460, Box 7523
Saint Petersburg, Florida 33701</td><td>Dr. Jorge Juncos
Emory University
Wesley Woods Health Center
1841 Clifton Road, NE, Third Floor
Atlanta, GA 30329</td></tr>
<tr><td>Dr. Justin Mohatt
Weill Cornell Medical College and New York-Presbyterian Hospital
525 E. 68th Street
Rm. F-1109; Box 140
New York, NY 10065</td><td>Harvey Singer, MD
The Johns Hopkins University
Dept. of Neurology
The David M. Rubenstein Child Health Bldg., Suite 2158
200 North Wolfe Street
Baltimore, MD 21287</td></tr>
<tr><td>Dr. Kevin Black
Washington University School of Medicine
Department of Psychiatry
660 South Euclid Avenue,
Campus Box: 8134
St. Louis, MO 63110
United States of America</td><td>Dr. Keith Coffman
Division of Neurology
Children's Mercy Kansas City
2401 Gillham Road
Kansas City, MO 64108
United States of America</td></tr>
<tr><td>Dosing</td><td colspan="2">Ecopipam is available as 12.5, 50 or 100 mg film coated tablets (FCT). The dose range for treatment will be a maximum of 100 mg/day.

The subject will be dosed according to the titration schedule in PSY302 as follows:</td></tr>
</table>

	<table><tr><td colspan="4">IF 75LBS OR LESS AT START OF OPEN LABEL STUDY</td></tr><tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr><tr><td>Days 1-3</td><td>1 tablet orally each day at bedtime</td><td>12.5 mg tablet of ecopipam</td><td>12.5 mg/day</td></tr><tr><td>Days 4-7</td><td>2 tablets orally each day at bedtime</td><td>12.5 mg tablet of ecopipam</td><td>25 mg/day</td></tr><tr><td>Days 8-end of study</td><td>1 tablets orally each day at bedtime</td><td>50 mg tablet of ecopipam</td><td>50 mg/day</td></tr><tr><td colspan="4"></td></tr><tr><td colspan="4">IF 76LBS OR MORE AT START OF OPEN LABEL STUDY</td></tr><tr><td>Day</td><td># of Tablets</td><td>Tablet Type</td><td>Ecopipam Dose</td></tr><tr><td>Days 1-7</td><td>2 tablet orally each day at bedtime</td><td>12.5 mg tablet of ecopipam</td><td>25 mg/day</td></tr><tr><td>Days 8-14</td><td>1 tablet orally each day at bedtime</td><td>50 mg tablet of ecopipam</td><td>50 mg/day</td></tr><tr><td>Days 15-end of study</td><td>1 tablets orally each day at bedtime</td><td>100 mg tablet of ecopipam</td><td>100 mg/day</td></tr><tr><td colspan="4"></td></tr></table> The subject will be instructed by the treating physician that if, at any time during the treatment period, they encounter adverse events, they can lower their dose under the supervision of the treating physician. As far as possible, dose decreases will be accomplished by splitting the tablets as directed by the treating physician. If necessary, the subject will be provided with lower strength tablets. At the discretion of the treating physician, the dose may be increased upon resolution of the adverse event. Ecopipam will be dosed at night before bedtime. However, the investigator is at liberty to instruct his subject to take ecopipam during the day if appropriate (e.g., some subjects in previous studies have experienced insomnia following treatment with ecopipam and daytime dosing may be preferable in this case).
Number/Type of Subjects	The enrollment goal for PSY302 is 30-40 subjects. Assuming that all subjects request continued treatment, then there will be 30-40 subjects eligible for PSY302A. Subjects will be children ages 7-17 years with Tourette's Syndrome.
Inclusion Criteria	The subject was previously enrolled in study PSY 302, which had the following inclusion criteria: 1. Subjects must have TS based on the clinician-administered DCI for TS. 2. Subjects must exhibit both motor and vocal tics. 3. Subjects must have a minimum score of 20 at both Screening and Baseline (just prior to the first treatment) on the YGTSS. 4. Subjects must be age (≥ 7 to < 18 years of age) 5. Subjects must weigh ≥ 20 kg (45 lbs.) 6. Adolescent females of childbearing potential who are sexually active must be using effective contraception (i.e., oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for the duration of their participation in the study. They must also agree to use contraception for 30 days after their last dose of study drug. 7. Sexually active male subjects must use a barrier method of contraception during the

	study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug. 8. Subject's parent or legal guardian must execute a written informed consent. 9. Subject must execute a written informed assent. To participate in this Open Label Safety Protocol, the subject must still fulfill all these Inclusion Criteria. All subjects must enter this study within 90 days of completing PSY302.
Exclusion Criteria	The subject was previously enrolled in study PSY 302, which had the following exclusion criteria: • Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening. • Subjects with a major depressive episode in the past 2 years • Subjects with a history of attempted suicide • Subjects with clinically significant suicidality (based on C-SSRS scale) • Subjects with a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization, or attempted/ completed suicide with the exception of a hospitalization for post-partum depression. • Subjects with a history of seizures (excluding febrile seizures that occurred >2 years in the past) • Subjects with a myocardial infarction within 6 months. • Girls who are currently pregnant or lactating. • Subjects with a lifetime history of significant psychiatric disorder(s) as rated using the American Psychiatric Association DSM-5 Cross-Cutting Symptom Measures rating scale. • Subjects with current or recent (past 3 months) DSM-IV substance abuse or dependence (with the exception of nicotine). • Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), opiates) at Screening. Subjects with urine positive only for benzodiazepines and/or marijuana (i.e., a user but not an abuser as based on DSM-IV criteria) may be eligible. The following Exclusion Criteria are <u>waived</u> for this Expanded Use Protocol 302A: • Subjects who have a need for medication (other than ecopipam) with possible effects on TS symptoms (i.e., alpha agonists, dopamine D2 antagonists, tetrabenazine) • Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., dopamine antagonists or agonists [including buproprion], tetrabenazine. • Subjects who have had treatment with: - investigational medication within 3 months of starting study - depot neuroleptics within 3 months of starting study - other psychotropics with possible effects on TS symptoms (i.e., lithium, tetrabenazine) within 2 weeks prior to Screening. - oral neuroleptics within 4 weeks - selective serotonin reuptake inhibitors unless the dosage has been stable for a minimum of 4 weeks prior to study start and not prescribed to relieve the neurological signs of TS WITH THE EXCEPTION OF MAO-INHIBITORS (WHICH ARE NOT PERMITTED), THE ADDITION OR CHANGE IN DOSE OF ANY MEDICATION RELATIVE TO WHAT WAS TAKEN DURING THE DOUBLE

	BLIND STUDY MUST BE CAREFULLY MANAGED BY THE INVESTIGATOR AND MONITORED FOR POSSIBLE INTERACTIONS
Protocol Treatment	• **Investigational drug:** Ecopipam Tablets, 12.5, 50 mg & 100 mg • • As noted above, subjects participating this study must establish their ecopipam dose by following the titration schedule listed above. • • Ecopipam should be taken at night before bedtime since sedation has been observed. However, the subject may also be instructed to take ecopipam during the day if warranted. For example, since some subjects in previous studies have experienced insomnia following treatment with ecopipam, daytime dosing may be preferable for these subjects. • • The subject will be instructed that at any time during the treatment period they encounter adverse events, they can lower their dose under the supervision of the physician. As far as possible, dose decreases will be accomplished by splitting the tablets as directed by the treating physician. If necessary, the subject will be provided with lower strength tablets. At the discretion of the treating physician, the dose may be increased upon resolution of the adverse event. The dose for this subject will be a maximum of 100 mg/day. •
Duration of Treatment	Up to 52 weeks, based upon a summary of the subject's status provided by the treatment physician at 12 months, at which time the subject will be re-assessed to determine if further treatment is warranted. If yes, then the subject can be treated for another 52 weeks as long as ecopipam has not been approved for sale.
Criteria for Evaluation	• • **Safety Assessments:** Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs) throughout the 12-month treatment period. The baseline assessments include vital signs, clinical laboratory testing, and compilation of concomitant medications. Subjects will also be assessed with the Child Depression Inventory and the Columbia-Suicide Severity Rating Scale • • **Efficacy Assessments:** Efficacy will be assessed every three months using the Yale Global Tic Severity Score (YGTSS) and the physician rated Clinical Global Impression – Severity scale.
Statistical Methods	This is an open label safety protocol. The treating physician will provide a clinical summary of the status of the subject, including adverse events after the 12-month assessment. The treating physician will provide a detailed summary of the subject's experience while on ecopipam to determine whether the subject may continue on ecopipam for another 12 months. At the end of treatment, Psyadon will submit a written summary, including adverse effects to the FDA.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
ATC	Anatomic Therapeutic Classification
AUC	area under the plasma-concentration time course profile
AUC(0-24 hr)	area under the plasma-concentration time course profile from time 0 (dosing) to 24 hours after dosing
BUN	blood urea nitrogen
CDI	Child Depression Inventory
CFR	Code of Federal Regulations
CGI	Caregiver Global Impression
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CNS	Central nervous system
CO2	bicarbonate
CRA	Clinical research associate
CRO	Clinical research organization
CTC	Common Toxicity Criteria
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DD	Drug Dictionary
DLT	Dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCl	Hydrochloride
HPRT	hypoxanthine-guanine phosphoribosyltransferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IQ	Intelligence quotient
IV	Intravenous
Ki	Inhibition constant
LDH	lactic dehydrogenase

LFT	Liver function test(s)
MAO-I	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NOEL	No observable effect level
PGI	Physician Global Impression
PET	Positron emission tomography
PK	Pharmacokinetic(s)
PO	Oral (per os)
PSYRX	Psyadon drug code indicator
QD	Once daily
RBC	red blood cell (count)
SAE	serious adverse event
SC	Subcutaneous
SCH	Schering-Plough drug code indicator
SIB	Self-injurious behavior
TEAE	Treatment-emergent adverse event(s)
tmax	time from dosing to the maximum observed concentration
TPN	Total parenteral nutrition
TS	Tourette's Syndrome
US	United States
WBC	white blood cell (count)
WHO	World Health Organization
YGTSS	Yale Global Tic Severity Score

2. TREATING PHYSICIAN AND SPONSOR PERSONNEL

The contact information for the treating physician for this open label safety protocol is shown above.

