Official Title: A Phase 2, Multicenter, Randomized, Double-blind, Active- and Placebo-controlled Trial of the Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder

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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-64005

REVISED CLINICAL PROTOCOL

A Phase 2, Multicenter, Randomized, Double-blind, Active- and Placebo-controlled Trial of the Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder

Protocol No. 277-201-00001
IND No. 133026

CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, MD 20850 United States
Immediately Reportable Event	Clinical Safety and Pharmacovigilance 24-hour Drug Safety Hotline: [redacted] 24-hour Drug Safety Fax:
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Protocol 277-201-00001

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: OPC-64005	Protocol No.: 277-201-00001 IND No.: 133026
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-blind, Active- and Placebo-controlled Trial of the Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder
Clinical Phase:	2
Treatment Indication:	Adult Attention-deficit/Hyperactivity Disorder
Objective(s):	Primary: To assess the efficacy of OPC-64005 (20 - 30 mg/day) relative to atomoxetine (40 - 80 mg/day) in adult subjects with attention-deficit/hyperactivity disorder (ADHD) Other: To estimate the difference in effect between OPC-64005 (20 - 30 mg/day) and placebo and its variability in adult subjects with ADHD in order to plan for the next trial. To assess the safety and tolerability of OPC-64005 (20 - 30 mg/day) in adult subjects with ADHD compared with both control arms.
Trial Design:	This is a multicenter, randomized, double-blind, active- and placebo-controlled, parallel-design trial. The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur at 3 (± 1) days after the last dose, and a follow-up telephone contact to occur 30 (+ 2) days after the last dose.
Subject Population:	Approximately 201 adult male and female subjects with ADHD will be randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo.

Protocol 277-201-00001

Inclusion Criteria:	Key inclusion criteria include the following: • Subjects with a primary *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2). Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that they are currently receiving treatment. The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability. • Male and female outpatients 18 to 55 years of age, inclusive, at the time of informed consent. • Subjects who are not currently receiving an approved pharmacological treatment for ADHD who have an Adult ADHD Investigator Symptom Rating Scale (AISRS) with Adult Prompts score of ≥ 26 and subjects who are receiving any pharmacological treatment for ADHD at screening who have an AISRS with Adult Prompts score of ≥ 22. • Subjects who have a score of ≥ 4 on the Global Clinical Impression-Severity (CGI-S) scale.
Trial Site(s):	Approximately 25 trial sites in the United States

Protocol 277-201-00001

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Double-blind investigational medicinal product (IMP) will be provided to the investigator(s) by the sponsor (or contractor) and will consist of active OPC-64005 10-mg tablets and matching placebo tablets as well as atomoxetine 40-mg capsules (the active comparator) and matching placebo capsules. The IMP will consist of tablets and capsules in weekly child-resistant blister cards, each containing sufficient tablets and capsules for 7 (+ 2) days. When accessed by the site, the interactive voice response system (IVRS) or interactive web response system (IWRS) will assign specific blister cards to be dispensed to a subject. During the Titration Period (Days 1 - 4), subjects randomized to the OPC-64005 arm will receive 20 mg OPC-64005 (ie, two 10 mg OPC-64005 tablets) and atomoxetine placebo daily, subjects randomized to the atomoxetine arm will receive 40 mg of atomoxetine and OPC-64005 placebo daily, and subjects randomized to the placebo arm will receive both OPC-64005 placebo and atomoxetine placebo daily. During the Treatment Period (Days 5 - 56), subjects randomized to the OPC-64005 arm will receive 30 mg OPC-64005 and atomoxetine placebo daily, subjects randomized to the atomoxetine arm will receive 80 mg of atomoxetine and OPC-64005 placebo daily, and subjects randomized to the placebo arm will receive both OPC-64005 placebo and atomoxetine placebo daily. If a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.

Trial Assessments:	**Efficacy:** 18-item, investigator-administered Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV), 18-item Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV), AISRS with Adult Prompts, CGI-S, Global Clinical Impression-Improvement (CGI-I), Adult ADHD Quality of Life Scale (AAQoL), and Profile of Mood States-Brief Form™ (POMS). **Pharmacokinetics:** Blood sampling for IMP plasma concentrations. **Safety:** Adverse events, physical examination, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests, C-SSRS, and Drug Effects Questionnaire (DEQ). **Screening/Other:** Demographic information; medical, medication, and psychiatric history; identification of comorbidities (in part, using the Mini International Neuropsychiatric Interview); HIV, hepatitis B surface antigen (HBsAg), and anti hepatitis C virus (HCV) status; urine alcohol and drug screen; urine pregnancy test.

Protocol 277-201-00001

Criteria for Evaluation:	**Primary Endpoint:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit on the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group. **Other Endpoint(s):** • Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/early termination [ET]; all visits have a ± 1-day window) in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits for the AISRS with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups • CGI-I score at each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the 18-item CAARS–S:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits in the AAQoL score in the OPC-64005, atomoxetine, and placebo groups • OPC-64005 potential for abuse liability and dependence as assessed by the DEQ at baseline and each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window)

Protocol 277-201-00001

Statistical Methods:	Details of the planned statistical analysis will be presented in the statistical analysis plan (SAP). Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. **Primary:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit on the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group. Bayesian posterior probability of true baseline corrected difference at Day 56 (± 1 day) between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on the 18-item, investigator-administered CAARS-O:SV given estimates of means and SD in the treatment arms will be calculated. Uninformative prior will be used in calculations. Estimates for means and SD will be derived from mixed-effect model as described below. The change from baseline in the 18-item, investigator-administered CAARS-O:SV will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week, an interaction term of treatment by visit week, and baseline 18-item, investigator-administered CAARS-O:SV as covariate. The need of additional fixed effects and its interactions in the model will be explored. Other continuous efficacy endpoints will also be analyzed using MMRM methodology. Complete model details will be specified in the SAP.
Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 9 months. The duration of the trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a 3 [± 1]-day safety follow-up phone call, and a 30 [+ 2]-day safety follow-up phone call).

Protocol 277-201-00001

Table of Contents

Protocol 277-201-00001

Protocol 277-201-00001

Protocol 277-201-00001

Protocol 277-201-00001

List of In-text Tables

Protocol 277-201-00001

List of In-text Figures

Protocol 277-201-00001

List of Appendices

Protocol 277-201-00001

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin
AAQoL	Adult ADHD Quality of Life Scale
ACDS v1.2	Adult ADHD Clinical Diagnostic Scale, version 1.2
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
AISRS	Adult ADHD Investigator Symptom Rating Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
BMI	Body mass index
BUN	Blood urea nitrogen
CAARS-O:SV	Conners' Adult ADHD Rating Scales–Observer: Screening Version
CAARS-S:SV	Conners' Adult ADHD Rating Scales–Self-Report: Screening Version
CGI-I	Global Clinical Impression-Improvement
CGI-S	Global Clinical Impression-Severity
CIOMS	Council for International Organizations of Medical Science
C_{max}	Maximum (peak) plasma concentration
CRO	Clinical Research Organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DA	Dopamine
DAT	Dopamine transporter
DBP	Diastolic blood pressure
DEQ	Drug Effects Questionnaire
DNA	Deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition
ECG	Electrocardiogram
EC_{50}	Concentration of plasma to obtain 50% of the maximum effect in vivo
eICF	Electronic informed consent form
ET	Early termination
FBR	Future biospecimen research
FDA	(United States) Food and Drug Administration
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HbA1c	Glycated hemoglobin

HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDDM	Insulin-dependent diabetes mellitus
IMP	Investigational medicinal product
IND	Investigative new drug
IQ	Intelligence quotient
IRB	Institutional review board
IRE	Immediately reportable event
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactic dehydrogenase
LLT	Lowest level term
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ-ADHD	Massachusetts General Hospital Treatment Response Questionnaire (ATRQ) - ADHD
M.I.N.I.	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect model repeated measures
MTD	Maximum tolerated dose
NE	Norepinephrine
NET	Norepinephrine transporter
NOAEL	No observed adverse effect level
OC	Observed case
OPC	Otsuka Pharmaceutical Co.
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
OTC	Over the counter
PET	Positron emission tomography
PK	Pharmacokinetic
POMS	Profile of Mood States-Brief Form™
PQC	Product quality complaint
QD	Once daily
QTcB	Q-T interval corrected using Bazett's formula
QTcF	Q-T interval corrected using Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SERT	Serotonin transporter
TEAE	Treatment-emergent adverse event

TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

Protocol 277-201-00001

1 Introduction

OPC-64005 is a novel monoamine system modulator that is synthesized by Otsuka Pharmaceutical Co., Ltd and is being developed for the treatment of attention-deficit/ hyperactivity disorder (ADHD).

1.1 Nonclinical Data

OPC-64005 doses (mg/kg) are indicated as the free base form for all in vivo nonclinical studies.

1.1.1 Efficacy Pharmacology

OPC-64005 exhibits inhibitory activities on serotonin (5-HT), norepinephrine (NE), and dopamine (DA) reuptake into rat brain synaptosomes.[1] OPC-64005 shows selective affinities for human 5-HT, NE, and DA transporters (inhibition constant values = 1.62, 6.57, and 123.06 nmol/L, respectively).[2,3] In addition, OPC-64005 has demonstrated the potential to modulate monoamine systems. In vivo microdialysis demonstrated that extracellular 5-HT, NE, and DA levels in the rat medial prefrontal cortex were dose dependent and simultaneously increased by OPC-64005 with greater potency relative to paroxetine, sertraline, duloxetine, and bupropion.[4,5] In addition, OPC-64005, orally administered at doses of 0.2 mg/kg and greater, produced statistically significant increases in extracellular 5-HT, NE, and DA (area under the curve as an integrated measurement of percent of basal values during 0 to 360 minutes after administration) to 206.7%, 176.5%, and 164.8%, respectively, compared to the vehicle group. In the medial prefrontal cortex, where there is a low density of dopamine transporter (DAT), extracellular DA levels are thought to be regulated by norepinephrine transporter (NET).[6] The effects of DAT inhibition on the extracellular DA level were therefore evaluated in the striatum, where there is a high density of DAT. OPC-64005 significantly increased extracellular DA levels in the rat striatum at 2.5 mg/kg and higher doses.[7]

OPC-64005 also showed significant antidepressant-like effects in the rat forced swimming test following oral administration once daily for 2 days at 5 and 10 mg/kg[8,9] and for 14 days at 2.5, 5, and 10 mg/kg.[10,11] Furthermore, OPC-64005 demonstrated significant anxiolytic-like effects in the rat elevated plus maze test following single oral administration at 2.5, 5, and 7.5 mg/kg.[12]

From the results of these nonclinical pharmacology studies, OPC-64005 may have the potential to improve depressive symptoms related to monoamine imbalance.

Protocol 277-201-00001

1.1.2 Safety Pharmacology

OPC-64005 showed no effect on general signs and behavior at single oral doses of 3 and 10 mg/kg in male rats. At 30 mg/kg, vocalization and increased body tone were noted only during handling.[13] OPC-64005 at a single oral dose of 3 mg/kg showed no effect on the respiratory system in male rats.[14] OPC-64005 increased respiratory rate and minute volume at 10 mg/kg and higher and decreased tidal volume at 30 mg/kg. OPC-64005 showed no effect on the cardiovascular system in conscious male monkeys at a single oral dose of 0.3 mg/kg.[15] OPC-64005 increased mean blood pressure at 1 mg/kg and higher, increased heart rate, and shortened QT interval at 3 mg/kg and higher.

OPC-64005 at 1 µmol/L and higher inhibited human ether-a-go-go related gene current (hERG) with a half maximal inhibitory concentration of 3.34 µmol/L.[16] In isolated guinea pig right ventricular papillary muscles, OPC-64005 at 1 µmol/L showed no effect on any action potential parameters.[17] However, OPC-64005 at 10 µmol/L and 100 µmol/L shortened action potential duration at 30% and 60% of repolarization. At 100 µmol/L, OPC-64005 shortened the action potential amplitude and action potential duration at 90% repolarization and decreased the maximum upstroke velocity of action potential. In isolated guinea pig right atrial preparations, OPC-64005 at up to 30 µmol/L showed no effects on heart rate and contraction force.[18] However, OPC-64005 at 100 µmol/L showed negative chronotropic and inotropic effects and induced sinus arrest in 3 of 5 preparations within 30 minutes after application.

1.1.3 Nonclinical Absorption, Distribution, Metabolism, and Excretion

1.1.3.1 Absorption

Following single oral administration of OPC-64005 at 1 mg/kg as the free base form to fed male rats[19] and at 1 mg/kg to fed male monkeys[20] maximum (peak) plasma concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), and terminal-phase elimination half-life were respectively 38.26 and 39.23 ng/mL, 283.2 and 972.9 ng·h/mL, and 2.915 and 8.435 hours. Although dose-dependent increases in plasma C_{max} and $AUC_{0-\infty}$ were observed in both rats and monkeys at doses ranging from 0.1 to 3 mg/kg, the increases in systemic exposure were not dose proportional. Orally administered [phenyl-^{14}C (U)]-OPC-277 (^{14}C-OPC-64005) was highly absorbed in both rats (>91%) and monkeys (> 77%).[21,22] The absolute bioavailability of OPC-64005 (free base form) was 49.9% in rats and 57.1% in monkeys.

A slight food effect was observed in rats and monkeys and a slight sex difference was observed in rats.

1.1.3.2 Distribution

Following single oral administration of ^{14}C-OPC-64005 in rats, the radioactivity was distributed throughout the entire body.[21] The concentrations of radioactivity in many tissues were higher than the plasma concentration. The concentrations of radioactivity in most tissues peaked at 2 or 4 hours postdose and then decreased slowly, which was similar to the plasma concentration. The pattern of distribution was similar between males and females. The tissue-to-plasma partition ratios in males were lower than those in females in many tissues.

In vitro protein binding of ^{14}C-OPC-64005 was 95.59% to 96.79% in human serum, indicating high protein binding of OPC-64005 in human serum.[23] In mouse, rat, rabbit, dog, and monkey serum, protein binding was 85.35% to 96.92%.

1.1.3.3 Metabolism

Following oral administration of OPC-64005 in rats and monkeys, the metabolites OPC-124789, OPC-124975, OPC-124990, OPC-124996, OPC-144013 (OPC-64005 glucuronide), DM-6401, DM-6402, and a sulfate of MOP-184703 were identified in the plasma in both species.[24] In an investigation of the in vitro metabolism of OPC-64005, OPC-144013, OPC-124975, and DM-6401 were the main metabolites produced using human liver S9 and human hepatocytes, and OPC-124789, OPC-124990, and OPC-124996 were also observed; no unique human metabolites were observed.[25] In an in vitro metabolism study of ^{14}C-OPC-64005 using recombinant human cytochrome P450 (CYP) enzymes, ^{14}C-OPC-64005 was slightly metabolized by CYP1A2, CYP2B6, CYP2D6, and CYP3A4.[26]

1.1.3.4 Excretion

Following single oral administration of ^{14}C-OPC-64005 to rats, the urinary and fecal excretions of radioactivity within 168 hours postdose respectively accounted for 62.11% to 64.98% and 31.23% to 33.62% of the administered dose, and the biliary and urinary excretions of radioactivity within 48 hours postdose respectively accounted for 63.52% to 72.18% and 19.64% to 29.37% of the administered dose.[21,27] A high rate of enterohepatic circulation was seen in male rats. Following oral administration of ^{14}C-OPC-64005 in monkeys, the urinary and fecal excretions of radioactivity within

168 hours postdose respectively accounted for 77.58% and 20.40% of the administered dose.[22]

1.1.4 Toxicology

The toxic potential of OPC-64005 was investigated in single- and repeated-dose oral toxicity studies in rats and monkeys, in vitro and in vivo genotoxicity studies, and reproductive and developmental toxicity studies in rats and rabbits. OPC-64005 doses (mg/kg) are indicated as the free base form in all in vivo toxicity studies.