The contact information for the Medical Monitor (Rudolf Kwan, MD) will be included on the informed consent along with any other contact persons at Psyadon.

Rudolf Kwan, M.D.
Consulting Medical Director
- Telephone: 908-522-3208
- Mobile: 908-787-7847
E-mail: rudolf.kwan@gmail.com

3. RATIONALE OF ECOPIPAM USE FOR TOURETTE'S SYNDROME

Ecopipam hydrochloride (HCl) is a potent, selective antagonist of human D_1 dopamine receptors that is being investigated for use in the treatment of neurological disorders. Based on neuropathology and pharmacologic evidence, dopamine has an unambiguous role in movement disorders such as Parkinson's Disease and Huntington's Chorea. There is likewise strong evidence for dopamine's role in other neurological syndromes based on a variety of supporting data (e.g., self-injurious behavior in Lesch-Nyhan Disease, tardive dyskinesia, pathological gambling, Tourette's Syndrome, and others). In an open label study in adults with TS, Ecopipam has been shown to significantly reduce the severity of both the motor and vocal tics that are characteristic of TS (Gilbert et al., Clin Neuropharm 37: 26–30, 2014).

4. PROTOCOL OBJECTIVES

- The primary objectives of this open label safety protocol is to monitor the long-term (up to 52 weeks) effects of ecopipam and to provide ecopipam for the symptomatic treatment of TS in children 7-17 years per the request of a treating physician on behalf of the family. At this point in development of the product, it is not definitively known if ecopipam has efficacy in the treatment of TS, but subjects from the PSY 302 study who experience an associated improvement while participating in the blinded segment of the study and wish to remain on study medication are eligible for this study.

4.1 OPEN LABEL TREATMENT PLAN

4.1.1 Overall Design and Plan

Protocol PSY 302A is an open label safety protocol evaluating ecopipam in subjects with TS per the request of the subject (or their parent/legal guardian) and with the agreement of the treating physician. The treating physician will keep a record of the subject's recent medical history, including their previous response to ecopipam (efficacy/safety), documented history of previous treatments, and why the treating physician has determined that the potential benefit justifies the potential risks of the treatment use as documented in the Investigator Brochure. The treating physician will also evaluate why the potential risks are not unreasonable in the context of the disease /condition of the subject to be treated.

The subject will visit the clinic at the Investigator's site to close out their participation in Study PSY 302. The subject will subsequently have in-clinic evaluations at Baseline and at 3, 6, 9 and 12 months after starting this Open Label Safety protocol. At each visit, the subject will have their vital signs checked, will have blood tests per protocol, will be evaluated using the following rating scales: CDI, C-SSRS, YGTSS, and CGI-S. At the end of a 12-month dosing period, the subject will be evaluated for continued dosing for another 12 months.

With respect to dose and dosing regimen, because the subject will have stopped taking study medication by the time this Open Label Safety Protocol begins, the subject will need to re-establish their optimal

dose under this Open Label Safety protocol by using the same incremental dosing as described in PSY302, which is as follows:

IF 75LBS OR LESS AT START OF OPEN LABEL STUDY			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-3	1 tablet orally each day at bedtime	12.5 mg tablet of ecopipam	12.5 mg/day
Days 4-7	2 tablets orally each day at bedtime	12.5 mg tablet of ecopipam	25 mg/day
Days 8-end of study	1 tablets orally each day at bedtime	50 mg tablet of ecopipam	50 mg/day
IF 76LBS OR MORE AT START OF OPEN LABEL STUDY			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Days 1-7	2 tablet orally each day at bedtime	12.5 mg tablet of ecopipam	25 mg/day
Days 8-14	1 tablet orally each day at bedtime	50 mg tablet of ecopipam	50 mg/day
Days 15-end of study	1 tablets orally each day at bedtime	100 mg tablet of ecopipam	100 mg/day

All doses taken at home should be taken at night before bedtime. However, the treating physician may advise the subject to take ecopipam during the day if warranted (e.g., some subjects experience insomnia following treatment with ecopipam and daytime dosing may be preferable for these subjects). Ecopipam is provided as 12.5, 50 mg and 100 mg film-coated tablets. The dose range for the treated subject will be a maximum of 100 mg/day. The subject may increase or decrease their dose of ecopipam as recommended by the treating physician, not exceeding 100 mg/day. The tablets may be split to titrate the dose according to the physician's instructions.

4.1.2 Baseline Assessment under Open Label Safety Protocol

The Baseline Assessment will occur following the completion of PSY302. Prior to the first dose under PSY 302A, the parent/guardian will provide informed consent, the subject will provide informed assent, the Inclusion/Exclusion criteria will have been met, the results of the laboratory tests will be known, and the rating scales completed.

4.1.3 Treatment Phase

- Prior to the Baseline Assessment at the clinic, supplies of ecopipam tablets will be shipped to the Investigator's site. The Treatment Phase will start following the successful completion of all the Baseline Assessments (see 5.1.2). At the start of the Treatment Phase, the Investigator will provide the subject with the appropriate number/strengths of tablets to complete the titration period. If the subject tolerated the maximum dose under PSY302, then tablets of this strength will be supplied sufficient to last until the next visit (i.e., enough to last for 3 months). Subsequent supplies of appropriate strengths of ecopipam will be dispensed at the 3, 6, and 9 month clinic visits.

-
- At the 12-month visit at the clinic the investigator will perform an evaluation and review other data. The treating physician will provide a summary to the Sponsor. If the subject wishes to continue and there is concurrence by the physician and Sponsor to continue, then the treating physician will permit another 12-month treatment phase and coordinate the distribution of another three months of clinical trial material to the subject's parents and/or caregiver. At the end of treatment, a comprehensive summary of the subject's experience using ecopipam will be submitted to the IND.

4.1.4 End-of-Treatment

At the end of treatment, the subject will decrease their dose of ecopipam according to the following schedule:

IF 75LBS OR LESS AT END OF TREATMENT			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1	3 tablets orally each day at bedtime	12.5 mg ecopipam tablet	37.5 mg/day
Day 2	2 tablets orally each day at bedtime	12.5 mg ecopipam tablet	25 mg/day
Day 3	1 tablet orally each day at bedtime	12.5 mg ecopipam tablet	12.5 mg/day
Down titration only occurs if subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			

IF 76LBS OR MORE AT END OF TREATMENT			
Day	# of Tablets	Tablet Type	Ecopipam Dose
Day 1	3 tablets orally at bedtime	50 mg ecopipam and two 12.5 mg tablets	75 mg/day
Day 2	1 tablet orally at bedtime	50 mg ecopipam tablet	50 mg/day
Day 3	2 tablet orally at bedtime	12.5 mg ecopipam tablet	25 mg/day
Day 4	1 tablet orally at bedtime	12.5 mg ecopipam tablet	12.5 mg/day
Down titration only occurs if subject completes the dosing per the protocol. If subject withdraws due to adverse events, then cessation of dosing will be immediate.			

If the subject discontinues treatment due to an adverse event, all efforts will be made to have the subject come back to the clinic for a follow-up (end-of-treatment visit) examination within a 30-day period. In the event that is not possible, the treating physician can arrange an out-patient visit. In addition, follow-up (visits in person or by telephone) up to 60 days after the last dose or major medical event may be done to record any adverse events or their resolution.

4.2 SELECTION OF SUBJECT POPULATION

4.2.1 Inclusion Criteria

As an Open Label Safety protocol, there are no formal inclusion criteria other than that the subject who participates must (1) have been previously administered ecopipam for investigational treatment of documented TS under protocol PSY302; (2) have met inclusion criteria of PSY302; (3) have requested continued access to ecopipam following the end of the study; and, (4) have the endorsement of the treating physician based on the belief that the benefit outweighs the potential risks of being treated long-term with ecopipam. All subjects must enter this study within 90 days of completing PSY302.

The treating physician will maintain a record with the subject's recent medical history, subject's previous response to ecopipam (efficacy/safety), documented history of previous treatments that have failed, and why the treating physician has determined that the potential benefit justifies the potential risks of the treatment use. The risk-to-benefit summary will include a discussion of major risk findings detailed in the Investigator Brochure as to why those potential risks are not unreasonable in the context of the disease /condition of the subject to be treated.

4.2.2 Exclusion Criteria

The subject was previously enrolled in study PSY 302, which had the following exclusion criteria:

- Subjects who have unstable medical illness or clinically significant abnormalities on laboratory tests, or ECG at Screening.
- Subjects with a major depressive episode in the past 2 years
- Subjects with a history of attempted suicide
- Subjects with clinically significant suicidality (based on C-SSRS scale)
- Subjects with a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization, or attempted/ completed suicide with the exception of a hospitalization for post-partum depression.
- Subjects with a history of seizures (excluding febrile seizures that occurred >2 years in the past)
- Subjects with a myocardial infarction within 6 months.
- Girls who are currently pregnant or lactating.
- Subjects with a lifetime history of significant psychiatric disorder(s) as rated using the American Psychiatric Association DSM-5 Cross-Cutting Symptom Measures rating scale.
- Subjects with current or recent (past 3 months) DSM-IV substance abuse or dependence (with the exception of nicotine).
- Subjects with positive urine drug screen (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), benzodiazepines, barbiturates, phencyclidine (PCP), opiates) at Screening. Subjects with urine positive only for benzodiazepines and/or marijuana (i.e., a user but not an abuser as based on DSM-IV criteria) may be eligible within 6 months of starting the study.

The following Exclusion Criteria are <u>waived</u> for this Expanded Use Protocol 302A:

- Subjects who have a need for medication (other than ecopipam) with possible effects on TS symptoms (i.e., alpha agonists, dopamine D2 antagonists, tetrabenazine)
- Subjects who have a need for medications which would have unfavorable interactions with ecopipam, e.g., dopamine antagonists or agonists [including buproprion], tetrabenazine.
- Subjects who have had treatment with:
    - investigational medication within 3 months of starting study
    - depot neuroleptics within 3 months of starting study

- other psychotropics with possible effects on TS symptoms (i.e., lithium, tetrabenazine) within 2 weeks prior to Screening.
- oral neuroleptics within 4 weeks
- selective serotonin reuptake inhibitors unless the dosage has been stable for a minimum of 4 weeks prior to study start and not prescribed to relieve the neurological signs of TS

WITH THE EXCEPTION OF MAO-INHIBITORS (WHICH ARE NOT PERMITTED), THE ADDITION OR CHANGE IN DOSE OF ANY MEDICATION RELATIVE TO WHAT WAS TAKEN DURING THE DOUBLE BLIND STUDY MUST BE CAREFULLY MANAGED BY THE INVESTIGATOR AND MONITORED FOR POSSIBLE INTERACTIONS

4.2.3 Removal of Subject from Therapy or Assessment

The treating physician or subject may stop ecopipam treatment at any time for safety or personal reasons. Where possible, the subject who discontinues treatment will undergo end-of-treatment procedures at the time of discontinuation. Date and reason(s) of premature discontinuation and date of last dose of ecopipam will be described in the summary provided to the Sponsor.

4.3 TREATMENTS

4.3.1 Treatments Administered

The treatments administered are presented below:

- After all the Baseline Assessments have been completed (Section 5.1.2), the first dose of investigational ecopipam medication may be taken at the subject's home or at the Investigator's facility. Dosing will be as described above.
- Dosing will be in the evening unless directed otherwise by the physician. The subject will take ecopipam by mouth at bedtime.
- At any time, the number of tablets may be decreased if adverse events arise following consultation with the treating physician. Tablets may be split and used to titrate the dosing per the physician's instructions. If needed, the Investigator may supply appropriately strengths of ecopipam tablets.
- At any time, the number of tablets may be increased to maintain a desirable level of activity following consultation with the treating physician.
- Subjects will be instructed that they are not allowed to take more than 100 mg/day.

4.3.2 Identity of Investigational Products

The ecopipam tablets will be supplied as open-label. The product release certificates for ecopipam will be included in the drug report for this protocol. The labels contain the following information:

- Name, address and telephone number of the Sponsor
- Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and dose strength
- Lot number
- Protocol Number
- Protocol identifier
- Subject identification number
- Directions of use
- "Caution: New Drug - Limited by Federal (US) law to investigational use"
- "Keep out of reach of children"
- Storage Conditions

- Expiration Date

A 3-month supply of the investigational ecopipam tablets will be shipped directly to Investigator's site. Drug supplies may be shipped after the following documentation has been received:

- A copy of the final signature page for the protocol, signed and dated by the treating physician
- Written proof of approval of both the protocol and its consent form by the Institutional Review Board (IRB) of the location where the physician is located and assessments will be conducted
- A copy of the IRB-approved Subject Information and Consent Form to be used in the individual subject Open Label Safety treatment protocol.
- The IRB membership list or Health and Human Services Assurance number

Ecopipam must be stored as instructed on the drug label. Ecopipam must be kept in a secure location and carefully stored within its original container and protected from light. The treating physician must maintain records of delivery to the subject. At the each clinic visit (3, 6, 9, and 12 months) and/or discontinuation, the subject's parents or caregiver must return all unused medication. The treating physician and/or staff at the end of the 12-month treatment period and/or discontinuation will conduct drug accountability. A Drug Dispensing Log must be kept current by the Investigator and should contain the following information:

- Shipments (dates or manifest #)
- Lot #
- Quantity Received
- Quantity Remaining
- Final inventory on completion of treatment period

All records and inventory must be maintained in the Individual Subject's Open Label Safety Protocol PSY 302A folder at the treating physician's clinic and made available for inspection by Sponsor's representative(s), upon request. At the end of the treatment period, all used and unused ecopipam will be brought from the subject's facility to the treating physician's clinic for inventory and reconciliation.

4.3.3 Selection of Doses in the Open Access Protocol

The optimal dose of ecopipam will be determined by using the dose titration schedule described in Section 5.1.1. Other studies with ecopipam have been conducted with single doses ranging from 25 to 800 mg, multiple doses up to nine days of 25 to 400 mg per day, PET studies, long-term studies in obesity, studies in children with Lesch-Nyhan Disease and in adults with Tourette's Syndrome. These are detailed in the Investigator's Brochure.

4.3.4 Prior and Concomitant Medications

Any medication (including over-the-counter medications) administered to the subject during the treatment with ecopipam (starting after informed consent/ informed assent) will be recorded. Non-pharmacologic therapies/ procedures will be recorded. The treating physician will record any AE on the MEDWATCH form for which the concomitant medication was administered. Prior and concomitant medications should be maintained in the subject's record.

4.3.5 Treatment Compliance

During the treatment period with ecopipam, the treating physician will monitor the subject's compliance by review with the caregiver. Any variation from the recommended dosing regimen will be documented by the caregiver and discussed with the physician.

4.3.6 Drug Accountability

Ecopipam tablets will be shipped directly from the IND Sponsor (Psyadon) to the Investigator in 3-month increments. At the 12-month assessment, the subject's parents or caregiver will return to the clinic with all unused medication for drug reconciliation by the physician. Should the subject discontinue prior to the 12-month assessment, the end-of-treatment assessment will accomplish the same goal. The combined records of the treating physician and subject's parents and/or caregiver will be used for recordkeeping in compliance with 21 CFR 312.62. Drug accountability and reconciliation can be matched against the Sponsor's drug shipments to the site.

Under no circumstances will the treating physician allow ecopipam to be used other than as directed by this protocol. Ecopipam may not be dispensed to any individual except the individual named subject approved to receive drug under this Open Label Safety treatment protocol. An accurate and timely record of the receipt of all ecopipam supplies; dispensing of ecopipam drug to the subject; collection of unused drug returned by the subject; and subsequent return of unused drug to the Sponsor must be maintained. This includes, but may not be limited to: (a) documentation of receipt of ecopipam supplies, (b) drug dispensing/return reconciliation, (c) ecopipam drug accountability and (d) all shipping service receipts.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Psyadon or the FDA. All unused ecopipam drug will be returned to the treating physician at the conclusion of treatment under this open access protocol. On completion of drug accountability and reconciliation procedures by the treating physician or personnel and documentation by Psyadon personnel, ecopipam drug that is to be returned to Psyadon must be sealed with tamper-evident seals and shipped back to Psyadon following all local regulatory requirements.

The treating physician will coordinate the recording of drug and doses administered by the caregiver. The treating physician will provide records to Psyadon as part of their periodic summaries and final summary after treatment. Psyadon will review drug accountability upon receipt of the periodic summaries and at the completion of the treatment with ecopipam.

4.4 PROCEDURE AND METHODS

4.4.1 Schedule of Procedures and Assessments

A schedule of assessments is outlined in **Table 7**. Out-patient safety monitoring will be accomplished by office visits at the treating physician site every three months, but may be more frequent depending on the adverse event profile. Based on those safety data, dosing may be adjusted.

At the 12-month visit, there will be a determination of participation for another 52 weeks. If the treating physician concurs the subject should continue treatment for another 52-week period, then they will receive sufficient drug through the next 3-month interval.

Should the subject discontinue prior to these scheduled in-clinic evaluations, every effort will be made to have the subject come in for a follow up visit in the clinic within a 30-day period. This end-of-treatment visit should be accomplished within 30 days of discontinuation due to an adverse event. Further follow-up after a 30-day period can continue by phone and e-mail as necessary.

Baseline Assessment (In-Clinic)

The following assessments for PSY 302A will be done at Baseline:

- Vital signs
- Clinical laboratory tests

- Concomitant medication
- Safety assessment
- Informed consent/ informed assent
- Baseline YGTSS
- CDI
- C-SSRS
- CGI-Severity

Following the successful completion of these Baseline Assessments and getting the informed consent/ informed assent documents signed, a 3-month supply of investigational ecopipam tablets will be given to the subject and or the subject's parents/guardian. The treating physician and/or their staff will review the drug accountability procedures with the subject's parents/guardian.

Out-Patient Evaluation

Out-patient evaluation will be on an ongoing basis with the subject's caregiver to ascertain tolerance to the ecopipam medication and any serious adverse events. This information exchange may be by a combination of phone, e-mail, and video-conferencing. The caregiver will also maintain records of dosing. Caregivers will be asked to report serious adverse events as they occur by notifying the treating physician.

3, 6, 9, and 12-month Assessment (In-Clinic)

For each quarterly assessment, the treating physician will evaluate the subject at the clinic. The evaluation will include updates from the subjects' parents and/or caregiver to ascertain tolerance to the ecopipam medication and any serious adverse events. The evaluation is comprised of the following:

- Vital signs
- Clinical laboratory tests
- Concomitant medication
- Safety assessment
- YGTSS
- CDI
- C-SSRS
- CGI-Severity
- CGI-Improvement

At the 3, 6, 9 month visits, the physician will determine if continued treatment is warranted based on the YGTSS scores and the occurrence of adverse events. Treatment will be discontinued in the event that sufficient continued benefit is not evident or limiting side effects are seen that cannot be treated with either ameliorating drugs/behavioral interventions.

Should the subject elect to continue for another 12-month period (and concurrence by the IND Sponsor and caregiver), another 3-month supply of ecopipam medication, the Investigator would give it to the subject's parents/guardian.

The treating physician and/or their staff will reconcile the drug accountability by inventory of the shipments to the subject vs. subject use. All unused drug will be held by the clinic except for an amount needed by the subject until the 3-month supply arrives.

End-of-Treatment Assessment

At the end of treatment, the subject will decrease their dose of ecopipam according to the schedule described in Section 5.1.4.