1.1.4.1 Single-dose Toxicity

In single-dose oral toxicity studies, the approximate lethal dose was between 30 and 100 mg/kg in male rats, between 100 and 300 mg/kg in female rats, and between 30 and 100 mg/kg in male and female monkeys. In a single-dose oral toxicity study in monkeys, clonic convulsion was observed in 1 female at 100 mg/kg (lethal dose).[28,29]

1.1.4.2 Repeated-dose Toxicity

In a 4-week repeated-dose oral toxicity study in rats, deaths occurred in females at 30 mg/kg/day, and clonic convulsion was observed in females at this dose.[30] Tremor, accelerated touch response, increased spontaneous motor activity, decreased body weight or suppressed body weight gain, and decreased food consumption were observed in males at 30 mg/kg/day and in females at 10 mg/kg/day and higher. In blood biochemistry, decreased glucose in males and decreased cholesterol and increased phosphorus and γ- and β-globulin in females were observed at 30 mg/kg/day. Creatine phosphokinase and aspartate aminotransferase (AST) were increased in males and females at 30 mg/kg/day. Increased γ-globulin was also observed in females at 10 mg/kg/day. Almost all changes observed during the treatment period showed reversibility. The no observed adverse effect level (NOAEL) was therefore estimated to be 10 mg/kg/day for males and 3 mg/kg/day for females. For OPC-64005 on Day 28, the C_{max} was 954 and 415 ng/mL and the AUC from time zero to 24 hours ($AUC_{0\text{-}24h}$) was 16160 and 5120 ng·h/mL in males and females, respectively.

In a 4-week repeated-dose oral toxicity study in monkeys, since death occurred in 1 male and 2 females on Days 1 to 3 at the highest dose of 30 mg/kg/day, administration at that dose was discontinued.[31] After a withdrawal period (5 days for males and 6 days for females), the highest dose was reduced to 20 mg/kg/day for administration to the surviving 4 males and 3 females for 4 weeks. However, 1 male and 2 females at 20 mg/kg/day died or were sacrificed in a moribund condition, and whole body tremor

and decreased body weight or suppressed body weight gain during the dosing period in both sexes and prolonged corrected QT interval (QTc) for heart rate at Week 4 in males were observed at this dose. Limb tremor (males and females), decreased body weight, or suppressed body weight gain in females were observed at 10 mg/kg/day. The NOAEL was therefore estimated to be 3 mg/kg/day for both males and females. At the NOAEL on Day 28, the C_{max} was 595.5 and 367 ng/mL and the $AUC_{0\text{-}24h}$ was 4771 and 3207 ng·h/mL in males and females, respectively.

In a 13-week repeated-dose oral toxicity study in rats, tremor in males at 30 mg/kg/day and accelerated touch response, decreased body weight or suppressed body weight gain, and decreased food consumption in males at 10 mg/kg/day and/or 30 mg/kg/day and in females at 10 mg/kg/day were observed.[32] In hematology, blood biochemistry, and urinalysis, decreases in eosinophils, glucose, and triglycerides were observed in males at 30 mg/kg/day. In the females, increased reticulocytes, total cholesterol, phospholipids, total protein, calcium, phosphorus, β-globulin, and γ-globulin, decreased water consumption and urine volume, and increased urine osmolarity were observed at 10 mg/kg/day. In histopathology, hypertrophy of centrilobular hepatocytes with increased smooth endoplasmic reticulum in the liver and apoptosis of acinar cells in the pancreas were observed in males at 10 mg/kg/day and higher. In addition, fatty change of the hepatocytes with increased lipid droplets in the mid zone of the lobules in the liver and ventral-lobe-specific atrophy of the prostate at 10 mg/kg/day and higher and focal accumulation of foamy cells in the lung and bronchus at 30 mg/kg/day were observed in males, and none of these changes were observed in the 4-week repeated-dose oral toxicity study. All changes observed during the treatment period showed reversibility after withdrawal of administration. The NOAEL was therefore estimated to be 3 mg/kg/day for both males and females and at that dose the plasma C_{max} and $AUC_{0\text{-}24h}$ of OPC-64005 at Week 13 were, respectively, 257.7 ng/mL and 4053 ng·h/mL in males and 429.7 ng/mL and 6457 ng·h/mL in females.

In a 13-week repeated-dose oral toxicity study in monkeys, limb tremor and decreased body weight or suppressed body weight gain were observed in males and females at 10 mg/kg/day.[33] The NOAEL was therefore estimated to be 3 mg/kg/day for both males and females and at that dose the plasma C_{max} and $AUC_{0\text{-}24h}$ of OPC-64005 at Week 13 were, respectively, 375.9 ng/mL and 4649 ng·h/mL in males and 414.1 ng/mL and 4665 ng·h/mL in females.

1.1.4.3 Genotoxicity

The genotoxic potential of OPC-64005 was investigated in vitro by means of the bacterial reverse mutation test.[34] No mutagenicity was observed at up to the highest noncytotoxic dose of 124 µg/plate with rat liver S9 and 62 µg/plate without rat liver S9. The potential genotoxicity of OPC-64005 was investigated in vitro by means of the forward mutation test in cultured mammalian cells.[35] No mutagenicity was observed at up to 20 µmol/L without S9 by 3-hour exposure, at up to 50 µmol/L with S9 by 3-hour exposure or at up to 10 µmol/L without S9 by 24-hour exposure.

The potential genotoxicity of OPC-64005 was investigated in vivo by means of the bone marrow micronucleus test in male Sprague Dawley rats.[36] No increase in the incidence of micronuclei in bone marrow erythrocytes was observed in male rats at the highest evaluated dose of 10 mg/kg/day administered orally for 2 days. The potential genotoxicity of OPC-64005 was investigated in vivo by means of an unscheduled deoxyribonucleic acid (DNA) synthesis test in male Sprague Dawley rats.[37] No DNA damage in hepatocytes was observed at up to the highest dose of 30 mg/kg.

1.1.4.4 Reproductive and Developmental Toxicity

In a fertility and early embryonic development study in male rats, decreased body weight or suppressed body weight gain and decreased food consumption at 3 and 10 mg/kg/day and accelerated touch or sound response at 10 mg/kg/day were observed in parental males.[38] However, OPC-64005 did not affect either male reproductive function or early embryonic development. In a fertility and early embryonic development study in female rats, decreased body weight gain and food consumption at 1 mg/kg/day and higher, decreased body weight at 3 and 10 mg/kg/day, and accelerated touch or sound response at 10 mg/kg/day were observed.[39] A slight prolongation of mean estrous cycle was observed at 10 mg/kg/day, but no treatment-related changes were observed in early embryonic development. The NOAEL was therefore estimated to be lower than 1 mg/kg/day for general toxicity in parental females, 3 mg/kg/day for female reproductive function, and 10 mg/kg/day for early embryonic development.

In an embryo-fetal development toxicity study with rats, maternal toxicity at 10 mg/kg/day, the highest dose tested, was characterized by accelerated touch or sound response and decreased body weight and food consumption.[40] Placental weights were increased, fetal body weights were decreased, and lower numbers of ossified cervical vertebral bodies at 10 mg/kg/day indicated an effect on fetal growth. Embryo-fetal

survival was unaffected by maternal administration of OPC-64005, and there were no fetal external, visceral, or skeletal anomalies or variations in the OPC-64005-treated groups. The NOAEL in rats was 1 mg/kg/day for maternal toxicity, 10 mg/kg/day for maternal reproductive function, and 1 mg/kg/day for embryo-fetal development.

In an embryo-fetal development toxicity study with rabbits, oral administration of 30 mg/kg/day, the highest dose tested, resulted in abortion of 3 dams on gestation Days 21, 25, or 27, and maternal toxicity exemplified by decreased body weight and food consumption were observed in dams given 10 or 30 mg/kg/day.[41] No OPC-64005 related changes occurred on fetal growth or survival. No fetal external, visceral, or skeletal malformation or variations, including ossification, were attributed to OPC-64005. The NOAEL was 3 mg/kg/day for maternal toxicity, 10 mg/kg/day for maternal reproductive function, and 30 mg/kg/day for embryo-fetal development in rabbits.

Please refer to the Investigator's Brochure (IB) for more detailed information.

1.2 Clinical Data

OPC-64005 doses (mg) are indicated as the free base form for all clinical trials.

1.2.1 Phase 1 Single-Dose Trial in Healthy Adult Subjects (United States, Trial 277-09-201)

This phase 1 trial was a multicenter, randomized, double-blind, placebo-controlled, ascending single-dose trial in healthy adult male and female subjects to administer OPC-64005 at doses of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, and 60 mg. Consequently, the mean C_{max} and $AUC_{0-\infty}$ increased dose-dependently.

Adverse events (AEs) occurred in 39 of 88 subjects and 12 of 30 subjects in all OPC-64005 groups and placebo group, respectively. No serious adverse events (SAEs) were reported. Adverse events reported in 2 or more subjects were: application site erythema (6/30 subjects; all related to electrocardiogram [ECG] patches) and dizziness (2/30 subjects) in the placebo group; dizziness and headache (2/6 subjects each) in the 25 mg group; nausea and vomiting (2/6 subjects each) in the 50 mg group; and nausea and dizziness postural (3/6 subjects each) in the 60 mg group.

Based on the results of this trial, OPC-64005 was well tolerated at doses up to 60 mg.

1.2.2 Phase 1 Single-Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-10-001)

This phase 1, placebo-controlled, ascending single-dose trial in healthy Japanese adult male subjects was conducted (Trial 277-10-001). This trial was designed to assess the pharmacokinetics (PK), safety, and tolerability of a single dose of OPC-64005 at doses of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, or placebo to healthy adult males, and to randomize 8 subjects each (6 subjects for OPC-64005 and 2 subject for placebo) and 9 subjects each (6 subjects for OPC-64005 and 3 subjects for placebo) to the 1 to 20 mg groups and the 25 to 70 mg groups, respectively. However, 60 mg was the highest dose assessed in this trial.

Adverse events occurred in 22 of 84 subjects and 4 of 34 subjects in all OPC-64005 groups and the placebo group, respectively. Adverse events observed in 2 or more subjects were: presyncope* (3/*34 subjects) and orthostatic hypotension (2/34 subjects) in the placebo group; presyncope* (3/6 subjects) in the 40 mg group; presyncope* (4/6 subjects) in the 50 mg group; and presyncope* (6/12 subjects), tachycardia (3/12 subjects), nausea (4/12 subjects), vomiting (2/12 subjects), blood pressure increased (2/12 subjects), and heart rate increased (2/12 subjects) in the 60 mg group. All AEs observed during this trial were assessed as mild or moderate in severity. In addition, supraventricular tachycardia observed in the 60 mg group was assessed as a SAE at the Sponsor's discretion, although the investigator and subinvestigator assessed this event as nonserious. This subject was suspected to have underlying sinus node dysfunction. The MTD was not determined in this trial for the following reasons: this cohort did not meet the definition of MTD as defined in the protocol; supraventricular tachycardia observed in this subject was difficult to assess; and the investigator and subinvestigator did not change the assessment of 'nonserious' for supraventricular tachycardia even after the Sponsor had assessed the event as 'serious'. Although the result suggested the possibility to proceed to the next dose step of 70 mg, dose escalation in this trial was terminated at a dose of 60 mg.

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*The reported verbatim term was "[redacted]."

Protocol 277-201-00001

1.2.3 Phase 1 Multiple-Dose Trial to Evaluate Pharmacokinetics, Safety, and Pharmacodynamics in Healthy Adult Male and Female Subjects (United States, 277-10-206)

This was a phase 1, double-blind, multiple-dose, parallel-group trial to assess the pharmacokinetics, tolerability, safety, and plasma and cerebrospinal fluid biomarkers of multiple ascending oral doses of OPC-64005 in healthy subjects.

Subjects were administered daily 10, 20, or 30-mg doses of OPC-64005 (n= 6 per dose cohort) or placebo (n = 2 per dose cohort) for 14 days in Part 1 of the trial. In Part 2, subjects were administered a daily 30-mg dose of OPC-64005 (n = 10), placebo (n = 4) or bupropion (n = 8) for 14 days.

In Part 1, 33 TEAEs were reported for 16 of 24 subjects (66.7%) and the most frequently reported TEAE was constipation. In Part 2, 77 TEAEs were reported for 21 of 22 subjects (95.5%) and the most frequently reported TEAE was headache.

OPC-64005 and metabolite C_{max} and AUC_{0-24h} increased more than proportionally after single and multiple once daily doses of 10- to 30-mg OPC-64005. Steady state for OPC-64005 was reached after 10 to 12 days of dosing. Assays to detect the presence of neurotransmitter metabolites in cerebrospinal fluid (CSF) suggested that the 30 mg dose of OPC-64005 had a significant impact on reuptake inhibition for NE and 5-HT. However, there was no clear evidence of DA related metabolites in CSF in either OPC-64005 samples or in those collected from subjects who received bupropion (positive control).

1.2.4 Phase 1, Multiple Ascending Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-12-001)

This phase 1 trial was a single-center, placebo-controlled, randomized, double-blind, multiple ascending oral dose trial of OPC-64005 in healthy Japanese adult male subjects (Trial 277-12-001).

The trial was planned for 3 dose-cohorts (20 mg for Cohort 1, 40 mg for Cohort 2, and 60 mg for Cohort 3). Each cohort consisted of 8 subjects, 6 subjects randomized to receive OPC-64005 and 2 subjects to receive placebo. Subjects were administered OPC-64005 for 14 days.

Subsequently the 40 mg dose in Cohort 2 was decreased to 30 mg due to the mean C_{max} on Day 14 following the repeated-dose administration of 20 mg OPC-64005 in Cohort 1 being higher than expected (178 ng/mL). Based on this result, it was assumed that the Day 14 exposure in Cohort 2 would be 2-times that of 20 mg with an estimated mean

C_{max} of 356 ng/mL, if the Cohort 2 dose was 40 mg which would greatly exceed the mean C_{max} at the maximum 60 mg dose in the single-dose trial (Trial 277-10-001) of 249.5 ng/mL. After the completion of Cohort 2 (30 mg), the decision was made not to proceed with Cohort 3 (60 mg) because sufficient data for PK and safety were obtained from Cohorts 1 and 2. The mean C_{max} for the 30 mg group following 14 days of multiple administrations was 292 ng/mL.

Treatment-emergent adverse events (TEAEs) occurred in 1 subject (1/6) in the 20 mg OPC-64005 group and 3 subjects (3/6) in the 30 mg OPC-64005 group. All of the TEAEs reported in the OPC-64005 groups were considered potentially drug-related. No TEAEs were reported in the placebo group.

The TEAEs observed during the trial were nausea, somnolence, and pruritic rash and all were reported in the OPC-64005 group: pruritic rash, 1 subject (1/6) in the 20 mg OPC-64005 group: nausea, 2 subjects (2/6) in the 30 mg OPC-64005 group: somnolence, 1 subject (1/6) in the 30 mg OPC-64005 group. Of the 4 TEAEs reported in this trial, 1 was moderate and 3 were mild in severity. The only TEAE leading to discontinuation of the investigational medicinal product (IMP) occurred while on a dose of 20 mg and was the rash pruritic which was moderate in severity and potentially drug-related.

Based on the results of this trial, multiple administration of 20 mg and 30 mg of OPC-64005 once daily for 14 days was well tolerated and no significant safety concerns were observed in healthy Japanese adult male subjects.

1.2.5 Phase 1 Trial to Evaluate Serotonin, Norepinephrine, and Dopamine Transporter Occupancy in Healthy Adult Male Subjects (United States, 277-10-205)

This phase 1 open-label trial was designed to evaluate serotonin transporter (SERT), NET, and DAT occupancy in human brain after oral administration of OPC-64005 in healthy male subjects.

Eighteen subjects were enrolled into the trial, 17 subjects were administered IMP, and 15 subjects completed the trial.

OPC-64005 was administered to each subject once or twice at a dose of 8, 20, or 60 mg. Each subject was to undergo 1 baseline PET scan prior to dosing and 2 PET scans after each subsequent dose of OPC-64005. The times of postdose scans occurred at approximately 3 hours and at 16 to 24 hours postdose, as feasible. Prior to the PET scan,

one of the following radioligands was administered: ^{11}C-DASB, a SERT ligand; ^{11}C-MRB, a NET ligand; and ^{11}C-PE2I, a DAT ligand.