If the subject discontinues ecopipam treatment due to an adverse event or any other reason prior to the 12-month assessment, the treating physician will evaluate the subject in the clinic as quickly as possible, preferably within a 30-day window. The evaluation will include updates from the subject's caregiver to ascertain tolerance to the ecopipam medication and any serious adverse events. The evaluation for the end-of-treatment visit is comprised of the following:

- Vital signs
- Clinical laboratory tests
- Concomitant medication
- Safety assessment
- YGTSS
- CDI
- C-SSRS
- CGI-Severity

The subject's parents or caregiver will provide the remainder of the unused ecopipam medication and drug use logs to the treating physician (or staff) to permit drug accountability and reconciliation.

A brief description of each procedure or assessment is provided below.

4.4.1.1 Vital Signs

Vital signs will be determined at the in-clinic visits at the baseline and 12-month assessments. They will include blood pressure, pulse, respiration, body temperature, and weight. If the subject discontinues due to an adverse event, vital signs will also be documented at the end-of-treatment visit, which should be within 30 days of discontinuation. Any significant findings prior to the start of drug treatment will be recorded as part of the subject's medical history. If there are changes after the baseline assessment that is defined as an adverse event, those will be recorded on the MEDWATCH form. The medical history and physical exam documentation will be kept in the Individual Subject Open Label Safety folder.

4.4.1.2 Clinical Laboratory Tests

At each clinic visit, the following clinical laboratory tests will be done:

Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, and white blood cell count with differential (neutrophils, bands lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine
Other	Glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin
Pregnancy Test	Urine test (for women of childbearing potential only)

4.4.1.3 Concomitant Medication Use

The use of all medications will be recorded, including prescription, OTC, and nutraceutical agents. The dose, regimen, and other aspects will be recorded in the drug accountability log – (see Appendix 1). Concomitant medications will be recorded on the subject use log (Appendix 1) and updated by the caregiver. All original records will be returned to the treating physician and/or their staff for recordkeeping.

4.4.1.4 Safety Monitoring

The physician will document the adverse event history of the subject in the clinic at the baseline and 12-month in-clinic assessments. Safety monitoring by the physician during the out-patient phase will be in conjunction with the parents and/or caregiver by phone or e-mail at least quarterly or more frequently as necessary. Should the subject discontinue due to an adverse event, the treating physician and/or their staff will coordinate an end-of-treatment assessment, preferably within 30 days of discontinuation.

With respect to reporting and recording adverse events, all adverse events will be recorded individually by the subject's parents or caregiver using a MEDWATCH form (Appendix 3). Those data will be used by the treating physician to prepare a MEDWATCH form (Appendix 2). The treating physician or their staff will complete a MEDWATCH form based on information provided by the parents, caregiver, and/or local physician. The AE recording and reporting system is detailed in Section 5.4.2.

An evaluation of the subject's symptoms of depression will be done at baseline and at every clinic visit using the Child Depression Inventory. In addition, the Investigator will review the exclusion criteria outlined to determine if the subject endorses suicidal thoughts, depression, or any other condition noted in the exclusion criteria.

If the subject experiences (i) a significant change in their behavior, (ii) any appearance of suicidal thought or depression, or, (iii) if the subject's CDI shows signs of a new depression disorder, the dose of ecopipam will be immediately reduced and the subject re-evaluated to see if these symptoms abate. In the event the symptoms persist, the subject's treatment with ecopipam under this Open Label Safety protocol will be stopped and appropriate clinical intervention (e.g., hospitalization) will be arranged as needed.

4.4.1.5 Daily Drug Use

Daily drug dosing will be recorded in a log (Appendix 1) along with concomitant medications. The originals will be completed by the parent/ caregiver and transferred to the treating physician as part of the recordkeeping.

4.4.1.6 YGTSS

The primary activity outcome measure will be the YGTSS. The YGTSS is a clinician-completed rating scale used to quantify overall tic severity as well as specific subdomains of tic number, frequency, duration, intensity, and complexity. Each of these subdomains is scored, on a 5-point scale, separately for motor and vocal tics and then summed across both motor and vocal tics to yield a tic severity score ranging from 0 to 50. The YGTSS also provides for an overall impairment rating (0 = ''none'' to 50 = ''severe''). The YGTSS has demonstrated acceptable internal consistency, good interrater reliability, and acceptable convergent and divergent validity.

4.4.1.7 Clinical Global Impression Scales

The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The improvement scale will be used at every visit after the Screening and Baseline Visits. The scale ranges from 1 = "very much improved" to 7 = very much worse." The CGI severity scale will be used at each study site visit and ranges from 1 = "not ill at all" to 7 = "among the most extremely ill."

Table 7: Schedule of Procedures and Assessments

Procedure	Baseline Assessment [a]	Clinic Visits at 3, 6, and 9 Months[a]	12-month Assessment [a]	End-of-Treatment Assessment [a]
Vital Signs (blood pressure, pulse, respiration, body temperature, and weight)	X	X	X	X
Clinical Laboratory Tests (hematology, biochemistry, and pregnancy urinalysis)	X	X	X	X
Safety Monitoring (including evaluation for depression per the CDI and C-SSRS scales)[b]	X	X	X	X
Informed Consent	X [c]			
Record Adverse Events (all) & MEDWATCH for Serious Unexpected AEs	X [d]	X [d]	X [d]	X [d]
Concomitant Medication Use	X [e]	X [e]	X [e]	X [e]
Dispense drug: Ecopipam Tablets	X [f]	X [f]	X [f]	X [f]
YGTSS	X	X	X	X
CGI-Severity	X	X	X	X
CGI-Improvement		X	X	X

[a] All visits will be at the Investigator's site.

[b] Safety monitoring by the treating physician and/or their staff will be every 3 months and in conjunction with the parents and/or caregiver by phone or e-mail as necessary. Should the subject discontinue due to an adverse event, the treating physician and/or their staff will coordinate an end-of-treatment assessment, preferably within 30 days of discontinuation.

[c] Informed consent from the parents or guardian and the subject informed assent will be signed prior to enrolling in PSY302A and before shipping or dispensing drug.

[d] All adverse events (AEs) will be recorded by the physician and/or staff who will complete a MEDWATCH form for serious unexpected events. AEs will be collected and documented at all in-clinic visits, any phone calls, and at any other time the caregiver reports an event to the physician during the treatment phase.

[e] Concomitant medication will be documented at the in-clinic visits.

[f] Ecopipam medication will be shipped directly from the IND Sponsor (Psyadon) to the Investigator in 3-month increments. At the 12-month assessment, the subject's parents or caregiver will return to the clinic with all unused medication and use logs for drug reconciliation by the physician. Should the subject discontinue prior to the 12-month assessment, the end-of-treatment assessment will accomplish the same goal. The combined records of the treating physician and subject's parents and/or caregiver will be used for recordkeeping in compliance with 21 CFR 312.62. Drug accountability and reconciliation can be matched against the Sponsor's drug shipments to either site.

4.4.2 Safety Assessments

Safety assessments will include vital signs, standard clinical lab tests, and the CDI and C-SSRS ratings scales.

4.4.2.1 Adverse Events, Serious Adverse Events, and Reporting

DEFINITION AND SCOPE OF AN ADVERSE EVENT

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this protocol, the medicinal product is ecopipam. The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- any new disease or exacerbation of an existing disease;
- any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from ecopipam drug; and/or
- recurrence of an intermittent medical condition (e.g., headache) not present at Baseline.

An abnormal laboratory test result may be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the treating physician to be an AE if it:

- results in the withdrawal of drug treatment;
- results in withholding of drug treatment pending some investigational outcome;
- medical evaluation that results in the initiation of an intervention (e.g., potassium supplementation for hypokalemia); and
- any out of range laboratory value that the treating physician's judgment, fulfills the definitions of an AE with regards to subject's medical profile.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. All laboratory abnormalities considered to constitute an AE should be reported on the MEDWATCH form.

It is the responsibility of the treating physician to review all laboratory findings and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

REPORTING ADVERSE EVENTS

All AEs encountered during drug treatment – from mild to severe – and regardless of relationship to ecopipam drug will be recorded. Any AEs during the out-patient phase will be documented by the subject's parents or caregiver on a MEDWATCH form (Appendix 3) and communicated to the treating physician or their staff. The treating physician (or staff) will record these individual events on a MEDWATCH form (see Appendix 2), which will be maintained in the Individual Subject Open Label Safety Protocol folder. Follow up information relating to the original event can be added to the original MEDWATCH form as a dated addendum.

Using the criteria below, the physician will evaluate these AEs by severity, relationship to treatment with ecopipam tablets, and classification of causality.

ASSESSING SEVERITY OF ADVERSE EVENTS

Adverse events will be categorized as follows:

- **MILD:**
  - Discomfort noticed, but no disruption of normal daily activity
- **MODERATE:**
  - Discomfort sufficient to reduce or affect normal daily activity
- **SEVERE:**
  - Incapacitating, with inability to work or to perform normal daily activity.

ASSESSING RELATIONSHIP TO TREATMENT WITH ECOPIPAM TABLETS

Considerations for assessing the relationship of an AE to the ecopipam treatment include:

- temporal relationship of the onset of the event to the initiation of treatment with ecopipam tablets;
- the course of the event, considering especially the effect of discontinuation of ecopipam treatment or reintroduction of ecopipam treatment, as applicable;
- whether the event is known to be associated with ecopipam treatment, or with other similar treatments;
- the presence of risk factors in the subject known to increase the occurrence of the event; and/or
- the presence of non- treatment-related factors that are known to be associated with the occurrence of the event.

CLASSIFICATION OF CAUSALITY

Considerations for assessing causality of an AE to ecopipam treatment include:

Not Related: A causal relationship between ecopipam treatment and the AEs not a reasonable possibility.

Related: A causal relationship between ecopipam treatment and the AEs a reasonable possibility. The Investigator/treating physician must further qualify the degree of certainty as **possible** or **probable**.

4.4.2.2 Serious Adverse Events (SAE)

A SAE must be reported to Psyadon in an expedited fashion. A SAE is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (e.g., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- requires in subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the investigational drug ecopipam).

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situation.

The following hospitalizations are not considered to be SAEs because there is no "AE" (e.g., there is no untoward medical occurrence) associated with the hospitalization:

- respite care;
- planned hospitalization required by the protocol;
- planned hospitalization prior to informed consent (where the condition requiring the hospitalization has not changed after ecopipam drug administration); or
- for administration of ecopipam drug or insertion of access for administration of ecopipam drug.

In addition to the above, other events of interest which includes treatment-emergent significant laboratory abnormality and "overdose" are to be captured using the SAE procedures but are to be considered as SAEs only if they met 1 of the above criteria. All events of these types are to be reported on the MEDWATCH form whether or not they meet the criteria for SAEs.

EXPEDITED REPORTING OF SAES

SAEs must be reported to Psyadon in an expedited fashion. SAEs must be followed until the event resolves or the event or sequelae stabilize.

The treating physician and/or their staff must report any deaths and/or life-threatening events immediately by telephone and/or e-mail to:

Richard Chipkin, PhD
301-319-2020
rchipkin@psyadonrx.com

The immediate report should be followed-up within 1 business day by faxing or emailing the completed MEDWATCH form to:

Richard Chipkin, PhD
RChipkin@Psyadonrx.com
Fax Number: 301-556-1659

For Urgent Safety Issues call: 301-319-2020 or 301-502-6438

A copy of the MEDWATCH form with pertinent records (redacted for any subject identifying information) should be provided to Psyadon by FAX or e-mail as expeditiously as possible. This should include the Investigator's assessment of causality.

All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization. Any follow-up information received on SAEs should be forwarded as expeditiously as possible (e.g., within 1 business day of its receipt). If follow-up information changes the treating physician's assessment of causality, this should also be noted on the follow-up MEDWATCH form.

Serious adverse events, regardless of causality assessment, must be collected through the termination visit and for 30 days following ecopipam drug discontinuation. Any SAE that occurred within 7 days of treatment termination must be entered on the MEDWATCH form.

Any SAE event judged by the treating physician to be related to the drug treatment should be reported to the Sponsor regardless of the length of time that has passed since treatment with ecopipam completion.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents requested by the Sponsor.

The treating physician should notify the IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to Psyadon.

EXPEDITED REPORTING TO THE FDA

Psyadon will evaluate the SAE reports and inform regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (e.g., within specific timeframes).

4.4.3 Completion/Discontinuation of Treatment

The subject may elect to discontinue use of ecopipam treatment at any time for safety or personal reasons. If the subject discontinues treatment, the subject is to complete the end-of-treatment evaluation procedures.

The reason for the subject's discontinuation will be assigned to one of the following: (1) death or discontinuation due to an AE or (2) personal reasons by the subject that are unrelated to safety or perceived benefit. The subject may indicate one or more of these as secondary reasons for discontinuation. Protocol disposition information will be recorded by the treating physician.

Since this is an Open Label Safety treatment for an individual subject requested by the treating physician, if the subject discontinues treatment for any reason, the subject cannot be replaced with another subject. Each subject is considered on a case-by-case basis.

4.5 DATA QUALITY ASSURANCE

Data collected will be organized, performed, and reported in compliance with the protocol, working practice documents, and applicable regulations and guidelines. Documentation will be maintained in the Individual Subject Open Label Safety Protocol folder provided by the Sponsor

A monitoring visit may be made by Psyadon or a designated CRO's qualified compliance officer.

Data Collection

The treating physician will enter the information required by the protocol into the subject's records. These records will be maintained in the Individual Subject Open Label Safety folder provided by the Sponsor.

A CRA may visit the treating physician to review for completeness and accuracy of the records against the source documents. CRAs will highlight any discrepancies found in the documentation and ensure that appropriate treating physician or staff address the discrepancies.

All original recordings will be forwarded to Psyadon with a copy retained at the treating physician's clinic at the end of treatment. The recording will be kept by Psyadon in its central document repository within the Individual Subject Open Label Safety Protocol folder provided by the Sponsor. The treating physician will provide a summary of the treatment of ecopipam in the subject at periodic times (6- and 12-month intervals). After one year, a comprehensive summary of the treatment in this subject will be provided to determine whether treatment may continue for an additional year. At the end of treatment, a comprehensive summary will be provided to Psyadon.

Psyadon will submit a final summary of the subject's treatment to the FDA. A listing of concomitant medications by drug and drug class, as well as all AEs, will be included in the final summary provided by the physician and in the final summary submitted to FDA.

4.5.1.1 Safety Analyses

Assessment of safety will be performed. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and other results.

ADVERSE EVENTS

Verbatim description for all AEs will be provided in the summary report provided to FDA.

LABORATORY VALUES

Clinical laboratory results at baseline will be evaluated as part of the PSY 302 study and for markedly abnormal values associated with a serious adverse event that results in discontinuation.

VITAL SIGNS

Vital sign values will be evaluated. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

5. PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

5.1 INSTITUTIONAL REVIEW BOARDS / INDEPENDENT ETHICS COMMITTEES

This individual subject Open Label Safety protocol, amendments, and informed consent form (ICF) will be reviewed and approved by the treating physician center's Institutional Review Board/Independent Ethics Committee (IRB/IEC) before subjects are screened for entry. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/ICE for review and approval. Verification of the IRB/IEC unconditional approval of the protocol will be transmitted to Psyadon prior to the shipment of drug supplies to the treating physician. The treating physician or Psyadon will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per International Conference on Harmonization (ICH) guidelines and local IRB/IEC standards of practice.

5.2 ETHICAL CONDUCT & GOOD CLINICAL PRACTICES (GCP)

The treating physician agrees, when signing the Individual Subject Open Label Safety protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH GCPs to as well as all governing local regulations and principles for medical research for treating subjects on a compassionate basis.

The protocol, informed consent, and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations, e.g., Federal Regulations, Title 21 CFR Part 56. Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of protocol approval from the IRB/IEC Chairman must be sent to the treating physician with a copy to the Sponsor prior to the subject's assessments related to the individual subject access protocol and the release of ecopipam to the treating physician by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the treatment under this individual open access protocol, the treating physician will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Treatment progress under this protocol is to be reported to IRB/IECs annually (or as required) by the treating physician or Sponsor, depending on local regulatory obligations. If the treating physician is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. SAEs should be reported to the IRB/IEC in accord with local regulatory requirements.

This individual subject Open Label Safety protocol will be conducted in accordance with standard operating practices of Psyadon (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- In accordance to the principle of World Medical Association Declaration of Helsinki, 1996;
- ICH - E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use; and
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Subject Consent and IRB regulations).

5.3 SUBJECT INFORMATION AND INFORMED CONSENT/ INFORMED ASSENT

The subject (and/or their guardians/legally authorized representatives) will be provided with verbal and

written information describing the nature and duration of the treatment and the procedures to be performed. The subject (if over 18 years old) will be given a copy of the informed consent form (ICF) and written information, as applicable. The subject – if younger than 18 years old or represented by a legal guardian – will be asked to sign an informed assent form (IAF) and their parents and/or legal guardian to sign the ICF. These documents will be signed and executed at the beginning of treatment under this individual subject Open Label Safety protocol and all authorizations required by local law (e.g., Protected Health Information in North America) must be obtained prior to performing any tests or assessments under this protocol.

The subject or subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented. A sample of the IAF and ICF will be included in protocol documentation submitted to FDA.

As part of administering the IAF and ICF documents, the treating physician must explain to the subject and subject's legally authorized representative that the drug is being provided outside a study for his or her own treatment use; that the drug is investigational and not approved by FDA for this clinical indication; that the drug is being given for treatment at the request of the treating physician, per the family's request; the procedures involved; the expected duration; the potential risks and benefits involved; and any potential discomfort. The subject must be informed that treatment with ecopipam is voluntary and that he/she may withdraw from treatment at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The IAF and ICF should be written in non-technical language. The subject and the subject's legally authorized representative should be given ample time to read these documents at the physician's office. The IAF and ICF may be made available to the parents or guardians prior to the Baseline visit so they have the opportunity to review the consent at home. The subject will be given time to ask as many questions about the treatment protocol and other treatment options available to them prior to signing the consent form. Furthermore, the subject will be given a copy of the signed document. If the subject does not have the ability to provide written or verbal assent to participate and be treated with ecopipam, then participation in the Open Label Safety treatment protocol will not be permitted. A signed ICF by the subject's parents or legally authorized guardian must be obtained prior to any assessments or treatment under this protocol.

An unsigned copy of an IRB/IEC and Sponsor-approved written ICF and IAF must be prepared in accordance with ICH E 6, Section 3, and all applicable local regulations (e.g., 21 CFR 50), and provided to the Sponsor to the subject and/or guardian. A signed ICF and IAF must be completed prior to participation in this open access protocol. The form(s) must be signed and dated by the appropriate parties. The original signed ICF and IAF for the subject will be verified by the Sponsor and kept in the Individual Subject Open Label Safety folder provided by the Sponsor at the treating physician's office; a signed copy will be given to the subject.

5.4 ADMINISTRATIVE PROCEDURES

5.4.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. The protocol will be followed as written. Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of the subject, the scope of treatment, or monitoring, require additional approval by the applicable IRBs/IECs of the treating physician and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the

treating physician, or by the Sponsor, in the interest of preserving the safety of the subject being treated under the Open Label Safety treatment protocol. If an immediate change to the protocol is felt by the treating physician to be necessary for safety reasons, the Sponsor's Medical Monitor must be notified promptly and the IRB/IEC must be informed within 5 working days.

Changes affecting only administrative aspects of treatment under this protocol do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB/IEC detailing such changes. The protocol, all amendments, IB's, and IRB/IEC approvals will be maintained in the in the Individual Subject Open Label Safety folder provided by the Sponsor.

5.4.2 Adherence to the Protocol

The treating physician will provide treatment in strict accordance with the protocol, which has been written to enable the treating physician's compliance with ICH E6, Section 4, "Investigator Guideline for Good Clinical Practices."