Receptor occupancy increased with increasing OPC-64005 plasma concentration for SERT and NET, while no clear trend was visible for DAT. The estimated overall E_{max} for SERT occupancy ranged from 73.3% to 84.8% and the overall EC_{50} ranged from 5.5 to 8.84 ng/mL. The estimated overall E_{max} for NET occupancy was 117% and the EC_{50} was 18.8 ng/mL. At 24 hours postdose, % receptor occupancy for SERT and NET receptors were greater than 74% and 71%, respectively. At the 60 mg OPC-64005 dose, DAT receptor occupancy ranged from 1% to 16% at plasma concentrations of 18.1 to 205 ng/mL.

Twelve of 17 subjects (70.6%) had 43 TEAEs across all doses of OPC-64005, with most TEAEs reported after dosing with 60-mg of OPC-64005. The most frequently occurring TEAEs (reported by more than 2 subjects overall) were nausea (8 subjects), dizziness (4 subjects), and headache (3 subjects). All of these TEAEs were considered by the investigator to be potentially related to the IMP except for one incidence of headache.

1.2.6 Phase 1 Trial to Evaluate Dopamine Transporter Occupancy in Healthy Adult Male Subjects (Japan, Trial 277-13-001)

This phase 1 open-label, single-dose, positron emission tomography (PET) trial was designed to evaluate DAT occupancy in the human brain following oral administration of OPC-64005 in 6 healthy adult male subjects.

An established DAT ligand, ^{18}F-FE-PE2I, was used in this trial.

Six subjects were divided into 2 groups of 3 subjects each, receiving either a single oral dose of 30 mg or 60 mg of OPC-64005. The PET scans were performed 3 times (predose, 2 hours postdose, and 24 hours postdose) for each subject.

During the trial, 5 of the 6 subjects had 14 TEAEs reported. In the 30 mg group, all 3 subjects had 6 TEAEs while in the 60 mg group 2 subjects had 8 TEAEs. Treatment-emergent AEs considered potentially drug-related were reported by 2 subjects (4 TEAEs) in the 30 mg group and by 2 subjects (8 TEAEs) in the 60 mg group.

The most frequently occurring TEAE (reported by more than 2 subjects overall) was nausea (3/6 subjects). Other frequently reported TEAEs (reported by 2/6 subjects overall) were vomiting, chills, body temperature decreased, and headache. All of the TEAEs reported were considered mild in severity and no moderate or severe TEAEs were reported.

The DAT occupancy following a single 30 or 60 mg dose was below 20% at 2 and 24 hours postdose (plasma concentration range was 4.68 - 154 ng/mL)

1.2.7 Phase 1 Trial to Evaluate Dopamine Transporter Occupancy in Healthy Adult Male Subjects (Japan, 277-14-001)

This phase 1 open-label PET trial was designed to evaluate DAT occupancy in the human brain after repeated oral administration of OPC-64005 for 14 days in healthy adult male subjects.

Eight subjects were enrolled and were administered the IMP. Five of these subjects completed the trial.

A 30-mg dose of OPC-64005 was administered once daily for 14 days. Sixty-minute PET scans were performed 3 times for each of the 5 subjects (predose, at 2 hours postdose on Day 14, and at 24 hours postdose after the last OPC-64005 administration on Day 14). The DAT ligand, ^{18}F-FE-PE2I, was administered intravenously before each PET scan.

Two of the 8 enrolled subjects experienced the TEAE of mild rash, which was considered related to the IMP. These subjects were discontinued due to the TEAE. No other TEAEs were reported, and there were no safety concerns in this trial.

The mean DAT occupancy was 27.8% at 2 hours postdose and 24.4% at 24 hours postdose (OPC-64005 plasma concentration range was 138 - 257 ng/mL and 60.8 - 127 ng/mL, respectively). Mean DAT occupancy remained within the targeted DAT occupancy range of 10% to 30% up to 24 hours postdose, although individual variability was noted.

Please refer to the IB for more detailed information.

1.3 Known and Potential Risks and Benefits

Risks associated with the administration of OPC-64005 will be minimized through appropriate screening of healthy subjects according to the protocol selection criteria and carefully monitored dosing. Safety assessments will include vital signs, ECGs, physical examinations, clinical laboratory assessments, and monitoring for AEs. In clinical trials of OPC-64005, investigators and subinvestigators must pay very close attention to any subjective or objective adverse signs and symptoms that subjects may report or that the investigator or subinvestigator may observe by means of physical examination or laboratory assessment. The subjects may or may not derive any benefit from this trial.

The dose of OPC-64005 to be tested in this trial (20 mg up-titrated to 30 mg) will be within the range of doses demonstrated to be safe and well tolerated.

Known risks associated with the administration of atomoxetine are as described in the prescribing information (http://www.strattera.com). The dose of atomoxetine to be administered in this trial (40 mg up-titrated to 80 mg) is in accordance with this prescribing information.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Dopamine hypoactivity has been implicated in attention-deficit/hyperactivity disorder (ADHD), as evidenced by stimulant-mediated improvement of inattentive and hyperactive/impulsive behavior in the majority of presenting and treated children, adolescents, and adults diagnosed with ADHD.[42,43,44,45,46] In addition to DAT inhibition, norepinephrine transport inhibition is also a pharmaceutical target for effective treatment of ADHD symptomatology. Since NET inhibitors can also inhibit DA transport in the prefrontal cortex, NET inhibition leads to enhanced dopaminergic signaling that may, in part, underlie the clinical utility of NET inhibitors in ADHD.

Data from single- and multiple-dose positron emission tomography studies confirm the in vitro neuropharmacology and microdialysis-based characterization of OPC-64005 as a triple-reuptake-inhibitor with a unique balance of monaminergic transporter inhibition for 5-HT, NE, and DA (data on file). Based on this pharmacology, including potent NET inhibition and modest DAT inhibition at the proposed clinical doses, it is a reasonable hypothesis that OPC-64005 will be effective for the treatment of the core symptoms (inattention, impulsivity, and hyperactivity) of ADHD. In addition, OPC-64005 inhibition of SERT is comparable to that of marketed antidepressants, at clinical doses. Since there is high comorbidity of mood symptoms in the general ADHD population, SERT inhibition may yield clinical benefit in non-core symptoms of ADHD as well.

2.2 Dosing Rationale

Dose selection for this trial is based on safety, tolerability, and PK data from single and multiple-dose PK studies. In addition, pharmacodynamic outcomes from 3 separate PET studies were used as guidance to support dose selection. In particular, we targeted a high dose with approximately 90% NET occupancy to address symptoms of inattention; and we targeted approximately 25 to 30% DAT occupancy in efforts to provide greater

magnitude of efficacy, and faster onset of action compared with other members of the nonstimulant class, including atomoxetine (no DAT inhibition).

OPC-64005 has been administered to healthy subjects at daily oral doses ranging from 1 to 60 mg and at treatment durations ranging from single dose to 14 daily doses.

In Trial 277-10-206 (conducted in the United States [US]), mean peak concentration (C_{max}) values on Day 14 after multiple daily doses of 20 or 30 mg of OPC-64005 were 195 ng/mL and 274 ng/mL, respectively. Steady state of OPC-64005 was reached after 10 to 12 days of dosing in this trial. In Trial 277-12-001 (conducted in Japan), C_{max} values after once daily dosing for 14 days were 178 ng/mL and 292 ng/mL at OPC-64005 doses of 20 and 30 mg, respectively. Steady state was reached by Day 7 in both the 20-mg and 30-mg groups in this trial.

In Trial 277-10-205 the overall concentration of plasma to obtain 50% of the maximum effect in vivo (EC_{50}) for SERT occupancy ranged from 5.5 to 8.84 ng/mL, and the EC_{50} for NET occupancy was 18.8 ng/mL. Dopamine transporter occupancy was relatively low (< 20%) in 2 single-dose-trials (277-10-205 and 277-13-001) at plasma concentration ranges of 18.1 to 205 ng/mL and 4.68 to 154 ng/mL, respectively. In a multiple-dose trial (277-14-001), mean DAT occupancy was 27.8% at 2 hours postdose (plasma concentration range 138 - 257 ng/mL) and 24.4% at 24 hours postdose (plasma concentration range 60.8 - 127 ng/mL) after repeated administration of OPC-64005 at 30 mg once daily for 14 days.

Doses of OPC-64005 up to 30 mg were used in Trial 277-10-206. In Trial 277-12-001, administration of 20 and 30 mg of OPC-64005 once daily for 14 days was well tolerated, and no significant safety concerns were observed in healthy Japanese adult male subjects.

Considering the pharmacodynamics, pharmacokinetics, and safety results obtained from completed multiple-dose trials, a daily dose of 30 mg was selected as the target dose for administration in the current trial.

The dosage of atomoxetine (40 mg daily starting dose to a target dose of 80 mg daily) is the dose and regimen recommended in the Food and Drug Administration (FDA) approved prescribing information. Extrapolation from the available animal PET data[47] suggests that a dose of atomoxetine in the clinically relevant range corresponding to 1.0 to 1.8 mg/kg would result in > 90% NET occupancy, which is comparable with the observed NET receptor occupancy observed with OPC-64005 at 30 mg at steady state (study on file).

Protocol 277-201-00001

The trial duration of 8 weeks was selected for this exploratory phase 2 trial on the basis that the majority of approved and marketed drugs for treatment of ADHD have demonstrated maximal effectiveness in 8 weeks or less.

The 4-day Titration Period and up-titration design is being employed in this trial in consideration of the dosage and administration instructions for atomoxetine[48] in adults, which states that atomoxetine should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of 80 mg.

2.3 Trial Objectives

The primary objective of this trial is to assess the efficacy of OPC-64005 (20 - 30 mg/day) relative to atomoxetine (40 - 80 mg/day) in adult subjects with attention-deficit/hyperactivity disorder (ADHD).

Other objectives are:

- To estimate the difference in effect between OPC-64005 (20 - 30 mg/day) and placebo and its variability in adult subjects with ADHD in order to plan for the next trial.
- To assess the safety and tolerability of OPC-64005 (20 - 30 mg/day) in adult subjects with ADHD compared with both control arms.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, active- and placebo-controlled trial designed to evaluate the efficacy and safety of OPC-64005 in the treatment of adult subjects with attention-deficit/hyperactivity disorder.

Approximately 201 adult subjects with ADHD will be randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo to provide for 150 subjects who complete the trial (50 per arm).

The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur 3 (± 1) days after the last dose, and a follow-up telephone contact to occur 30 (+ 2) days after the last dose. A schematic of the trial design is provided in Figure 3.1-1.

Protocol 277-201-00001

Screening Period: The Screening Period will last up to 28 days and will begin when informed consent is signed. The purpose of the Screening Period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to wash out prohibited concomitant pharmacotherapy, including current ADHD therapies, if applicable.

Titration Period: At the end of the Screening Period, the subjects will be randomized (1:1:1) to receive OPC-64005, atomoxetine, or placebo during the Titration Period (Days 1 - 4).

Treatment Period: During the Treatment Period (Days 5 - 56), subjects who are randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. Subjects randomized to the atomoxetine arm for Titration will continue in the atomoxetine arm for Treatment. Subjects randomized to the placebo arm for Titration will continue in the placebo arm for Treatment. During the 8-week Titration/Treatment Period, subjects will have weekly or biweekly visits to the clinical site. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card. Assessments to be performed during the trial are listed in Table 3.7-1.

If any subject discontinues the trial early, every effort should be made to complete the Day 56 (± 1 day)/early termination (ET) evaluations. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone at 3 (± 1) days and 30 (+ 2) days after the last dose of OPC-64005, atomoxetine, or placebo.

The total duration of this trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a 3 [± 1]-day safety follow-up phone call, and a 30 [+ 2]-day safety follow-up phone call).

Protocol 277-201-00001

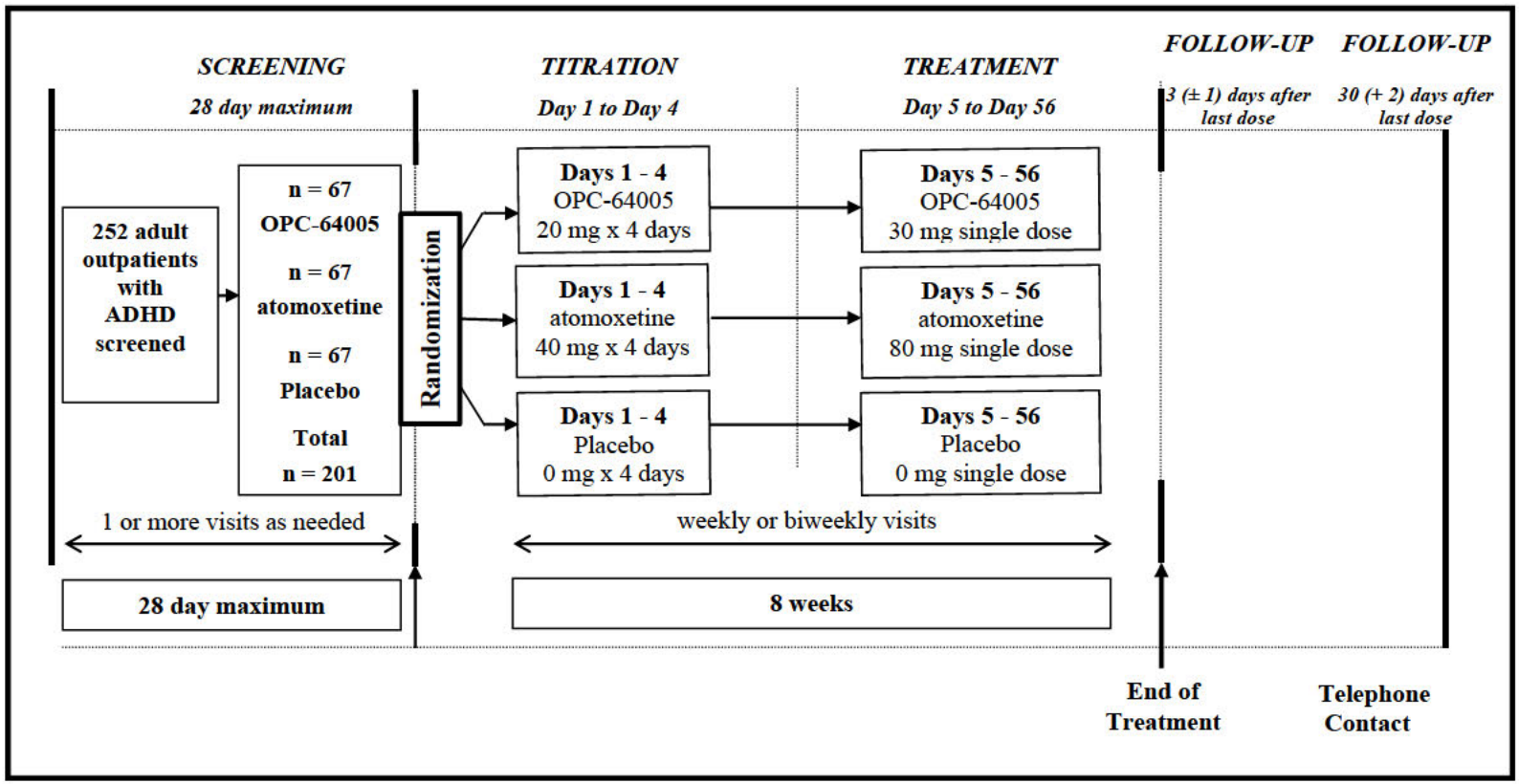

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

OPC-64005 will be provided as 10-mg tablets, atomoxetine will be provided as 40-mg capsules, and placebo will be provided as both tablets (matching the OPC-64005 tablets) and as capsules (matching the atomoxetine capsules). Details of the dosing schedule and formulations to be administered are shown in Table 3.2-1.