5.4.3 Monitoring Procedures

The Sponsor will maintain contact with the treating physician periodically and designated staff by telephone, and/or letter, and/or email or visits. Psyadon may conduct monitoring visits. The treating physician will allow a representative of Psyadon to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCPs and Good Laboratory Practices. The subject's original medical records (source documents) will be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to the Open Label Safety protocol and data accuracy in accordance with federal regulations. All records at the treating physician's office are subject to inspection by the FDA.

In accordance with ICH E6, Section 6.10, source documents include, but are not limited to the following:

- Clinic, office, hospital charts;
- Copies or transcribed health care provider notes;
- Recorded data from automated instruments such as Interactive Voice-response Systems, x-rays, and other imaging reports, e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives);
- Pain, quality of life, medical history questionnaires completed by subjects;
- Records of telephone contacts;
- Diaries or evaluation checklists;
- Drug distribution and accountability logs maintained in pharmacies or by research personnel;
- Laboratory results and other laboratory test outputs, e.g., urine pregnancy test result documentation and urine dip-sticks;
- Correspondence regarding the subject's treatment between physicians or memoranda sent to the IRBs/IECs;
- Questionnaires that are completed directly by the subject and serve as their own source; and
- Correspondence between the treating physician and caregivers regarding adverse events.

5.4.4 Recording of Data

The Sponsor will provide forms for the caregiver to document receipt of investigational ecopipam tablet medication and document the daily dose and concomitant medication log. In order to provide the Sponsor with accurate, complete, and legible reports, the following criteria are to be maintained:

- All entries are to be typed or printed using a black ink ballpoint pen (for paper forms provided to the caregiver or treating physician)
- There should be an effort to not have any erasures, write-overs, use of correction fluid or tape, and the original entry must remain legible. Errors are to be corrected by placing a line through the entry. The correct entry should appear next to the error, dated, and initialed by the responsible person making the change. If the investigator is keeping a log, the name of anyone making corrections must appear on the log collected at the beginning of the Open Label Safety treatment and as assignments change throughout the treatment of the subject. Each error is to be corrected separately.
- The treating physician must sign and date all forms where noted. A signature stamp may not be used.
- Changes to forms or the subject's data that has been previously signed by the treating physician must be initialed and dated by the treating physician after the change is made. Changes made to forms or subject's data or the treating physician must likewise sign summaries provided to the Sponsor via written requests issued by the Sponsor.
- All subject data and correction forms should be maintained in the Individual Subject Open Label Safety folder provided by the Sponsor.
- Neither the subject's name or any other identifying information (e.g., address, parent's names, etc.) are to appear on documents transmitted to the Sponsor in order to maintain confidentiality.

5.4.5 Retention of Records

The circumstances of completion or termination of the treatment of ecopipam for the named subject notwithstanding, the treating physician has the responsibility to retain all protocol and subject documents, including but not limited to the protocol, copies of forms, Investigator's Brochure, regulatory agency registration documents, e.g., FDA 1572 form, ICFs, and IRB/IEC correspondence and subject source documents. The treating physician and Psyadon will retain these documents in accordance with their records retention policy but for not less than five years after the subject has completed treatment.

It is requested that at the completion of the required retention period, or should the treating physician retire or relocate, the treating physician contact the Sponsor, allowing the Sponsor the option of permanently retaining the records.

5.4.6 Handling of Ecopipam Drug

The IND Sponsor (Psyadon) will supply all investigational ecopipam medication directly to Investigator's site. Drug supplies must be kept in a secure area and stored according to the conditions specified on the drug labels. The subject's parents or caregiver will be responsible for receipt of the ecopipam medication and logs of usage. They will bring back any unused supplies to the physician's clinic at the 3, 6, 9, and 12-month assessments or upon treatment discontinuation under this protocol. The treating physician (or staff) will reconcile the drug shipments against the usage logs to confirm drug accountability. Any discrepancies will be documented. The treating physician should not destroy any partly used supplies.

A copy of the drug accountability records will be provided to the Sponsor at the end of the treatment. An accurate record of the date and amount of ecopipam drug dispensed to the subject must be available for inspection at any time. A representative of Psyadon may review these documents along with all other protocol conduct documents at every visit to the treating physician's office or assessment site once ecopipam drug has been received by the treating physician.

At the conclusion of the subject's treatment and as appropriate during the course of treatment, the treating physician will return all used and unused drug containers and a copy of a completed drug disposition form to the Sponsor at the Sponsor's address. A copy of all drug shipment, storage, dispensing and drug return records should be maintained in the Individual Subject Open Label Safety folder provided by the Sponsor.

5.4.7 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of treatment will be kept confidential by the treating physician, the physician's staff, and Institutional Review Board and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the protocol without the written consent of the Sponsor. No data collected as part of the treatment will be utilized in any written work, including publications, without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the treating physician. All persons assisting in the performance of this Open Label Safety protocol must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the treating physician and Sponsor (provided by the Sponsor).

5.4.8 Discontinuation of Treatment under Open Label Safety Protocol

The Sponsor reserves the right to discontinue treatment under this protocol for medical reasons or by Sponsor at any time for any reason. The treating physician reserves the right to discontinue treatment of ecopipam under the Open Label Safety protocol should his/her judgment so dictate. The treating physician will notify the IRB/IEC in case of treatment discontinuation. Subject and protocol records must be retained as noted above. Treatment under this protocol will cease upon regulatory approval for the sale of ecopipam.

Appendix 2: Drug Accountability Log for Subject XY (subject's initials)

Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____
Number of Bottles Received: _____	Date Received: _____	Tablets per Bottle: _____	Strength: _____

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Comments:

Psyadon or Clinical Monitor signature:_____ Date: _____

-

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Date of Administration	**Dose or Strength**	**Time of Day**	**Concomitant Medications** (list type of drug and strength)	**Balance of Unused or Returned Material** (please note whole sealed bottles and partial bottles with pill counts)

Comments:

Psyadon or Clinical Monitor signature:_____ Date: _____

Appendix 2 Treating Physician Safety Reporting Form: MEDWATCH Form

A copy of the MEDWATCH form that will be used by the treating physician or their staff to capture adverse event data is provided, beginning on the following page.

•

Form Approved: OMB No. 0910-0291, Expires: 09/01/05
See OMB statement on reverse.

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr Report #

Lif Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — in confidence
2. Age at Time of Event: or Date of Birth:
3. Sex: ☐ Female ☐ Male
4. Weight: ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem (e.g., defect/malfunction)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - ☐ Death: ____ (mo/day/yr)
   - ☐ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☐ Disability
   - ☐ Congenital Anomaly
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
   - ☐ Other: ____
3. Date of Event (mo/day/year)
4. Date of This Report (mo/day/year)
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, Frequency & Route Used
   #1
   #2
3. Therapy Dates (If unknown, give duration) (mo/da or best estimate)
   #1
   #2
4. Diagnosis for Use (Indication)
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # (If known)
   #1
   #2
7. Exp. Date (If known)
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# (For product problems only)
   - -
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other: ____
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

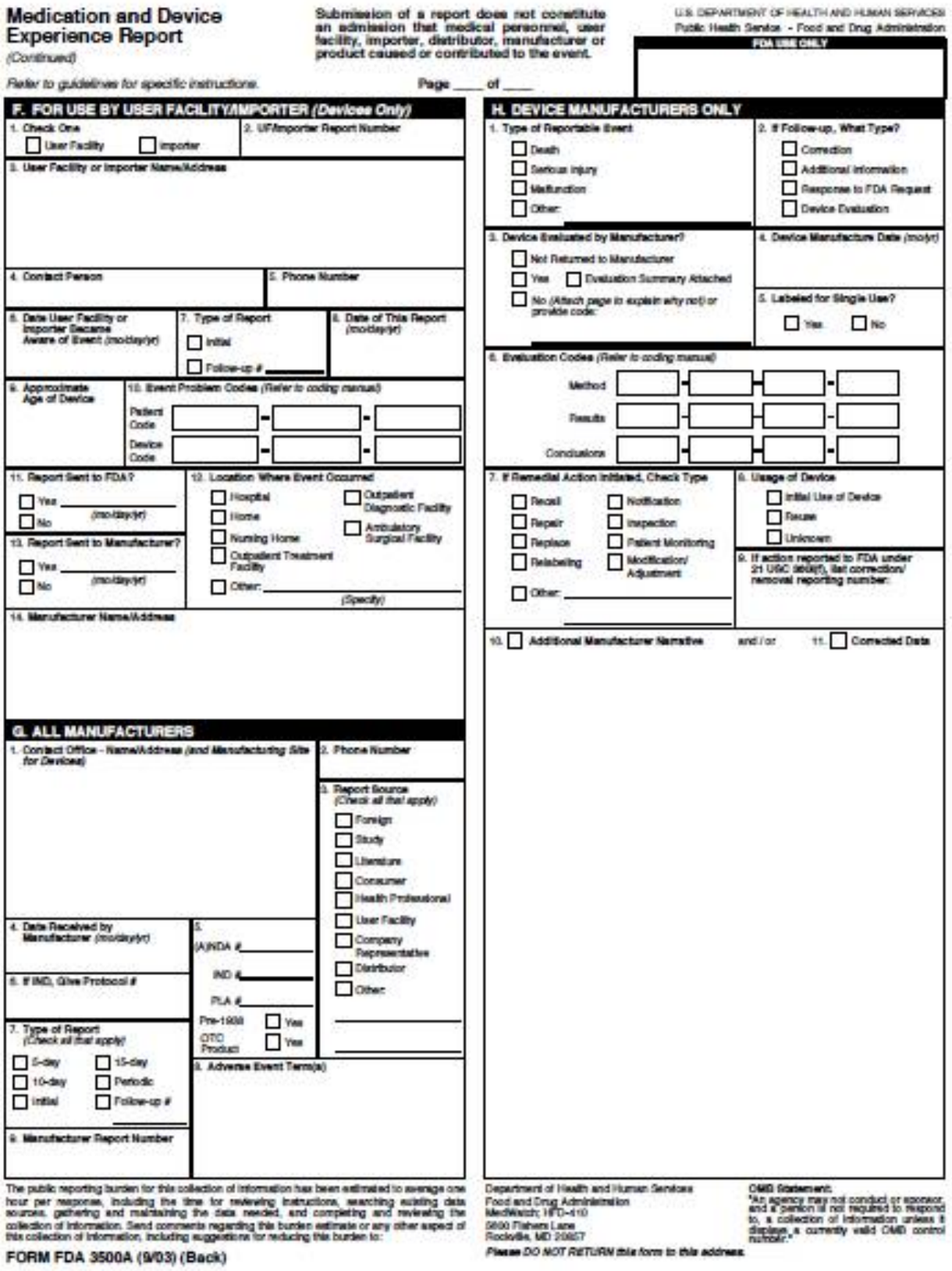
E. INITIAL REPORTER

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

FORM FDA 3500A (9/03)