During the Titration Period, subjects in the OPC-64005 group will receive daily 20-mg oral doses of OPC-64005 along with oral doses of atomoxetine placebo. Subjects in the atomoxetine group will receive daily 40-mg oral doses of atomoxetine along with oral doses of OPC-64005 placebo. Subjects in the placebo group will receive daily oral doses of both OPC-64005 placebo and atomoxetine placebo.

During the Treatment Period, subjects in the OPC-64005 group will receive daily 30-mg oral doses of OPC-64005 and atomoxetine placebo. During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. Subjects in the atomoxetine group will receive daily 80-mg oral doses of atomoxetine and OPC-64005 placebo. During the Treatment Period, if a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose. Subjects in the placebo group will receive daily oral doses of both OPC-64005 placebo and atomoxetine placebo. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.

All tablets/capsules are to be taken together orally once daily and can be taken without regard to meals. Every effort should be made to take the IMP at the same time every morning, every day.

Protocol 277-201-00001

Table 3.2-1 Dosing Schedule

Trial Days	Time	Dose
1 - 4[a] (Titration Period)	AM dosing	20 mg OPC-64005: two 10-mg tablets and one placebo tablet of OPC-64005 and two atomoxetine placebo capsules QD or 40 mg atomoxetine: one 40-mg capsule and one placebo capsule of atomoxetine and three OPC-64005 placebo tablets QD or Placebo: three OPC-64005 placebo tablets and two atomoxetine placebo capsules QD
5 - 56[a] (Treatment Period)	AM dosing	30 mg OPC-64005[b]: three 10-mg tablets of OPC-64005 and two atomoxetine placebo capsules QD or 80 mg atomoxetine[c]: two 40-mg capsules of atomoxetine and three OPC-64005 placebo tablets QD or Placebo: three OPC-64005 placebo tablets and two atomoxetine placebo capsules QD

QD = daily.

[a]Blood samples for PK analyses will be collected predose and at 1 and 3 hours postdose at the Baseline (Day 1) Visit, predose and at 2 hours postdose at the Day 7 (± 1 day) Visit, predose and at 3 hours postdose at the Day 14 (± 1 day) Visit, and predose at the Day 21 (± 1 day) Visit.

[b]May be reduced to 20 mg if the 30 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.

[c]May be reduced to 40 mg if the 80 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 80 mg for atomoxetine) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

Approximately 252 adult (18 - 55 years) subjects with a diagnosis of ADHD will be screened to randomize approximately 201 subjects to yield approximately 150 completers.

Subjects must meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria for ADHD (any presentation) as confirmed by the Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2).[49] To confirm that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (M.I.N.I.) will be used to identify and exclude other psychiatric conditions.[50] Subjects identified with a current or lifetime history of bipolar disorder, schizophrenia, other psychotic disorder, or

personality disorder will not be eligible for enrollment. Medication history, specifically for the treatment of ADHD, will be assessed using the Massachusetts General Hospital Treatment Response Questionnaire (ATRQ) - ADHD (MGH-ATRQ-ADHD).[51] At screening, subjects not currently receiving an approved pharmacological treatment for ADHD must have an Adult ADHD Investigator Symptom Rating Scale (AISRS) with Adult Prompts score of ≥ 26. Subjects receiving any pharmacological treatment for ADHD at screening must have an AISRS with Adult Prompts score of ≥ 22 and will wash out from their current ADHD therapy prior to the baseline (ie, Day 1) evaluations for a period equivalent to 5 half-lives. At baseline, all subjects must have an AISRS with Adult Prompts score of ≥ 26 to be enrolled.

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject identification number upon signing the electronic informed consent form (eICF) based on sequential enrollment in the trial. Subjects will be assigned a unique subject number upon randomization, prior to dosing on Day 1. The clinical site will maintain a list identifying all subjects by their subject identification number and initials.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws) and documented using an electronic informed consent system. The eICF will be approved by the same institutional review board (IRB) that approves this protocol.

Each eICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[52] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific eICF used in the trial before submission to the IRB.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial participants will be provided with controlled access to the eICF application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature. The participant will be given a printed, signed copy of the eICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Subjects may be asked to sign additional eICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

Screening	
1.	Subjects who are able to provide electronic informed consent (as required by IRB) prior to the initiation of any protocol-required procedures.
2.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete subject-reported outcomes measures; and to be reliably rated on assessment scales.
3.	Male and female outpatients 18 to 55 years of age, inclusive, at the time of informed consent.
4.	Subjects with a primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the ACDS v1.2. Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that they are currently receiving treatment. The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability.
5.	Subjects who are not currently receiving an approved pharmacological treatment for ADHD who have an AISRS with Adult Prompts score of ≥ 26 and subjects who are receiving any pharmacological treatment for ADHD at screening who have an AISRS with Adult Prompts score of ≥ 22.
6.	Subjects who have a score of ≥ 4 on the CGI-S.
7.	Subjects willing to discontinue all prohibited psychotropic medication starting from the time of signing the informed consent and up to the 30 (+ 2)-day follow-up period.
8.	Subjects must be able and willing to utilize the AiCure Platform for each daily dose.
9.	Subjects likely to possess the capacity to utilize the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone.
Baseline	
10.	Subjects who have an AISRS with Adult Prompts score of ≥ 26.
11.	Subjects who have a score of ≥ 4 on the CGI-S.

CGI-S = Global Clinical Impression-Severity; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

Protocol 277-201-00001

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

1.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
2.	All males and WOCBP who do not agree to practice 2 methods of birth control during the trial and for 30 days after the last dose of IMP. Two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. This exclusion does not apply for subjects confirmed, by medical record and/or prospective assessment, to be sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months, confirmed by FSH blood level; or men who have had a bilateral orchidectomy).
3.	Subjects with a history of inadequate response or suboptimal tolerability to atomoxetine. (The subject was treated with an adequate dose for an adequate period of time, yet failed to show satisfactory response.) This will be confirmed using the MGH-ATRQ-ADHD.
4.	Criterion deleted by Amendment 2.
5.	Criterion deleted by Amendment 2.
6.	Subjects who report allergies (lifetime treatment history) to stimulant or nonstimulant ADHD medications.
7.	Subjects with a current need for involuntary commitment or who have been hospitalized for psychiatric illness within 6 months of screening.
8.	Subjects with other DSM-5 disorders including psychosis (current or lifetime), bipolar disorder (current or lifetime), current major depressive disorder, or current panic disorder; or another psychiatric diagnosis that the investigator believes is primary or that will confound efficacy or safety assessments of the trial or interfere with participation in the trial otherwise. Psychiatric diagnosis will be established using the M.I.N.I.
9.	Subjects with a clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, narcissistic, avoidant, obsessive compulsive, or dependent personality disorders.
10.	Subjects receiving new onset psychotherapy (eg, individual, group, marriage, or family therapy) within 42 days of screening or who will initiate psychotherapy at any time during participation in the trial. Those who are receiving ongoing psychotherapy for over 42 days are permitted to enroll. Psychotherapy should not be started or changed during a subject's participation in the trial.
11.	Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 6 months or subjects who meet criteria for any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
12.	Subjects who have met DSM-5 criteria for substance use disorder within the past 180 days; including all substances of potential abuse, excluding caffeine and nicotine.
13.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) and/or an abnormal result for free T4 at screening.

Protocol 277-201-00001

Table 3.4.3-1 Exclusion Criteria	
14.	Subjects who currently have clinically significant dermatological, neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, or active or chronic hepatitis B or C. Medical conditions that are minor or well controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.
15.	Subjects with Insulin-dependent diabetes mellitus (IDDM) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria: • HbA1c < 7.0%, • Screening glucose (non-fasting) < 200 mg/dL. (If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. Fasting glucose must be ≤ 125 mg/dL.), • Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** Subject's diabetes is not newly diagnosed during screening for the trial.
16.	Subjects presenting with, or having a history of, uncontrolled hypertension (diastolic blood pressure > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, **OR** development of symptoms.
17.	Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery.
18.	Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc.
19.	Subjects with a history of obstructive sleep apnea.
20.	Subjects with known intellectual disability (intellectual developmental disorder), including mild adaptive functioning impairment, or clinical evidence of intellectual disability based on the opinion of the investigator.
21.	Subjects with a positive drug screen for cannabinoids or illicit drugs will be excluded and may not be retested or rescreened. There will be no exceptions, including subjects from states in which cannabinoids are considered legal. Subjects with a positive urine drug screen resulting from use of prescription or OTC medications may be retested or rescreened, at the discretion of the investigator.

Table 3.4.3-1 Exclusion Criteria	
22.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75,000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) AST > 2 × upper limit of normal 5) ALT > 2 × upper limit of normal 6) Creatinine ≥ 2 mg/dL 7) HbA1c ≥ 7% 8) Abnormal free T4 (free T4 is measured only if result for TSH is abnormal) 9) QTcF and/or QTcB > 450 msec NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
23.	Subjects receiving any of the prohibited medications within the specified period prior to the first dose of trial medication or who would be likely to require prohibited concomitant therapy during the trial.
24.	Subjects who received OPC-64005 in any prior clinical trial.
25.	Subjects with a history of neuroleptic malignant syndrome.
26.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.
27.	Prisoners or subjects who are compulsorily detained (involuntarily hospitalized or incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
28.	Subjects who participated in a clinical trial within the last 180 days or who participated in more than 2 clinical trials within the past year.
29.	Any subject who, in the opinion of the investigator, should not participate in the trial.
30.	Employees or relatives of employees of the trial site cannot participate in the trial.
31.	Siblings and other family members, and those having the same place of residence as another subject, will be excluded. Subjects whose family/household member has completed participation in the trial may be considered for enrollment.

ALT = alanine aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; IQ = intelligence quotient; OTC = over the counter; QTcB = corrected QT interval, Bazett's method; QTcF = corrected QT interval, Fridericia's method; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months (confirmed by follicle-stimulating hormone [FSH] blood level).

3.5 Endpoints

3.5.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline to the Day 56 Visit on the investigator-administered Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.

3.5.2 Other Endpoint(s)

Other efficacy endpoints are:

- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits for the AISRS with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups
- CGI-I score at each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the OPC-64005 group relative to the atomoxetine, and placebo groups
- Change from baseline to each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) in the 18-item Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV) score in the OPC-64005 group relative to the atomoxetine and placebo groups
- Change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits in the Adult ADHD Quality of Life Scale (AAQoL) score in the OPC-64005 group relative to the atomoxetine and placebo groups
- OPC-64005 potential for abuse liability and dependence as assessed by the Drug Effects Questionnaire (DEQ) at baseline and each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window)

3.6 Measures to Minimize/Avoid Bias

During the entire trial, treatment will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (OPC-64005, atomoxetine, or placebo) at any visit.

Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Data Sciences Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the interactive voice response system/interactive web response system (IVRS/IWRS), and reporting SAEs to regulatory agencies. The interim analysis will be conducted by an independent biostatistician from the OPDC Data Sciences Department and the treatment code will remain blinded for all others until the unblinding at the final analysis after trial completion.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

Protocol 277-201-00001

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
ENTRANCE CRITERIA										
Inclusion/exclusion criteria	X	X								
Demographic information	X									
Medical history	X									
Psychiatric history to confirm DSM-5 ADHD diagnosis using the ACDS v1.2	X									
Diagnosis confirmation and identification of comorbidities using the M.I.N.I.	X									
Investigator assessment of previous and current ADHD treatment using the MGH-ATRQ-ADHD	X	X								
HIV, HBsAg, and anti-HCV	X									
Urine pregnancy test[a]	X	X				X		X		
SAFETY										
Physical examination[b]	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X		X	X	X		
Clinical laboratory	X	X				X		X		
Urine alcohol and drug screen	X	X	X	X	X	X	X	X		
C-SSRS	X	X	X	X	X	X	X	X		

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
EFFICACY										
18-item, investigator-administered CAARS-O:SV[c]	X	X	X	X	X	X	X	X		
AISRS with Adult Prompts	X	X				X		X		
CGI-S	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X		
18-item CAARS-S:SV[c]		X	X	X	X	X	X	X		
AAQoL		X				X		X		
POMS	X	X	X	X	X	X	X	X		
CLINIC PROCEDURES										
Dispense IMP and download the AiCure platform or receive device with the AiCure platform predownloaded		X								
IMP administration[d]		X	X	X	X	X	X	X		
IMP return and accountability / AiCure compliance			X	X	X	X	X	X		
PK blood samples		X[e]	X[f]	X[g]	X[h]					
Pharmacogenomic sample for CYP2D6 testing		X								
FBR blood sample[i]		X								
DEQ		X	X	X	X	X	X	X		
Record AEs	X	X	X	X	X	X	X	X	X	X
Record concomitant medication	X	X	X	X	X	X	X	X	X	X

Protocol 277-201-00001

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
Return trial-provided mobile device (if applicable)								X		
Telephone contact									X	X

FBR = future biospecimen research; POMS = Profile of Mood States-Brief Form™.

[a]If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. Additional urine pregnancy testing may be done at the discretion of the investigator.

[b]A physical examination will be performed at the Screening, Baseline, and Day 56 (± 1 day)/ET Visits. Weight, height, and waist circumference will be recorded at the Screening Visit. A focused examination for the detection of rash will be performed at the Day 7, 14, 21, 28, and 42 Visits; all visits have a ± 1-day window. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged.

[c]The 18-item CAARS-S:SV should be conducted before the 18-item, investigator-administered CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.

[d]Subjects will receive daily doses of IMP starting on Day 1. At the baseline visit, subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to 6. During the treatment period, subjects will receive a treatment card(s) for dosing on scheduled visits. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.

[e]Day 1 samples collected predose and 1 and 3 hours postdose.

[f]Day 7 (± 1 day) samples collected predose and 2 hours postdose.

[g]Day 14 (± 1 day) samples collected predose and 3 hours postdose.

[h]Day 21(± 1 day) samples collected predose.

[i]FBR sample will be collected once the subject has provided consent for FBR.

Protocol 277-201-00001

3.7.1 Schedule of Assessments

3.7.1.1 Screening

The Screening Period begins after electronic informed consent has been obtained and will take place between Day −28 and Day −1 prior to enrollment. Completion of screening activities may require more than 1 visit. Screening evaluations will include the following:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ADHD using the ACDS v1.2.
- Comorbidities will be identified and recorded using the M.I.N.I.
- The investigator will assess and record previous ADHD medications using the MGH-ATRQ-ADHD. If applicable, washout from ADHD medications will begin. The washout period will be equivalent to 5 half-lives before Baseline (Day 1).
- Blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, urinalysis, and serology (see Table 3.7.3.2-1). Vital sign and ECG assessments should be completed before any blood samples are collected.
- A physical examination will be performed.
- Body weight, height, and waist circumference will be recorded.
- Vital sign measurements (including body temperature, blood pressure, pulse, and respiratory rate) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
- A urine pregnancy test will be performed for all women of childbearing potential (WOCBP). If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. Subjects with a positive serum test result will be excluded from the trial.
- Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine.
- The "Baseline/Screening" Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered.

- The AISRS with Adult Prompts will be administered. Subjects not currently receiving an approved pharmacological treatment for ADHD must have an AISRS with Adult Prompts score of ≥ 26. Subjects receiving any pharmacological treatment for ADHD at screening must have an AISRS with Adult Prompts score of ≥ 22.
- The investigator (or qualified designee) will complete the CGI-S. Subjects must have a CGI-S score of ≥ 4.
- A qualified and certified rater will administer the investigator-rated 18-item CAARS-O:SV.
- The Profile of Mood States-Brief Form™ (POMS) will be administered.
- AEs and concomitant medications will be recorded beginning with the signing of the eICF.

3.7.1.2 Baseline (Day 1)

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- A physical examination will be performed.
- Body weight, height, and waist circumference will be recorded.
- Vital sign measurements (including body temperature, blood pressure, pulse, and respiratory rate) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
- Blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1). Vital sign and ECG assessments should be completed before any blood samples are collected.
- A urine pregnancy test will be performed for all WOCBP. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. Subjects with a positive serum test result will be excluded from the trial.
- Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine.
- The "Since-Last-Visit" C-SSRS will be administered.
- If applicable, a washout from ADHD medications equivalent to 5 half-lives must have been completed.
- The AISRS with Adult Prompts will be administered. Subjects must have an AISRS with Adult Prompts score of ≥ 26.
- The investigator (or qualified designee) will complete the CGI-S. Subjects must have a CGI-S score of ≥ 4.