Medication and Device Experience Report
(Continued)

Refer to guidelines for specific instructions.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

Page ____ of ____

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER (Devices Only)

1. Check One: ☐ User Facility ☐ Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event (mo/day/yr)
7. Type of Report: ☐ Initial ☐ Follow-up # ____
8. Date of This Report (mo/day/yr)
9. Approximate Age of Device
10. Event Problem Codes (Refer to coding manual): Patient Code ___ - ___ - ___ Device Code ___ - ___ - ___
11. Report Sent to FDA? ☐ Yes ____ (mo/day/yr) ☐ No
12. Location Where Event Occurred: ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: ____ (Specify)
13. Report Sent to Manufacturer? ☐ Yes ____ (mo/day/yr) ☐ No
14. Manufacturer Name/Address

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)
2. Phone Number
3. Report Source (Check all that apply): ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____ ____
4. Date Received by Manufacturer (mo/day/yr)
5. (A)NDA # ____ IND # ____ PLA # ____ Pre-1938 ☐ Yes OTC Product ☐ Yes
6. If IND, Give Protocol #
7. Type of Report (Check all that apply): ☐ 5-day ☐ 15-day ☐ 10-day ☐ Periodic ☐ Initial ☐ Follow-up # ____
8. Manufacturer Report Number
9. Adverse Event Term(s)

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event: ☐ Death ☐ Serious injury ☐ Malfunction ☐ Other: ____
2. If Follow-up, What Type? ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer? ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No (Attach page to explain why not) or provide code: ____
4. Device Manufacture Date (mo/yr)
5. Labeled for Single Use? ☐ Yes ☐ No
6. Evaluation Codes (Refer to coding manual): Method ___ - ___ - ___ - ___ Results ___ - ___ - ___ - ___ Conclusions ___ - ___ - ___ - ___
7. If Remedial Action Initiated, Check Type: ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/ Adjustment ☐ Other: ____
8. Usage of Device: ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360(j), list correction/ removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

The public reporting burden for this collection of information has been estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

OMB Statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

FORM FDA 3500A (9/03) (Back)

-

Appendix 3 Subject's Caregiver Safety Reporting: MEDWATCH Form

A copy of the MEDWATCH form that will be used by the caregiver to capture adverse event data is provided, beginning on the following page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page)

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- ☐ Were hurt or had a bad side effect *(including new or worsening symptoms)*
- ☐ Used a product incorrectly which could have or led to a problem
- ☐ Noticed a problem with the quality of the product
- ☐ Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- ☐ Hospitalization – admitted or stayed longer
- ☐ Required help to prevent permanent harm *(for medical devices only)*
- ☐ Disability or health problem
- ☐ Birth defect
- ☐ Life-threatening
- ☐ Death *(Include date)*:_____
- ☐ Other serious/important medical incident *(Please describe below)*

_____
_____
_____

Date the problem occurred *(mm/dd/yyyy)*

Tell us what happened and how it happened. *(Include as many details as possible)*

_____
_____
_____ Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

_____
_____
_____ Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

⇨ **Go to Section B**

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

⇨ **Go to Section C (Skip Section B)**

For more information, visit http://www.fda.gov/MedWatch

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

FORM FDA 3500B (4/13) **MedWatch** Consumer Voluntary Reporting Page 1 of 3

Section B – About the Products			
Name of the product as it appears on the box, bottle, or package *(Include as many names as you see)*			
Name of the company that makes the product			
Expiration date *(mm/dd/yyyy)*	Lot number	NDC number	
Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?
Date the person first started taking or using the product *(mm/dd/yyyy)*: _____ Date the person stopped taking or using the product *(mm/dd/yyyy)*: _____		Why was the person using the product *(such as, what condition was it supposed to treat?)* _____ _____ _____	
Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☐ No			
Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☐ Didn't restart		Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☐ Yes ☐ No	
☐ *Go to Section D (Skip Section C)*			

Section C – About the Medical Device	
Name of medical device	
Name of the company that makes the medical device	
Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)* _____ _____ _____	
Was someone operating the medical device when the problem occurred? ☐ Yes ☐ No	If yes, who was using it? ☐ The person who had the problem ☐ A health professional *(such as a doctor, nurse, or aide)* ☐ Someone else *(Please explain who)* _____
For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*	
Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(If relevant) (mm/dd/yyyy)*
☐ *Go to Section D*	

For more information, visit http://www.fda.gov/MedWatch

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Section D – About the Person Who Had the Problem				
Person's Initials	Sex ☐ Female ☐ Male	Age *(at time the problem occurred)* or Birth Date	Weight *(Specify lbs or kg)*	Race

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*

Please list all allergies *(such as to drugs, foods, pollen, or others)*.

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*

List all current prescription medications and medical devices being used.

Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.

Continuation Page

Go to Section E

Section E – About the Person Filling Out This Form		
We will contact you only if we need additional information. Your name will not be given out to the public.		
Last name	First name	
Number/Street	City and State/Province	
Country	ZIP or Postal code	
Telephone number	Email address	Today's date *(mm/dd/yyyy)*
Did you report this problem to the company that makes the product (the manufacturer)? ☐ Yes ☐ No	May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product? ☐ Yes ☐ No	

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA.
Mail or fax the form to:

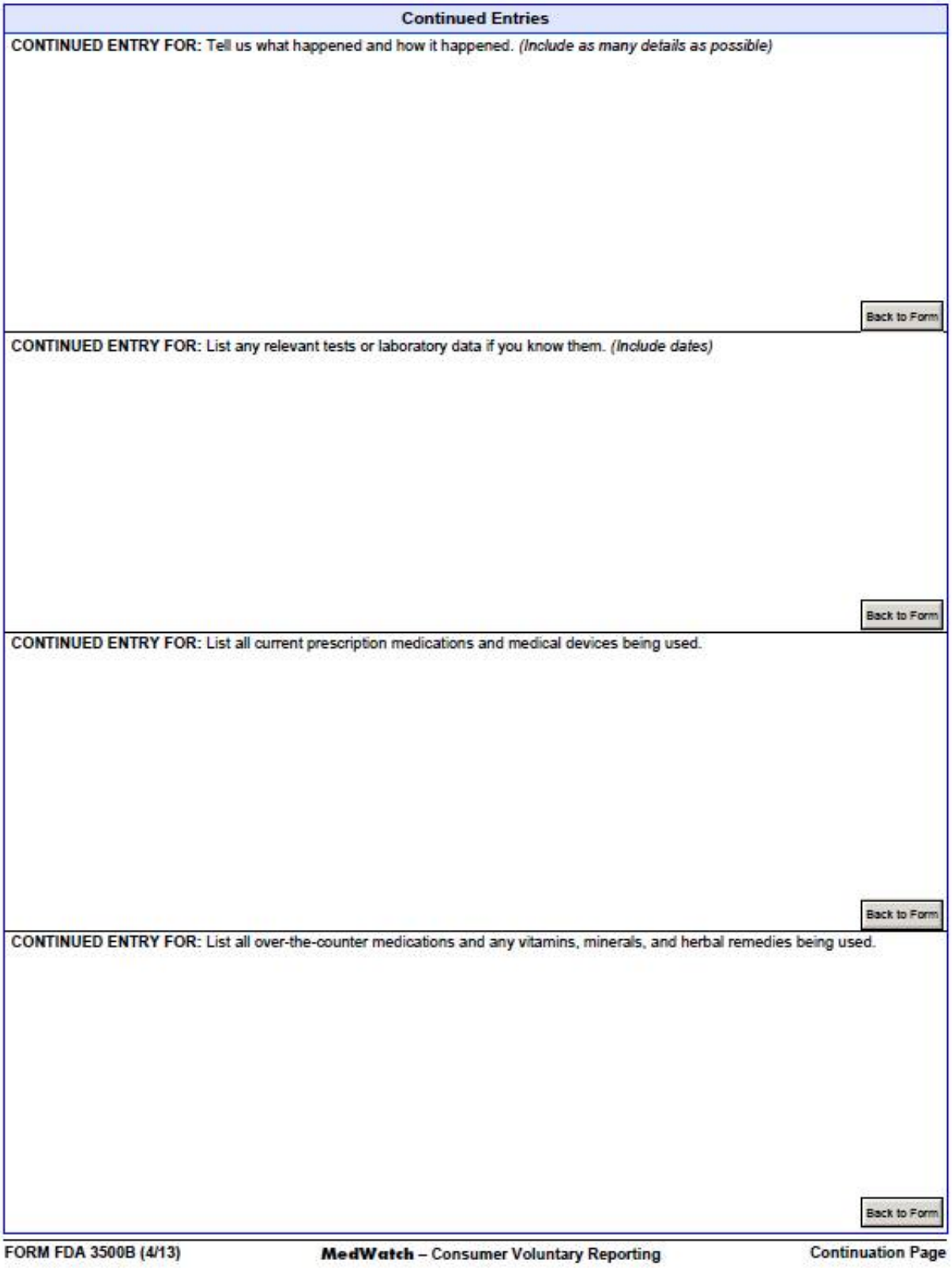
Mail:	Fax:
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

Thank you for helping us protect the public health.

For more information, visit http://www.fda.gov/MedWatch

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

FORM FDA 3500B (4/13) **MedWatch** Consumer Voluntary Reporting Page 3 of 3



Continued Entries

CONTINUED ENTRY FOR: Tell us what happened and how it happened. *(Include as many details as possible)*

Back to Form

CONTINUED ENTRY FOR: List any relevant tests or laboratory data if you know them. *(Include dates)*

Back to Form

CONTINUED ENTRY FOR: List all current prescription medications and medical devices being used.