- The subject will complete the 18-item CAARS-S:SV. The 18-item CAARS-S:SV should be conducted before the 18-item, investigator-administered CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.
- A qualified and certified rater will administer the investigator-rated 18-item CAARS-O:SV.
- Blood samples for PK analyses will be collected predose and at 1 and 3 hours postdose.
- Blood samples for pharmacogenomic CYP2D6 testing will be collected.
- Blood samples for FBR will be collected (once the subject has provided consent for FBR).
- The subject will complete the AAQoL.
- The POMS will be administered.
- The DEQ will be administered to assess the potential for abuse.
- AEs and concomitant medications will be recorded.
- Subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to 6.
- The IMP will be dispensed and the subject will download the AiCure platform or receive a provisioned device with the AiCure platform predownloaded, and will be trained on IMP compliance using this application. Subjects will be instructed to take their first dose of IMP from the titration card in the clinic.

3.7.1.3 Treatment Period Visits (Day 7 through Day 56 Visits)

- At each visit, a focused physical examination for the presence of rash will be performed. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged. A complete physical examination will be performed at the Day 56 (± 1 day)/ET Visit. See Section 3.7.3.3 for a description of follow-up activities to be completed if rash is detected. The investigator must immediately report any instances of rash to the Clinical Research Organization (CRO) medical monitor.
- At each visit, vital sign measurements (including body temperature, blood pressure, pulse, and respiratory rate) will be recorded. Blood pressure and pulse are to be measured after the subject has been in the sitting position at least 5 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. At the Day 14, 28, 42, and 56 Visits (all visits have a ± 1-day window), a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
- At the Day 28 (± 1 day) and Day 56 (± 1 day)/ET Visits, blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1). Vital sign and ECG assessments should be completed before any blood samples are collected.

- A urine pregnancy test will be performed for all WOCBP at the Day 28 (± 1 day) and Day 56 (± 1 day)/ET Visits. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
- At each visit, urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine.
- At the Day 28 (± 1 day) and Day 56 (± 1 day)/ET Visits, the AISRS with Adult Prompts will be administered.
- At each visit, the "Since-Last-Visit" C-SSRS will be administered.
- At each visit, the investigator (or qualified designee) will complete the CGI-S and CGI-I.
- The subject will complete the 18-item CAARS-S:SV. The 18-item CAARS-S:SV should be conducted before the 18-item, investigator-administered CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.
- At each visit, a qualified and certified rater will administer the investigator-rated 18-item CAARS-O:SV.
- At each visit, the POMS will be administered.
- Blood samples for PK analyses will be collected predose and at 2 hours postdose at the Day 7 (± 1 day) Visit, predose and at 3 hours postdose at the Day 14 (± 1 day) Visit, and predose at the Day 21 (± 1 day) Visit.
- At the Day 28 (± 1 day) and Day 56 (± 1 day)/ET Visits, the subject will complete the AAQoL.
- At each visit, the DEQ will be administered.
- At each visit, AEs and concomitant medications will be recorded.
- Subjects will receive a treatment card(s) for dosing on scheduled visits. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.
- At each visit, IMP returns, accountability, and subject compliance with the IMP will be assessed.
- At the Day 56 (± 1 day)/ET Visit, subjects will return the trial-provided mobile device (if applicable).

3.7.1.4 Safety Follow-up Period

A follow-up telephone contact will occur 3 (± 1) days and 30 (+ 2) days after the last dose of IMP for all subjects (completers and early withdrawals). At this time, AEs and concomitant medications will be recorded.

3.7.2 Efficacy Assessments

3.7.2.1 Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV; Investigator-Administered)

The investigator-administered CAARS-O:SV (Appendix 4) is designed to measure a cross-section of ADHD-related symptoms and behaviors in adults using observer scales.[53] The investigator-administered CAARS-O:SV consists of 30 items grouped into 3 subscales: Inattentive Symptoms (9 items), Hyperactive/Impulsive Symptoms (9 items), and ADHD Index (12 items). As is frequently done in adult ADHD trials, items will be modified using the Adler adult prompts and only the 18 DSM-5 criteria relevant items (9 Inattentive and 9 Hyperactive/Impulsive) will be administered. The primary efficacy assessment of ADHD symptoms is the ADHD Symptoms Total Score, which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales. The 18-item scale can be administered by an appropriately trained and qualified clinician in approximately 20 to 30 minutes.

3.7.2.2 Conners' Adult ADHD Rating Scale-Self-Report: Screening Version (CAARS-S:SV)

The CAARS-S:SV (Appendix 5) includes the same 30 items as the investigator-administered CAARS-O:SV, worded in the first person for the subject's impressions of their own ADHD behaviors (eg, "I talk too much," "I am always on the go..."). [53] As with the investigator-administered CAARS-O:SV, administration of the CAARS-S:SV in the current trial will be limited to the 18 DSM-5 criteria relevant items (9 Inattentive Symptoms and 9 Hyperactive/Impulsive Symptoms subscales). The evaluation of ADHD symptoms will be based on the 18-item ADHD Symptoms Total Score, which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales. The CAARS-S:SV can be completed in approximately 10 minutes.

3.7.2.3 Adult ADHD Investigator Symptom Rating Scale (AISRS With Adult Prompts)

The AISRS (Appendix 6) was published in 2010 by Drs. Lenard Adler, Thomas Spencer, and Joseph Biederman of New York University and Massachusetts General Hospital.[54] The AISRS consists of the 18 DSM ADHD symptoms with adult-relevant wording. It has been validated for use as a primary efficacy scale in adult ADHD treatment trials.

3.7.2.4 Clinical Global Impression - Severity of Illness Scale (CGI-S)

The CGI-S is an observer-rated scale that will be used to measure symptom severity.[55] To perform this assessment, the investigator or rater will respond to the following question: "Considering your total clinical experience with the ADHD population, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. Suggested anchor guidance is provided in Appendix 7.[56]

3.7.2.5 Clinical Global Impression - Improvement Scale (CGI-I)

The CGI-I is an observer-rated scale that will be used to measure the efficacy of the IMP.[55] The rater or investigator will rate whether the subject's total improvement relative to baseline is due entirely to drug treatment. Response choices include: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Suggested anchor guidance is provided in Appendix 8.[56]

3.7.2.6 Adult ADHD Quality of Life Scale (AAQoL)

The AAQoL (Appendix 9) is a validated, 29-item instrument for measuring the impact of ADHD symptoms on quality of life.[57] The scale assesses 4 distinct functional domains: life productivity, psychological health, life outlook, and relationships. Scores for individual items range from 1 ("never/not at all") to 5 ("extremely/very often"). Before total and subscale scores can be calculated, scores for individual questions that are worded negatively are reversed so that a higher score indicates a greater quality of life. Scores for each item are then converted to a 100-point scale and averages are calculated to obtain total score and subscale scores.

3.7.2.7 Profile of Mood States-Brief Form (POMS)

The POMS (Appendix 10) is a 30-item self-report scale that generates the following subscales: Tension or Anxiety, Anger - Hostility, Vigor - Activity, Fatigue - Inertia, Depression - Dejection, and Confusion - Bewilderment.[58] These subscales yield an overall total mood score. It will be used in the trial as an exploratory measure to assess potential changes in symptoms often associated with ADHD. The time period of interest for this trial is "during the past week".

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Mean Corpuscular Hemoglobin Concentration (MCHC) Mean Corpuscular Volume (MCV) Red Blood Cell (RBC) count White Blood Cell (WBC) count with differential Platelets Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity Serology: Hepatitis B surface antigen (HBsAg) Human Immunodeficiency Virus (HIV) Hepatitis C Virus Antibodies (anti HCV)	Serum Chemistry: Alkaline Phosphatase (ALP) Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Bilirubin, total Blood Urea Nitrogen (BUN) Calcium Cholesterol Creatinine Gamma Glutamyl Transferase (GGT) Glucose Lactic Dehydrogenase (LDH) Potassium Protein, total Sodium Triglycerides Glycated Hemoglobin (HbA1c) Thyroid-stimulating hormone (TSH) Additional Tests: Urine (or serum) pregnancy for WOCBP FSH (for female subjects who have been postmenopausal for at least 12 consecutive months) Free T4 (free T4 is measured only if result for TSH is abnormal) Urine for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine C Reactive Protein (CRP) (if rash is detected) Human herpes virus 6 (HHV-6) (if rash is detected and the signs and symptoms are suggestive of drug rash with eosinophilia and systemic symptoms [DRESS] or drug-induced hypersensitivity syndrome [DIHS]) Complete blood count with differential (if rash is detected)

A pregnancy test will be conducted in WOCBP prior to trial intervention; results must be available prior to the administration of the IMP.

3.7.3.3 Physical Examination and Vital Signs

A physical examination will be performed at screening, baseline, and at Day 56 (± 1 day)/ET. Physical examination findings will be recorded by body system (eg, head, eyes, ears, nose, and throat; thorax; abdomen; extremities; neurological; skin and mucosae). Body weight, height, and waist circumference will be measured and recorded at screening. A focused examination for the detection of rash, defined as any type of newly acquired skin eruptions that are nontraumatic, will be performed at the Day 7, 14, 21, 28, and 42 Visits; all visits have a ± 1-day window. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged. If rash is detected, the IMP should be discontinued and blood drawn for laboratory testing, including a complete blood count with differential and chemistry with liver function tests. Any rash, regardless of severity or seriousness, will lead to the discontinuation of IMP. Any subject who experiences a rash will be evaluated by a board-certified or board-eligible dermatologist. Depending on the severity, the subject will be asked to have a skin biopsy performed of the rash area(s). At the appearance of or discovery of the rash, the rash will be photographed by the investigator and vital signs (specifically, body temperature), symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine), a discussion of other possible causes of the rash (eg, allergic, contact dermatitis), and specific location(s) of the rash should be recorded. The investigator must immediately report any instances of rash to the CRO medical monitor. Refer to Appendix 11 through Appendix 14 for follow-up activities if rash is detected.

Vital signs will be measured and recorded at screening, baseline, and at each scheduled visit.

Measurement of vital signs will include body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate. At the Screening and Baseline Visits, blood pressure and pulse will be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Respiratory rate at each visit and blood pressure and heart rate at each Treatment Period visit will be performed after the subject has been in the sitting position for at least 5 minutes.

Abnormal vital signs values considered to be clinically significant may be repeated for confirmation at the investigator's discretion. If a screening vital sign finding with a clinically significant abnormal result (eg, diastolic blood pressure > 95 mmHg) is identified, repeat vital sign measurements to confirm the finding may be considered (eg, before excluding the subject from the trial).

3.7.3.4 Electrocardiogram Assessments

At Screening, Baseline, and the Day 14 (± 1 day), 28 (± 1 day), 42 (± 1 day), and 56 (± 1 day) Visits, a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.

3.7.3.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored at each visit using the C-SSRS.

Subjects expressing any sort of suicidality or who are otherwise thought to be at any risk of self-harm at any time during the course of the trial or follow-up, should be referred for appropriate evaluation and care according to applicable local standards, according to the best judgment of the principal investigator and in keeping with GCP.

The C-SSRS was developed by a team of researchers at Columbia University to address the need for standardized classification of suicide reports to assess suicide risk. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation, and a post baseline evaluation that focuses on suicidality since the last trial visit.

The baseline/screening version of the C-SSRS will be administered at the Screening Visit. The since-last-visit version of the C-SSRS will be administered at the Baseline Visit and at each subsequent scheduled visit.

3.7.3.6 Drug Effects Questionnaire (DEQ)

The DEQ will be used to assess the potential for abuse of the IMP. The DEQ is a 5-item questionnaire completed by the subject that includes the following questions: Do you FEEL a drug effect right now?, Are you HIGH right now?, Do you DISLIKE any of the effects you are feeling right now?, Do you LIKE any of the effects you are feeling right now?, and Would you like MORE of the drug you took, right now?[59]

3.7.4 Pharmacokinetic and Pharmacogenomic Assessments

3.7.4.1 Pharmacokinetic Assessments

3.7.4.1.1 Pharmacokinetic Blood Samples

Blood samples for the determination of OPC-64005 and its metabolite(s) will be collected at Baseline (Day 1) predose (within 15 minutes of dosing) and at 1 and 3 hours postdose, at the Day 7 (± 1 day) Visit predose (within 5 minutes of dosing) and at 2 hours postdose, at the Day 14 (± 1 day) Visit predose (within 5 minutes of dosing) and at 3 hours postdose, and at the Day 21 (± 1 day) Visit predose (within 5 minutes of dosing).

Samples may also be analyzed for atomoxetine and/or other analytes to confirm compliance. In addition, every effort will be made to obtain a PK blood sample from any subject who experiences an SAE. This sample should be obtained as soon as is practical after the onset of the SAE.

Every effort should be made to draw the sample at the appropriate time. If a sample cannot be drawn at the designated time, a window of ± 3 minutes for each blood draw is acceptable, provided the exact time of the draw is recorded.

Processing, storage, and shipping instructions are provided in Appendix 3.

3.7.4.2 DNA Blood Samples for Pharmacogenomic Testing

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) in order to extract DNA and determine the CYP2D6 genotype and predicted phenotype. Genotypes for other drug metabolizing enzymes and transporters will also be determined and may be reported as part of a future study. All samples will be shipped to the pharmacogenomics laboratory. Detailed handling and shipping instructions are provided in Appendix 3.

3.7.4.3 Future Biospecimen Research

A blood sample will be collected at the time point presented in the Schedule of Assessments (Table 3.7-1) from consenting subjects.

Research performed on this sample may include genetic analyses (deoxyribonucleic acid [DNA]), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

Processing, storage, and shipping instructions for FBR samples are provided in Appendix 3.

3.7.5 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up eSource for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Down Titration of Treatment

During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.5.

If a subject will miss/misses a trial visit, the investigator should contact the medical monitor to discuss the potential to retain the subject. Depending on how many doses of IMP the subject will miss/misses, the sponsor, medical monitor, and investigator will

determine if the subject is able to continue in the trial and at which dose the subject will resume, taking into consideration any scheduled and unscheduled dose adjustments.

3.8.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - SAE
- Death
- Reasons unrelated to medical condition (non-compliance with IMP, protocol deviation, physical decision, lack of efficacy, or other) (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Rash (regardless of severity or seriousness) (see Section 5.4)
- Pregnancy (see Section 5.6)
- Termination of all or part of the trial by the sponsor (site terminated by sponsor or trial terminated by sponsor)

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 3.8.3.2 must be followed.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial eICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. If a subject will miss/misses a trial visit, the investigator should contact the medical monitor to discuss the potential to retain the subject. Depending on how many doses of IMP the subject will miss/misses, the sponsor, medical monitor, and investigator will determine if the subject is able to continue in the trial and at which dose the subject will resume, taking into consideration any scheduled and unscheduled dose adjustments. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an eICF), but who is not randomized or assigned trial treatment. Subjects who sign an eICF but who are not started on treatment are permitted to be rescreened, with the exception of subjects who tested positive for drugs of abuse. In the event that the subject is rescreened for trial participation, and the rescreening is not completed within the original screening window, a new eICF must be signed. Subjects who are randomized but not treated are considered withdrawals.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Day 56 (± 1 day) Visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the follow-up visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP (ie, OPC-64005, atomoxetine, and placebo) to subjects. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered.

Details on the AiCure technology to be used in this trial to assess IMP compliance are provided below.

3.12.1 IMP Adherence and Reminder System

This trial will employ an IMP adherence monitoring platform ("AiCure Platform") for all subjects in the trial. The AiCure Platform uses artificial intelligence on smartphones to confirm IMP ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of IMP interruptions.

Use of this AiCure Platform will in no way supersede or replace the physician and/or prescribed IMP protocol of the subjects. Because the AiCure Platform does not change the IMP protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this AiCure Platform presents minimal risk to the subjects. Use of the AiCure Platform will be required for all subjects in the trial.

The monitoring AiCure Platform requires that all subjects take each dose of the IMP while using a smartphone. The AiCure Platform will be provided to subjects preloaded on a smartphone, or subjects will download the AiCure Platform onto their own mobile device at baseline (Day 1).

When at home, subjects will receive an IMP reminder at a time within a predefined window. This notification reminds subjects to take their IMP dose while using the AiCure Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the IMP. The application on the smartphone will make an automated determination of whether the subject has properly taken their IMP at the prescribed time. There is no need for the trial site staff to

review the administration, nor would the trial site staff need to be available at the time the subject takes their IMP. The amount of guidance that the device provides to the subjects is automatically reduced as the subject becomes more proficient at using the application.

After the device confirms proper IMP ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured data and video are reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the subjects may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with subjects, including automated messaging from the AiCure Platform device and contact by the trial site staff or other monitoring personnel. At no time is the phone number visible to the trial site staff or monitoring personnel on the AiCure Platform. Individuals outside the trial sites will not be provided with subject names, nor will they be given access to subject medical records.

3.12.2 Subject Risk

The AiCure Platform provides no more than minimal risk to subjects. This protocol only introduces a smartphone-based monitoring application that prompts the user to take their IMP, verifies ingestion, and stores encrypted data securely for analysis. When functioning properly, use of the AiCure Platform does not affect titration, dosage, route of administration, or treatment duration, conforming to any trial requirements as noted by trial site staff.

It is possible, though very unlikely, that the AiCure application can fail to remind subjects to take the IMP or tell them to take their IMP when not required. To date, AiCure has not encountered such a malfunction.

All trial data, including any identifiable subject information, will be obtained and encrypted by the application. Subjects will be coded according to the protocol and their identity will not be stored with the trial data obtained. After the subject has taken the IMP and confirmation of proper ingestion has been completed, the encrypted data will be automatically forwarded to a secure server. The server is compliant with the HIPAA, which protects the privacy and security of healthcare information. The data will be securely stored and only accessible to the trial site staff and other authorized personnel through two-way authentication.

The data may also be retained in a secure manner beyond the term of the trial and utilized to improve the operation of the AiCure Platform, categorize adherence activity by disease state or other useful categories, and/or for regulatory filings by the AiCure Platform Provider to support future applications for the AiCure Platform Provider's product. Individuals who are not associated with the care and treatment of subjects will not have access to subject identity or any medical records.

3.12.3 Subject Confidentiality

The AiCure Platform Provider will protect subjects' personal information to the full extent required by law. However, information from this trial, including de-identified video recording(s) of subject performance of various actions, may be submitted to the trial site, and potentially to the FDA. Both information obtained by the application, and information in the subject Informed Consent, may be examined by the trial site or the trial site's representatives, and may also be reviewed by the FDA and other regulatory agencies, IRBs, and or Ethics Committee(s). All of these parties are bound to safeguard the rights, safety, and well-being of all clinical trial subjects, and to maintain all information in confidence, with special consideration given to trials that may include vulnerable subjects.

The results of this trial may be presented at meetings or in publications; however, specific subjects will not be identified by name in these presentations and/or publications. Information from this trial may also be retained by the AiCure Platform Provider for the purpose of improving the AiCure Platform, to allow for future analysis of various facial and other parameters, the reporting of high level statistical analysis of the AiCure Platform, to improve the internal workings of the system running on the smartphone device, or for regulatory filings by the AiCure Platform Provider to support future applications for the Provider's product.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

Protocol 277-201-00001

4 Restrictions

4.1 Prohibited Medications

Subjects who are currently taking any therapy for adult ADHD at screening will washout from their current ADHD therapy for a period equivalent to 5 half-lives before the Baseline (Day 1) Visit. All subjects must agree to discontinue all prohibited medications during the Screening Period. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP at the Baseline (Day 1) Visit.

Table 4.1-1 List of Medications Prohibited Before the Trial

Medication		Required Washout Prior to Baseline
1.	Neuroleptic agents (depot)	One cycle plus 14 days
2.	Antidepressants Fluoxetine All other antidepressants	 28 days 14 days
3.	Benzodiazepines	14 days
4.	Hypnotics, including non-benzodiazepine sleep aids	14 days
5.	Neuroleptic agents (oral)	14 days
6.	CYP2B6 inhibitors, CYP2D6 inhibitors, CYP2D6 substrates with a narrow therapeutic index, and CYP3A4 inhibitors and inducers	14 days

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

Protocol 277-201-00001

Table 4.1-2 List of Medications Prohibited During the Trial	
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (ie, lithium) e) Benzodiazepines f) Hypnotics, including non-benzodiazepine sleep aids g) Stimulants h) Opioid analgesics, unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements, etc) j) Cannabinoids
2.	Investigational agents
3.	CYP2B6 inhibitors, CYP2D6 inhibitors, CYP2D6 substrates with a narrow therapeutic index, or CYP3A4 inhibitors and inducers. Selected CYP2B6 inhibitor is: ticlopidine. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, paroxetine, clomipramine, pyrilamine, diphenhydramine, quinidine, fluoxetine, terbinafine, halofantrine, tripelennamine. Selected CYP2D6 substrates are: thioridazine, pimozide, desipramine, eliglustat, metoprolol, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine, amitriptyline, encainide, imipramine, propafenone, propranolol, tramadol, trimipramine. Selected CYP3A4 inhibitors are: amiodarone, fluvoxamine, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone. The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial.
4.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.

GABA = gamma-aminobutyric acid.

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

Consumption of grapefruit, grapefruit juice, Seville oranges, or Seville orange juice within 72 hours prior to IMP administration and during the trial is prohibited. Also, food containing St. John's Wort (*Hypericum perforatum*) is prohibited for 14 days prior to IMP administration and during the trial. Investigators should inform subjects that normal consumption of caffeine is permitted.

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications

not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. All trial personnel should be familiar with the content of the OPC-64005 IB in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they have been participating in the therapy regularly (ie, at consistent intervals) for at least 6 weeks (42 days) prior to screening and commit to maintain their participation during the course of the trial with no changes or unless permission is obtained from the medical monitor.

Subjects will be instructed to refrain from drinking alcoholic beverages or using cannabinoids or illicit drugs during participation in the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity case (see Section 5.5).
- Rash (regardless of severity or seriousness) (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eSource. The intensity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eSource provided by the sponsor. Collection of all AEs is to begin after a subject has signed the eICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or

experienced earlier, or not expected based on the course of the condition. A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the eSource.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, potential serious hepatotoxicity, rash, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Adverse Events of Special Interest

Newly acquired skin eruptions that are nontraumatic will be considered adverse events of special interest (AESI). These may include, but are not limited to, eruptions such as skin rashes, skin irritations, skin reactions, or acneiform lesions.

Extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is nontraumatic are specified in Appendix 11 through Appendix 14. The trial site will have a local dermatologist available for immediate consultation during the trial for these AESIs.

5.5 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eSource.

5.6 Pregnancy

Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months [confirmed by FSH blood level]).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months [confirmed by FSH blood level]; or men who have had a bilateral orchidectomy), 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine and/or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.7 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/CRO medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind

was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.8 Follow-up of Adverse Events

5.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.8.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs up to 30 (+ 2) days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are identified or ongoing at the last scheduled contact must be recorded on the AE eSource page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE CRF page, according to the appropriate reporting procedures. Every effort will be made to obtain a PK blood sample from any subject who experiences an SAE. This sample should be obtained as soon as is practical after the onset of the SAE. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.8.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

Any new SAEs or IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are

captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic/Pharmacogenomic Analysis

Plasma concentrations of OPC-64005 will be summarized by time points using descriptive statistics. No formal statistical comparisons are planned. A separate population or pharmacokinetic/pharmacodynamic modeling may be performed using the data from this trial and other trials.

7 Statistical Analysis

7.1 Sample Size

This trial is exploratory in nature, focusing on estimation of treatment effect and its variability as well as collecting data for future decision making and as a result, sample size was chosen from practical considerations. The trial will enroll approximately 201 subjects in expectation to have about 150 completers at the end of the trial. It is evaluated via simulations that this sample size will be sufficient for making robust further development decision based on data from OPC-64005 and atomoxetine arms using concept of posterior probability.

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: Comprises all subjects who sign an eICF for the trial.

Randomized Sample: All subjects randomized into this trial.

Safety Sample: Comprises randomized subjects who received at least one dose of double-blind IMP as indicated on the dosing record.

Modified Intent-to-Treat Sample: All subjects in the Randomized Sample who took at least one dose of IMP and have a baseline and at least one post randomization evaluation for the investigator-administered CAARS-O:SV ADHD Symptoms Total Score (18-items).

7.3 Handling of Missing Data

The 18-item, investigator-administered CAARS-O:SV is utilized as the primary efficacy assessment of a subject's level of ADHD. The 18-item ADHD Symptoms Total Score (sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale) is considered to be the primary efficacy measure. Each item is rated on a 0 to 3 scale with 0 = Not at all, never; 1 = Just a little, once a while; 2 = Pretty much, often; and 3 = Very much, very frequently. Therefore, possible ADHD Symptoms Total Scores range from 0 to 54. If more than 1 item is missing in a subscale, the subscale (and the total) is considered as missing. For a single missing item, the mean score will be used to impute the missing item and then to compute the subscale or total scores.

In general, for primary analysis of efficacy endpoints, missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed case (OC) data from protocol-specified visits under the assumption of missing at random. The OC dataset consists of actual observations recorded at each visit and no missing data will be imputed.

7.4 Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary efficacy endpoint is the mean change from baseline to the Day 56 Visit on the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group compared with the atomoxetine group. Analysis will be performed using modified intent-to-treat data set.

Bayesian posterior probability of true baseline corrected difference at Week 8 between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on the 18-item, investigator-administered CAARS-O:SV given estimates of means and standard deviations (SD) in the treatment arms will be calculated. Estimates for means and SD will be derived from mixed-effect model as described below. Uninformative prior will be used in calculations.

The change from baseline in the 18-item, investigator-administered CAARS-O:SV will be analyzed using an MMRM methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week an interaction term of treatment by visit week, and baseline 18-item, investigator-administered CAARS-O:SV as a covariate. The need of additional fixed effects and its interactions in the model will be explored. In case the pre-specified

primary efficacy model does not converge, the algorithm to deal with convergence issues will be stated in the Statistical Analysis Plan (SAP).

7.4.2 Other Endpoint Analysis

Other key efficacy variables are as follows:

1) Mean change from baseline to each scheduled visit (other than Day 56) in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups
2) Mean change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits for the AISRS with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups
3) Mean change from baseline to each scheduled visit in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups
4) Mean CGI-I score at each scheduled visit in the OPC-64005 group relative to the atomoxetine and placebo groups
5) Mean change from baseline to each scheduled visit in the 18-item CAARS-S:SV in the OPC-64005 group relative to the atomoxetine and placebo groups
6) Mean change from baseline to the Day 28 (± 1 day) and Day 56 (± 1 day) Visits in the AAQoL in the OPC-64005 group relative to the atomoxetine and placebo groups

Estimates in mean change from baseline and its variability of above listed endpoints will be calculated using MMRM model similar to one described in the primary analysis.

Details on other analyses will be provided in the SAP.

7.4.3 Interim Analysis

An administrative interim analysis will be performed on the primary endpoint after 90 subjects complete 8 weeks of treatment. This analysis will be performed for purpose of planning future studies and will not change the trial conduct (ie, regardless of the interim analysis outcome, this trial will run to completion). Analysis methods will be the same as ones for the final analysis. Analysis will be performed by the OPDC Internal Independent Biostatistician who is not a member of the trial team in order to minimize/avoid bias.

7.5 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and body mass index (BMI) for the randomized subjects will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

Baseline disease severity and psychiatric history will be also be summarized by descriptive statistics for safety sample to identify any potential lack of balance between the treatment arms.

7.6 Safety Analysis

Safety analysis regarding safety and tolerability of OPC-64005 will be conducted based on the safety sample, which is defined in Section 7.2. In general, baseline measurements of safety variables are defined as their last measurements prior to the first dosing of IMP. Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, and ECGs.

7.6.1 Adverse Events

All AEs will be coded to the Lowest Level Term (LLT) in the Medical Dictionary for Regulatory Activities (MedDRA) that most accurately reflects the reported term. The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. Potentially clinically significant results in laboratory tests will also be summarized.

7.6.3 Physical Examination and Vital Signs Data

By-subject listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs will be provided. Potentially clinically significant results in vital signs will also be summarized.

7.6.4 Electrocardiogram Data

Mean change from baseline and incidence of clinically significant changes will be calculated for ECG parameters.

For the analysis of QT and QTc, data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB = QT/(RR)^{0.5}$
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

7.6.5 Other Safety Data

The DEQ will be completed at each scheduled visit (Days 7, 14, 21, 28, 42, and 56/ET; all visits have a ± 1-day window) as a measure of abuse potential and will be analyzed via summary statistics.

Suicidality will be monitored during the trial using the C-SSRS. The incidence of suicidality, suicidal behavior, and suicidal ideation will be calculated from the potential suicide events recorded on the C-SSRS and summarized by trial visit.

8 Management of Investigational Medicinal Product

For full details on the IMP, please refer to the OPC-64005 IB.

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as blister cards. Each card used in the dosing period will be labeled to clearly disclose the compound identification, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored according to the storage conditions indicated on the clinical label(s).

The trial site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day. Temperature excursions, outside of the specific conditions for the IMP (as noted on the label), will be immediately reported to the sponsor.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, and placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial sites. The IMP may only be destroyed by the trial sites, if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor or designated agent must be accompanied by the appropriate documentation and be clearly identified by the protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return or destruction of used IMP containers, unused IMP, and partially-used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)

- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the eICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Source documents and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected

into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application – rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory [or central ECG data], where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Food and Drug Administration regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eSource with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eSource, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor’s prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eSource. If further subject identification is required, subjects’ full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines.
The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved eICF will require similar modification. In such cases, after approval/favorable opinion of the new eICF by the IRB, repeat electronic informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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3 [redacted] Effects of OPC-277 against radioligand binding to various receptors, channels, transporters and enzymes. Otsuka Study No. 029247, Otsuka Report No. 023557, 2009.

4 [redacted] Effects of OPC-64005 on the extracellular serotonin, norepinephrine and dopamine levels in the rat medial prefrontal cortex: in vivo microdialysis study. Otsuka Study No. 029192, Otsuka Report No. 023766, 2009.

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6 Carboni E, Tanda GL, Frau R, Chiara GD. Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. J Neurochem. 1990;55:1067-1070.

7 [redacted] Effect of OPC-64005 on the extracellular dopamine levels in the rat striatum: in vivo microdialysis study. Otsuka Study No. 029215, Otsuka Report No. 023843, 2009.

8 [redacted] Effect of OPC-64005 on immobility time in the forced swimming test in rats. Otsuka Study No. 029546, Otsuka Report No. 024052, 2009.

9 [redacted] Effects of OPC-64005 and other antidepressants on spontaneous locomotor activity in rats. Otsuka Study No. 030257, Otsuka Report No. 024195, 2009.

10 [redacted] Effect of repeated administration of OPC-64005 on immobility time in the forced swimming test in rats. Otsuka Study No. 030182, Otsuka Report No. 024077, 2009.