Back to Form

CONTINUED ENTRY FOR: List all over-the-counter medications and any vitamins, minerals, and herbal remedies being used.

Back to Form

FORM FDA 3500B (4/13) **MedWatch – Consumer Voluntary Reporting** **Continuation Page**

Appendix 4: YGTSS

Put a circle around the appropriate score.

PLACE TOTALS OF NEXT 5 SECTIONS WHERE INDICATED BELOW.

1. NUMBER	Current Motor	Current Phonic	Worst Ever Motor	Worst Ever Phonic
None	0	0	0	0
Single tic	1	1	1	1
Multiple discrete tics (2-5)	2	2	2	2
Multiple discrete tics (>5)	3	3	3	3
Multiple discrete tics plus as least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics	4	4	4	4
Multiple discrete tics plus several (>2) orchestrated paroxysms of multiple simultaneous or sequential tics that where it is difficult to distinguish discrete tics	5	5	5	5

2. FREQUENCY	Motor	Phonic	Motor	Phonic
NONE No evidence of specific tic behaviors	0	0	0	0
RARELY Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.	1	1	1	1
OCCASIONALLY Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.	2	2	2	2
FREQUENTLY Specific tic behaviors are present on a daily basis. Tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.	3	3	3	3
ALMOST ALWAYS Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.	4	4	4	4
ALWAYS Specific tic behaviors are present virtually all the time. Tic free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.	5	5	5	5

3. INTENSITY

	Current		Worst Ever	
	Motor	Phonic	Motor	Phonic
ABSENT	0	0	0	0
MINIMAL INTENSITY Tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.	1	1	1	1
MILD INTENSITY Tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.	2	2	2	2
MODERATE INTENSITY Tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.	3	3	3	3
MARKED INTENSITY Tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.	4	4	4	4
SEVERE INTENSITY Tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.	5	5	5	5

4. COMPLEXITY

	Motor	Phonic	Motor	Phonic
NONE If present, all tics are clearly "simple" (sudden, brief, purposeless) in character.	0	0	0	0
BORDERLINE Some tics are not clearly "simple" in character.	1	1	1	1
MILD Some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables, or brief meaningful utterances such as "ah huh," "hi" that could be readily camouflaged.	2	2	2	2
MODERATE Some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey", brief echolalia).	3	3	3	3
MARKED Some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").	4	4	4	4
SEVERE Some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).	5	5	5	5

5. INTERFERENCE

	Motor	Phonic	Motor	Phonic
NONE	0	0	0	0
MINIMAL When tics are present, they do not interrupt the flow of behavior or speech.	1	1	1	1
MILD When tics are present, they occasionally interrupt the flow of behavior or speech.	2	2	2	2
MODERATE When tics are present, they frequently interrupt the flow of behavior or speech.	3	3	3	3
MARKED When tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.	4	4	4	4
SEVERE When tics are present, they frequently disrupt intended action or communication.	5	5	5	5

GO TO TOTALS SECTION ON NEXT PAGE

TOTAL OF COLUMNS FOR ABOVE 5 SECTIONS
CURRENT:

Total Motor Current	Total Phonic Current	Total Motor + Phonic Current

WORST EVER:

Total Motor Worst Ever	Total Phonic Worst Ever	Total Motor + Phonic Worst Ever

IMPAIRMENT	Current	Worst Ever
NONE	0	0
MINIMAL Tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis a vis the future, periodic, slight increase in family tensions because of tics, friends or acquaintances may occasionally notice or comment about tics in an upsetting way).	10	10
MILD Tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.	20	20
MODERATE Tics associated with some clear problems in self-esteem family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).	30	30
MARKED Tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.	40	40
SEVERE Tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with suicidal ideation, disruption of the family (separation/divorce, residential placement), disruption of social tics - severely restricted life because of social stigma and social avoidance, removal from school or loss of job).	50	50

Child Depression Inventory

Parent's name: _____ Relationship to the child: _____

Instructions:

For each of the statements below, select one response that best describes your observations of your child in the **past two weeks**.

Indicate your response for each item by **circling** the number that best corresponds to your choice. You may change an item response by drawing an ✗ through your original choice and selecting a new response.

Remember, for each statement, pick **one** answer that best describes your observations of your child in the PAST TWO WEEKS.

My child…	Not at all	Some of the time	Often	Much or most of the time
1. looks sad.	0	1	2	3
2. has fun.	0	1	2	3
3. does not like himself or herself.	0	1	2	3
4. blames himself or herself for things.	0	1	2	3
5. cries or looks tearful.	0	1	2	3
6. is cranky or irritable.	0	1	2	3
7. enjoys being with people.	0	1	2	3
8. thinks that he or she is ugly.	0	1	2	3
9. has to push himself or herself to do schoolwork.	0	1	2	3
10. has trouble sleeping at night.	0	1	2	3
11. looks tired or fatigued.	0	1	2	3
12. seems lonely.	0	1	2	3
13. enjoys school.	0	1	2	3
14. spends time with friends.	0	1	2	3
15. is showing worse school performance than before.	0	1	2	3
16. does what he or she is told.	0	1	2	3
17. has disagreements and conflicts with others.	0	1	2	3

Child Depression Inventory-Continued

Instructions:

1. For each item, transfer the circled number into the unshaded box to the left in the corresponding row of the grid.
2. Sum each column and write the totals in the corresponding Raw Score boxes at the bottom of each column.
3. Sum the two Raw Scores to obtain the Total Raw Score.

Emotional Problems	Functional Problems	Not at all	Some of the time	Often	Much or most of the time	Item
		0	1	2	3	1
		3	2	1	0	2
		0	1	2	3	3
		0	1	2	3	4
		0	1	2	3	5
		0	1	2	3	6
		3	2	1	0	7
		0	1	2	3	8
		0	1	2	3	9
		0	1	2	3	10
		0	1	2	3	11
		0	1	2	3	12
		3	2	1	0	13
		3	2	1	0	14
		0	1	2	3	15
		3	2	1	0	16
		0	1	2	3	17
Emotional Problems	+ Functional Problems	= Total	← Raw Scores			

Child Depression Inventory-Continued

Instructions:

1. Circle the Raw Scores from the Scoring Grid for each scale under the appropriate sex and age column.
2. Follow the corresponding row across to find the corresponding *T*-score and classification for each scale.
3. Transfer the *T*-scores to the appropriate boxes at the bottom of the page.
4. Connect the three circled values with straight lines to form a profile.

T	Females						Classification	Males						T
	Total		Emotional Problems		Functional Problems			Total		Emotional Problems		Functional Problems		
	7–12	13–17	7–12	13–17	7–12	13–17		7–12	13–17	7–12	13–17	7–12	13–17	
90+	39+	42+	21+	22+	21+	22+		39+	37+	20+	17+	23+	22+	90+
89	38	41		21	20			38	36					89
88	37	40	20							19		22	21	88
87		39				21		37	35		16			87
86	36			20	19			36	34					86
85	35	38	19			20				18		21	20	85
84	34	37		19	18			35	33		15			84
83		36	18					34	32			20	19	83
82	33					19				17				82
81	32	35		18	17			33	31		14	19		81
80		34	17			18	Very Elevated	32	30	16			18	80
79	31	33		17				31						79
78	30		16		16				29		13	18	17	78
77	29	32				17		30	28	15				77
76		31	15	16	15			29				17		76
75	28	30				16			27	14	12		16	75
74	27			15				28	26					74
73		29	14		14			27				16		73
72	26	28		14		15			25	13	11		15	72
71	25	27	13					26	24			15		71
70	24				13			25					14	70
69		26		13		14		24	23	12	10	14		69
68	23	25	12		12				22					68
67	22	24		12		13	Elevated	23		11			13	67
66	21		11					22	21		9	13		66
65		23			11				20				12	65
64	20	22		11		12		21		10		12		64
63	19	21	10		10			20	19		8			63
62				10		11	High Average	19	18	9			11	62
61	18	20	9									11		61
60	17	19			9			18	17		7		10	60
59	16	18		9		10		17	16	8		10		59
58			8											58
57	15	17		8	8	9		16	15				9	57
56	14	16	7					15	14	7	6	9		56
55		15			7									55
54	13		6	7		8		14	13	6		8	8	54
53	12	14						13	12		5			53
52	11	13		6	6	7		12				7	7	52
51		12	5						11	5				51
50	10			5				11	10		4			50
49	9	11	4		5	6	Average	10		4		6	6	49
48		10							9					48
47	8	9		4	4	5		9	8		3	5	5	47
46	7		3					8		3				46
45	6	8		3				7	7					45
44		7	2		3	4			6		2	4	4	44
43	5	6						6		2				43
42	4			2	2	3		5	5			3		42
41	3	5	1						4	1	1		3	41
40		4		1				4				2		40
39	2	3	0		1	2		3	3				2	39
38	1								2	0	0			38
37		2		0		1	Low	2				1		37
36	0	1			0			1	1				1	36
≤35		0				0		0	0			0	0	≤35
	T =		T =		T =			T =		T =		T =		

Columbia Suicide Severity Rating Scale

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

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

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

Appendix 6 Clinical Global Impression Scales – Improvement and Severity

CGI-Severity by Clinician/ Investigator
Consider your total clinical experience with this particular population, how ill is the subject at this time?
☐$_1$ Normal, not at all ill ☐$_2$ Borderline ill ☐$_3$ Mildly ill ☐$_4$ Moderately ill ☐$_5$ Markedly ill ☐$_6$ Severely ill ☐$_7$ Among the most extremely ill subjects

CGI-Improvement by Clinician/ Investigator (Neurobehavioral symptoms)		
Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to subject's condition at admission to the project, how much has the subject changed?		
☐$_1$ Very much improved	☐$_2$ Much improved	
☐$_3$ Minimally improved	☐$_4$ No change	
☐$_5$ Minimally worse	☐$_6$ Much worse	☐$_7$ Very much worse