Protocol 277-201-00001

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Appendix 1 Names of OPDC Personnel

For Medical Emergencies (use only if OPDC personnel listed above are unavailable):

[redacted]

[redacted]
Phone:
Fax:

[redacted]
Phone:
Fax:

[redacted]
Phone:
Fax:

Appendix 2 Institutions Concerned With the Trial

Institutional Review Board

[redacted], USA
Phone: [redacted]

Contract Research Organization
INC Research, LLC
3201 Beechleaf Court, Suite 600
Raleigh, NC 27604, USA
Phone: [redacted]

Central Laboratory
Covance Central Laboratory
8211 SciCor Drive
Indianapolis, IN 46214, USA

Bioanalytical Laboratory
Covance Laboratories
3301 Kinsman Boulevard
Madison, WI 53704, USA
[redacted]

Pharmacogenomics Laboratory and Biorepository for FBR Samples
Gentris, a CGI Company
133 Southcenter Court, Suite 400
Morrisville, NC 27560, USA
[redacted]

Biorepository for Backup PK samples
Fisher BioServices
685 Lofstrand Lane
Rockville, MD 20850 USA
[redacted]

Central Dermatologist
TBD

Histopathology Laboratory
TBD

Appendix 3 Handling and Shipment of Bioanalytical Samples

Handling of Specimens

All tubes must be labeled such that the protocol number, subject identification number, date of collection, and nominal sample collection time can be verified. The labels must be approved by the sponsor's bioanalytical scientist prior to use. It is important to note the exact time of the blood collection in eSource, not the scheduled PK collection time. The exact time of dosing will also be noted.

Plasma Samples for Pharmacokinetic Analysis

Blood (4 mL) will be collected into 4-mL Vacutainer® tubes containing sodium heparin anticoagulant. The tubes should be gently inverted 3 to 4 times and then centrifuged at 2000 to 3000 rpm for at least 10 to 15 minutes at 4°C. The rpm should be kept at the same setting throughout the trial. The separated plasma should then be pipetted into 2 polypropylene tubes and stored at −70°C (± 10°C). Trial sites that do not have access to a −70°C (± 10°C) freezer may utilize a −20°C (± 10°C) freezer for storage. One tube will subsequently be shipped on dry ice to the central laboratory. The backup tube will remain at the trial site until the first tube is received at the central laboratory. At that time, it should be shipped to the central laboratory.

Whole Blood Pharmacogenomic Samples for DMET Profiling

Blood (4 mL) will be collected into a 4-mL K2EDTA Vacutainer tube. Each tube should be gently inverted 3 to 4 times, transferred to the barcode-labeled polypropylene tube, which then must be stored at −70°C (± 10°C). Trial sites that do not have access to a -70°C freezer may utilize a −20°C (± 10°C) freezer for storage of metabolic samples. The tube will be shipped on dry ice to the central laboratory.

Blood Samples for Future Biospecimen Research

Blood (~10 mL) will be collected into an evacuated collection tube. The trial sites are expected to follow the instructions for collection, processing, storage, and shipment of blood samples as specified above. The tubes will be shipped to the central laboratory listed in Appendix 2.

Future biospecimen research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. The specimens will be stored under strict supervision in a limited access facility which operates to ensure the integrity of the specimens.

Shipment of the Specimens

Each frozen specimen must be sealed in a vial and labeled with a waterproof pen. The label must correspond to inventory sheets and must be firmly attached with transparent tape and should include the protocol number and subject number, plus date and nominal time of collection. An electronic Excel file will be provided with the header information that must be filled by the trial sites. Samples should be organized consecutively by

subject number. The inventory should contain the name, address, and telephone number of the contact person from the trial site. Samples must be neatly packed and restrained in a Styrofoam® container (place Styrofoam container supplied within a cardboard box) with dry ice. Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. Packages will not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday. The central laboratory must be alerted of shipments. Shipments will be via an overnight carrier to the central laboratory. The contact for the central laboratory (Appendix 2) must be notified of each shipment via e-mail with the electronic manifest attached on the shipment day. For each backup specimen, the same procedure will be followed once confirmation is received that the primary tube was received at the central laboratory. The central laboratory will subsequently be notified by the sponsor's bioanalytical scientist when to ship the backup specimens to the biorepository for longer-term storage.

Protocol 277-201-00001

Appendix 4 **18-Item, Investigator-Administered Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV)**

CAARS – Observer: Screening Version (CAARS – O:SV)

by C. K. Conners, Ph.D., D. Erhardt, Ph.D., & E. P. Sparrow, Ph.D.

Instructions: Listed below are items concerning behaviors or problems sometimes experienced by adults. Read each item carefully and decide how much or how frequently each item describes this person recently. Indicate your response for each item by circling the number that corresponds to your choice. Use the following scale: 0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; and 3 = Very much, very frequently.

The person being described...	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
1. Loses things necessary for tasks or activities (e.g., to-do lists, pencils, books, or tools). • Do you lose things (i.e. important work papers, keys, wallet, coats, etc.)? • A lot? More than others? • Are you constantly looking for important items? • Do you get into trouble for this (work, home)? • Do you need to put items (e.g., glasses, wallet, keys) in the same place each time, otherwise you will lose them?	0	1	2	3
2. Talks too much. • Do you talk a lot? • All the time? • More than other people? • Do people complain about your talking? • Is (was) it a problem? • Are you often louder than the people you are talking to?	0	1	2	3
3. Gets rowdy or boisterous during leisure activities. • Did you have a hard time playing quietly? • During leisure activity (non-structured times or on your own such as reading a book, listening to music, playing a board game), are you agitated or dysphoric? • Do you always need to be busy after work or while on a vacation?	0	1	2	3

Protocol 277-201-00001

The person being described...	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
4. Leaves seat when not supposed to. • Do you have trouble staying in your seat? At work? In class? At home, i.e., watching TV, eating dinner? In church or temple? • Do you choose to walk around rather than sit? • Do you have to force yourself to remain seated? • Is it difficult for you to sit through a long meeting or lecture? • Do you try to avoid going to functions that require you to sit still for long periods of time?	0	1	2	3
5. Has trouble waiting in line or taking turns with others. • Is it hard for you to wait your turn in conversation, in lines, while driving? • Are you frequently frustrated with delays? • Does it cause problems? • Do you put a great deal of effort into planning to not be in situations where you might have to wait?	0	1	2	3
6. Has trouble keeping attention focused when working or at leisure. • Do you have trouble paying attention when watching movies, reading or lectures? • Or on fun activities such as sports or board games? Is it hard for you to keep your mind on school or work? • Do you have unusual trouble staying focused on boring or repetitive tasks? • Does it take a lot longer than it should to complete tasks because you can't keep your mind on the task? Is (was) it even harder for you than some others your know? • Do you have trouble remembering what you read and do you need to re-read the same passage several times?	0	1	2	3

The person being described…	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
7. Is forgetful in daily activities. • Do you forget a lot of things in your daily routine? • Like what? Chores? Work? Appointments or obligations? • Do you forget to bring things to work such as work materials or assignments due that day? • Do you need to write regular reminders to yourself to do most activities or tasks, otherwise you will forget?	0	1	2	3
8. Has trouble listening to what other people are saying. • Do people (your wife, boss, colleague, friends) complain that you don't seem to listen or respond (or daydream) when spoken to or when asked to do tasks? • A Lot? • Does your mind seem to be elsewhere? • Do people have to repeat directions? • Do you find that you miss the key parts of conversations because of drifting off in your thoughts? • Does it cause problems?	0	1	2	3
9. Is always on the go. • Is it hard for you to slow down? • Do you feel like you (often) have a lot of energy and that you always have (had) to be moving, are (were) always "on the go?" • Do you feel like you're driven by a motor? • Do you feel unable to relax?	0	1	2	3
10. Fidgets (with hands or feet) or squirms in seat. • Can you sit still or are (were) you always moving your hands, feet, or in your chair? • Do you tap your pencil or your feet? A lot? • Do people notice? • Do you regularly play with your hair or clothing? • Do you consciously resist fidgeting or squirming?	0	1	2	3

The person being described…	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
11. Makes careless mistakes or has trouble paying close attention to detail. • Do you make a lot of mistakes (in school) or work? Is (was) this because you're careless? • Do you rush through work, or activities? • Do you have trouble with detailed work? • Do you overlook or miss details? • Is your work inaccurate? • Do you not check your work? • Do people complain that you're careless? • Are (were) you messy or sloppy? • Is your desk or workspace so messy that you have difficulty finding things?	0	1	2	3
12. Doesn't like academic studies/work projects where effort at thinking a lot is required. • Do you avoid tasks (work, chores, reading, board games) that are challenging or lengthy because it's hard to stay focused on these things for a long time? • Do you have to force yourself to do these tasks? • How hard is (was) it? • Do you procrastinate and put off tasks until the last moment possible?	0	1	2	3
13. Is restless or overactive. • Are you physically restless? • Do you feel restless inside? A lot? • Do you feel more agitated when you cannot exercise on an almost daily basis?	0	1	2	3
14. Gives answers to questions before the questions have been completed. • Do you give answers to questions before someone finishes asking? • Do you say things before it is your turn? • Do you say things that don't fit into the conversation? Do you do things without thinking? A lot?	0	1	2	3

The person being described…	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
15. Has trouble finishing job tasks or schoolwork. • Do you have trouble finishing things…work, chores? • Do you start things but quickly lose your focus and get easily sidetracked? • Do you often leave things half done and start another project? • Do you need consequences (such as deadlines) to finish? • Do you have trouble following instructions? (especially complex, multistep instructions that have to be done in a certain order with different steps) • Do you need to write down instructions, otherwise you will forget them?	0	1	2	3
16. Interrupts others when they are working or busy. • Do you talk when others are talking without waiting until you are acknowledged? • Do you butt into others' conversations before being invited? • Do you interrupt others' activities? • Is it hard for you to wait to get your point across in conversations or at meetings?	0	1	2	3
17. Appears distracted when things are going on around him/her. • Are (were) you ever very easily distracted by events around you such as noise (conversation, tv, radio), movement, or clutter? • Do you need relative isolation to get work done? • Can almost anything get your mind off of what you are (were) doing…like work, chores, or if you're talking to someone? • Is it hard to get back to a task once you stop?	0	1	2	3

The person being described...	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
18. Has problems organizing tasks and activities. • Do you have trouble organizing tasks into ordered steps? Is it hard prioritizing work and chores? • Do you need others to plan for you? • Do you have trouble with time management? • Does it cause problems? • Does difficulty in planning lead to procrastination and putting off tasks until the last moment possible?	0	1	2	3

Protocol 277-201-00001

Appendix 5 18-Item Conners' Adult ADHD Rating Scale-Self Report: Screening Version (CAARS-S:SV)

CAARS – Self-Report: Screening Version (CAARS – S:SV)

by C. K. Conners, Ph.D., D. Erhardt, Ph.D., & E. P. Sparrow, Ph.D.

Instructions: Listed below are items concerning behaviors or problems sometimes experienced by adults. Read each item carefully and decide how much or how frequently each item describes you recently. Indicate your response for each item by circling the number that corresponds to your choice. Use the following scale: 0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; and 3 = Very much, very frequently.

	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
1. I lose things necessary for tasks or activities (e.g., to-do lists, pencils, books, or tools).	0	1	2	3
2. I talk too much.	0	1	2	3
3. I have trouble doing leisure activities quietly.	0	1	2	3
4. I leave my seat when I am not supposed to.	0	1	2	3
5. I have trouble waiting in line or taking turns with others.	0	1	2	3
6. I have trouble keeping my attention focused when working.	0	1	2	3
7. I am forgetful in my daily activities.	0	1	2	3
8. I have trouble listening to what other people are saying.	0	1	2	3
9. I am always on the go.	0	1	2	3
10. I fidget (with my hands or feet) or squirm in my seat.	0	1	2	3
11. I make careless mistakes or have trouble paying close attention to detail.	0	1	2	3
12. I don't like homework or job activities where I have to think a lot.	0	1	2	3

Protocol 277-201-00001

	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
13. I am restless or overactive.	0	1	2	3
14. I give answers to questions before the questions have been completed.	0	1	2	3
15. I have trouble finishing job tasks or schoolwork.	0	1	2	3
16. I interrupt others when they are working or playing.	0	1	2	3
17. I am distracted when things are going on around me.	0	1	2	3
18. I have problems organizing my tasks and activities.	0	1	2	3

Protocol 277-201-00001

Appendix 6 Adult ADHD Investigator Symptom Rating Scale (AISRS With Adult Prompts)

ADULT ADHD INVESTIGATOR SYMPTOM REPORT SCALE (AISRS) QS

Date performed	Rater's Initials
DD MON YY	FIRST MIDDLE LAST

	None	Mild	Moderate	Severe
1. Do you make careless mistakes when working on a boring or difficult project?	0	1	2	3
2. Do you fidget or squirm with your hands or feet when you have to sit down for a long time?	0	1	2	3
3. Do you have difficulty keeping your attention when you are doing boring or repetitive work?	0	1	2	3
4. Do you leave your seat in meetings or other situations in which you are expected to remain seated?	0	1	2	3
5. Do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?	0	1	2	3
6. Do you feel restless or fidgety?	0	1	2	3
7. Do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	0	1	2	3
8. Do you have difficulty unwinding and relaxing when you have time to yourself?	0	1	2	3
9. Do you have difficulty getting things in order when you have to do a task that requires organization?	0	1	2	3
10. Do you feel overly active and compelled to do things, like you were driven by a motor?	0	1	2	3
11. Do you avoid or delay getting started on a task that requires a lot of thought?	0	1	2	3

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OTS162218_277-201-00001_AISRS_DRAFT_v1_2017_Jun_02 1 of 3

Protocol 277-201-00001

ADULT ADHD INVESTIGATOR SYMPTOM REPORT SCALE (AISRS) (Continued) QS				
	None	Mild	Moderate	Severe
12. Do you find yourself talking too much when you are in social situations?	0	1	2	3
13. Do you misplace or have difficulty finding things at home or at work?	0	1	2	3
14. When you're in a conversation, do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?	0	1	2	3
15. Do you find yourself being distracted by activity or noise around you?	0	1	2	3
16. Do you have difficulty waiting your turn in situations when turn taking is required?	0	1	2	3
17. Do you have problems remembering appointments or obligations?	0	1	2	3
18. Do you interrupt others when they are busy?	0	1	2	3

Developed by Lenard Adler MD, Thomas Spencer MD and Joseph Biederman MD © Massachusetts General Hospital and New York University School of Medicine

OTS162218_277-201-00001_AISRS_DRAFT_v1_2017_Jun_02 2 of 3

Protocol 277-201-00001

Appendix 7 Clinical Global Impression - Severity of Illness Scale (CGI-S)

Considering your total clinical experience with the ADHD population, how mentally ill is the patient 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 patients

1	Normal, not at all ill	Symptoms of disorder not present past seven days
2	Borderline ill	Subtle or suspected pathology
3	Mildly ill	Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function
4	Moderately ill	Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication
5	Markedly ill	Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress
6	Severely ill	Disruptive pathology; behavior and function are frequently influenced by symptoms; may require assistance from others
7	Among the most extremely ill patients	Pathology drastically interferes in many life functions; may be hospitalized

Rater Signature: _____ **Date (DD/MMM/YYYY):** ___ _____

Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry. 2007;4(7):28-37.

Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-222. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health.

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Protocol 277-201-00001

Appendix 8 Clinical Global Impression - Improvement Scale (CGI-I)

Compared to the patient's ADHD symptoms at the time of the baseline visit, how much has he/she changed?

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

1	Very much improved	Nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2	Much improved	Notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3	Minimally improved	Slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4	No change	Symptoms remain essentially unchanged
5	Minimally worse	Slightly worse but may not be clinically meaningful, may represent very little change in basic clinical status or functional capacity
6	Much worse	Clinically significant increase in symptoms and diminished functioning
7	Very much worse	Severe exacerbation of symptoms and loss of functioning

Rater Signature: _____ **Date (DD/MMM/YYYY):** _____ _____

Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry. 2007;4(7):28-37.

Modified from Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-222. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health

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Protocol 277-201-00001

Appendix 9 Adult ADHD Quality of Life Scale (AAQoL)

Adult ADHD Quality of Life Questionnaire (AAQoL)

The following questions are about how ADHD has impacted your life over the PAST 2 WEEKS. Please answer each question by circling your response. There are no right or wrong answers.

1. During the PAST 2 WEEKS, how difficult has it been for you to:	*Not at all*	*A little*	*Somewhat*	*A lot*	*Extremely*
Keep the house/apartment clean or uncluttered	1	2	3	4	5
Manage your finances (such as cashing checks, balancing your checkbook, paying bills on time)	1	2	3	4	5
Remember important things	1	2	3	4	5
Get your shopping done (such as for food, clothes or household items)	1	2	3	4	5
Pay attention when interacting with others	1	2	3	4	5

2. During the PAST 2 WEEKS, how often have you felt:	*Never*	*Rarely*	*Sometimes*	*Often*	*Very Often*
Overwhelmed	1	2	3	4	5
Anxious	1	2	3	4	5
Depressed	1	2	3	4	5
You have not been able to meet others' expectations of you (either at home or at work)	1	2	3	4	5
You annoyed people	1	2	3	4	5
Getting things done requires too much effort	1	2	3	4	5
People are frustrated with you	1	2	3	4	5

Contact Information: Meryl Brod, PhD, President, The BROD GROUP - 219 Julia Ave., Mill Valley, CA 94941
Tel: 415-381-5532, Fax: 415-381-0653, Email: mbrod@thebrodgroup.net; Website: www.thebrodgroup.net

Protocol 277-201-00001

2. During the PAST 2 WEEKS, how often have you felt:	*Never*	*Rarely*	*Sometimes*	*Often*	*Very Often*
You have overreacted in difficult or stressful situations	1	2	3	4	5
Your energy is well spent (has positive results)	1	2	3	4	5
Able to enjoy time spent with others	1	2	3	4	5
You can successfully manage your life	1	2	3	4	5
As productive as you would like to be	1	2	3	4	5

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Protocol 277-201-00001

AAQoL Psychometric Assessment
4/23/2014

3. During the PAST 2 WEEKS, how troubled have you been by:	Not at all	A little	Somewhat	A lot	Extremely
Tension in relationships	1	2	3	4	5
Not having quality time to spend with others	1	2	3	4	5

4. During the PAST 2 WEEKS, how bothered have you been by:	Not at all	A little	Somewhat	A lot	Extremely
Feeling fatigued	1	2	3	4	5
Fluctuations (ups and downs) in your emotions	1	2	3	4	5

5. During the PAST 2 WEEKS, how much of a problem has it been for you to:	Not at all	A little	Somewhat	A lot	Extremely
Complete projects or tasks (either at work or at home)	1	2	3	4	5
Get started with tasks you don't find interesting	1	2	3	4	5
Balance multiple projects	1	2	3	4	5
Get things done on time	1	2	3	4	5
Keep track of important items (such as keys, wallet)	1	2	3	4	5

6. During the PAST 2 WEEKS, how often have you felt:	Never	Rarely	Sometimes	Often	Very Often	Not Applicable
Good about yourself	1	2	3	4	5	----
People enjoy spending time with you	1	2	3	4	5	----

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Protocol 277-201-00001

6. During the PAST 2 WEEKS, how often have you felt:	*Never*	*Rarely*	*Sometimes*	*Often*	*Very Often*	*Not Applicable*
Your intimate relationship is going well emotionally	1	2	3	4	5	❑

Thank you!

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Tel: 415-381-5532, Fax: 415-381-0653, Email: mbrod@thebrodgroup.net; Website: www.thebrodgroup.net

Protocol 277-201-00001

Appendix 10 Profile of Mood States-Brief Form (POMS)

POMS™ Brief Form

BY DOUGLAS M. McNAIR, Ph.D., MAURICE LORR, Ph.D., JW P. HEUCHERT, Ph.D., & LEO F. DROPPLEMAN, Ph.D.

Name: _____ **Age:** _____ **Gender:** Male Female (Circle one)

Birth Date: ____/____/____ (Month Day Year) **Today's Date:** ____/____/____ (Month Day Year)

To the Administrator:

Place a checkmark ✔ in one box to specify the time period of interest.

To the Respondent:

Below is a list of words that describe feelings that people have. Please read each word carefully. Then circle the number that best describes

- ☐ how you have been feeling during the PAST WEEK, INCLUDING TODAY.
- ☐ how you feel RIGHT NOW.
- ☐ other: _____

If no box is marked, please follow the instructions for the first box.

POMS™

		Not at all	A little	Moderately	Quite a bit	Extremely
1.	Tense	0	1	2	3	4
2.	Angry	0	1	2	3	4
3.	Worn out	0	1	2	3	4
4.	Lively	0	1	2	3	4
5.	Confused	0	1	2	3	4
6.	Shaky	0	1	2	3	4
7.	Sad	0	1	2	3	4
8.	Active	0	1	2	3	4
9.	Grouchy	0	1	2	3	4
10.	Energetic	0	1	2	3	4
11.	Unworthy	0	1	2	3	4
12.	Uneasy	0	1	2	3	4
13.	Fatigued	0	1	2	3	4
14.	Annoyed	0	1	2	3	4
15.	Discouraged	0	1	2	3	4
16.	Nervous	0	1	2	3	4
17.	Lonely	0	1	2	3	4
18.	Muddled	0	1	2	3	4
19.	Exhausted	0	1	2	3	4
20.	Anxious	0	1	2	3	4
21.	Gloomy	0	1	2	3	4
22.	Sluggish	0	1	2	3	4
23.	Weary	0	1	2	3	4
24.	Bewildered	0	1	2	3	4
25.	Furious	0	1	2	3	4
26.	Efficient	0	1	2	3	4
27.	Full of pep	0	1	2	3	4
28.	Bad-tempered	0	1	2	3	4
29.	Forgetful	0	1	2	3	4
30.	Vigorous	0	1	2	3	4

Please ensure you have answered every item.

Protocol 277-201-00001

POMS™ Brief Scoring Grid

BY DOUGLAS M. McNAIR, Ph.D., MAURICE LORR, Ph.D., JW P. HEUCHERT, Ph.D., & LEO F. DROPPLEMAN, Ph.D.

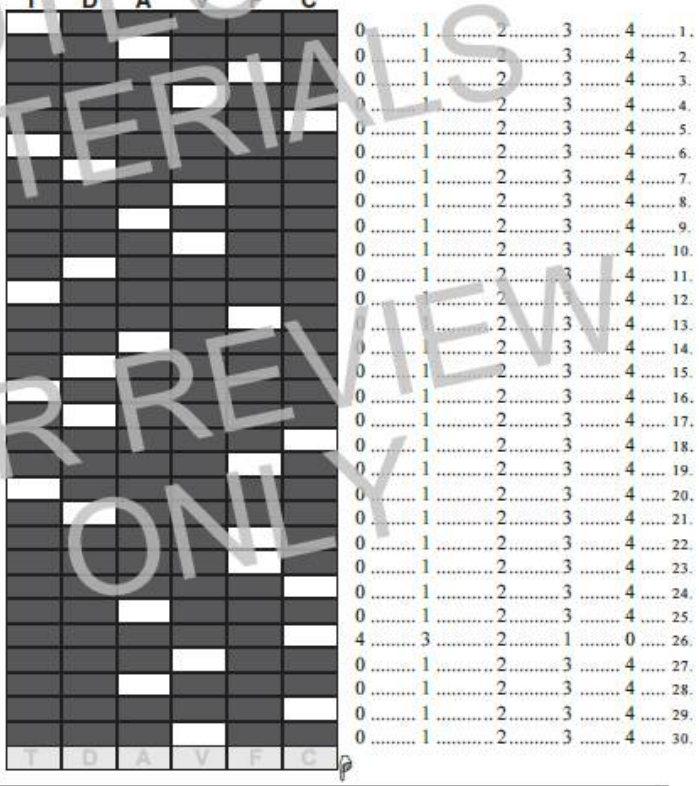
Name:_____ **Age:**_____ **Gender:** Male Female (Circle one)

Birth Date: ____/____/____ (Month / Day / Year) **Today's Date:** ____/____/____ (Month / Day / Year)

Instructions:

For each item, transfer each circled score into the corresponding unshaded box in the scoring section below. Each circled number should be copied once.

For example, if "3" is circled, transfer "3" to the corresponding unshaded box on the same row:



To obtain raw scores for factors T, D, A, V, F, and C, add the numbers in each column and enter the sum in the box at the bottom of the column.

Sum T, D, A, F, and C and subtract V in the boxes below to obtain the Total Mood Disturbance (TMD) score.

Plot the Raw Scores for each factor on the POMS Brief Profile on the next page of this QuikScore™ form. No *T*-scores are provided for the TMD.

Raw Score	T	+	D	+	A	+	F	+	C	−	V	=	TMD	Total Mood Disturbance

OTS162218_277-201-00001_POMS Brief Form_DRAFT_v1_2017_May_19

Protocol 277-201-00001

POMS™ Brief Profile

BY DOUGLAS M. McNAIR, Ph.D., MAURICE LORR, Ph.D., JW P. HEUCHERT, Ph.D., & LEO F. DROPPLEMAN, Ph.D.

Name:_____ **Age:**_____ **Gender:** Male Female (Circle one)

Birth Date: ____/____/____ (Month Day Year) **Today's Date:** ____/____/____ (Month Day Year)

Factor

T-Score	Ten	Dep	Ang	Vig	Fat	Con	T-Score
80+				20			80+
79							79
78				19			78
77							77
76			20	18	20		76
75						20	75
74			19		19		74
73				17		19	73
72			18				72
71				16	18	18	71
70			17				70
69		20		15	17	17	69
68			16				68
67	20	19		14	16	16	67
66		18	15				66
65	19			13		15	65
64		17	14		15		64
63	18						63
62		16	13	12	14	14	62
61	17						61
60		15	12	11	13	13	60
59	16						59
58	15	14	11	10		12	58
57					12		57
56	14	13	10	9		11	56
55		12			11		55
54	13		9	8		10	54
53		11			10		53
52	12		8	7		9	52
51		10					51
50	11		7	6	9	8	50
49		9					49
48	10		6		8	7	48
47		8		5			47
46	9		5		7	6	46
45	8	7		4			45
44			4			5	44
43	7	6		3	6		43
42		5	3			4	42
41	6			2	5		41
40		4	2			3	40
39	5			1	4		39
38		3	1				38
37	4				3	2	37
36		2	0	0			36
35	3					1	35
34		1			2		34
33	2					0	33
32	1	0			1		32
31							31
≤30	0				0		≤30

Protocol 277-201-00001

Appendix 11 OPC-64005 Skin AESI Workup Instructions

277-201-00001 Skin Adverse Event of Special Interest (AESI) Workup Instructions

Version 2.0 dated 18 Aug 2017

At any point during the trial, upon the report by the subject or upon the observation by site personnel of any type of newly acquired skin eruptions that are non-traumatic, they will be considered adverse events of special interest (AESIs), and the investigator or medical professional designee will take the following steps:

1. Discontinue administration of IMP regardless of the severity and seriousness of rash.
2. Collect a detailed history, including specific questioning for symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine) or other possible causes of the rash (eg, allergic, contact dermatitis).
3. Perform a physical examination of the area affected by the skin rash, listing all body parts affected (eg, left or right hand, forearm, upper arm, etc.).
4. Obtain vital signs (including body temperature).
5. Record all concomitant medications and nutritional supplements and compare them with the use of IMP and the onset and resolution of skin eruptions.
6. Take a picture of the area(s) of the rash using the Clinical Ink SureSource tablet. If the rash area is generalized, the torso, back, abdomen, and extremities should be photographed.

   NOTE: Photographs should not contain any personal identifiers or parts of the body that would identify the subject (such as unusual tattoos, full-face views, etc.).
7. Contact Otsuka's and INC's Medical Monitor for the trial.
8. Collect blood samples for laboratory testing, including a complete blood count with differential to detect lymphocytosis, atypical lymphocytes, and absolute (total) eosinophil count and chemistry with liver enzyme tests and C-reactive protein (CRP) testing (to rule out cases of systemic hypersensitivity).
   - Note: If the signs and symptoms are suggestive of drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), human herpes virus 6 (HHV-6) infection should be ruled out.
9. Complete the Skin AESI Worksheet for the trial site (Appendix 12).

10. Refer the subject to a local dermatologist assigned by the trial site for a consultation as soon as possible (Note that after 7 days without IMP, the subject may not continue in the trial regardless of the outcome of the investigation of the rash).
    a. For rash that is classified as SEVERE (defined as the inability to perform normal daily activities) or meets the definition of an SAE: If the subject agrees, have the local dermatologist obtain a biopsy for histopathological examination by a dermatopathologist. Consider direct immunofluorescence evaluation, particularly if the eruption is characterized by vesicles, bullae, or pustules.
    b. Have the local dermatologist complete the Skin AESI Worksheet (see Appendix 13) when the subject is evaluated.
        i. The local dermatologist will contact the trial Central Dermatologist for consultation (see Appendix 14)
11. Monitor the subject daily via telephone contact or in-clinic visits (per the investigator's discretion) to evaluate if the event is improving, unchanging, or worsening. When the event resolves, record the last day as the end date of the AE.
12. Repeat steps 3-11 as required.

Protocol 277-201-00001

Appendix 12 OPC-64005 Skin AESI Worksheet for Trial Site

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site

Version 2.0 dated 18 Aug 2017

To be completed by the trial site

Trial Protocol: 277-201-00001	
Adverse Event # (in SureSource):	
Site No.	Investigator:
Subject No.	Subject Initials:

	Date: (dd/mmm/yyyy)	Time: (hh:mm)
Date and time of rash onset		
Date and time of first dose (Day 1) of IMP		
Date and time of last IMP dose (before the rash)		

Vital Signs – Sitting Position

Time subject was placed into sitting position: _____ : _____

Time of sitting vitals assessment: _____ : _____

Temperature: _____ . _____ °F / °C

Heart rate: _____ _____ _____ bpm

Blood pressure: _____ _____ _____ / _____ _____ _____ mmHg

Respiration: _____ _____ bpm

Vital signs collected by: _____

Initials

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Adverse Event # (in SureSource):	
Site No.	Investigator:
Subject No.	Subject Initials:

Description of Rash:

Location(s) of Rash:

Locations of Adenopathy (if applicable):

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Adverse Event # (in SureSource):	
Site No.	Investigator:
Subject No.	Subject Initials:

NOTE: Ensure rash location(s) is clearly specified and photographed. If the body location is not obvious, label the photo or include a label with the body location in the photo, or take a "staging" shot of the body part and then a closer shot of the rash. Make sure all photos are in precise focus; some cameras will focus on items in the background behind the subject's skin.

****If rash location is generalized, the torso, back, abdomen, and extremities should be photographed.***

****Do not photograph any personal identifiers or other parts of the body.***

Were pictures taken? ☐ Yes ☐ No If no, please explain why not:

_____

_____

Note: Attach copies of adverse events, demographics, concomitant medications (including herbal and dietary supplements), medical history, lab reports, and vital signs source document records to this worksheet before forwarding to the dermatologists.

Please upload the completed Skin AESI Worksheets from the local and central dermatologists to the SureSource portal (ie, Appendix 13 and Appendix 14).

_____ _____

Signature of Investigator **Date (dd/mmm/yyyy)**

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Adverse Event # (in SureSource):	
Site No.	Investigator:
Subject No.	Subject Initials

Final review and disposition by the investigator (to be completed AFTER receipt of any pertinent laboratory tests or pathology results):

After review of the dermatologic consultation and subject history, does the investigator consider the rash to be IMP-related?

☐ Yes

☐ No (if it is determined that the rash is not related to the IMP and further treatment with the IMP is in the subject's best interest, the IMP may be restarted at the same dose provided no more than 7 days have elapsed since the IMP was stopped)

_____ _____

Signature of Investigator **Date (dd/mmm/yyyy)**

Protocol 277-201-00001

Appendix 13 OPC-64005 Skin AESI Worksheet for Local Dermatologist

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist

Version 2.0 dated 18 Aug 2017

To be completed by the Local Dermatologist assigned by the trial site

Trial Protocol: 277-201-00001	
Date of Consultation: (dd/mmm/yyyy)	Subject No./ Subject Initials

Rash Description, select all that apply:

	"X" all that apply	Details:
Papular		
Macular		
Pustular		
Vesicular		
Bullous		
Urticarial		
Other _____		

Erythematous		
Blanchable		
Pigmented		
Ecchymotic		
Other _____		

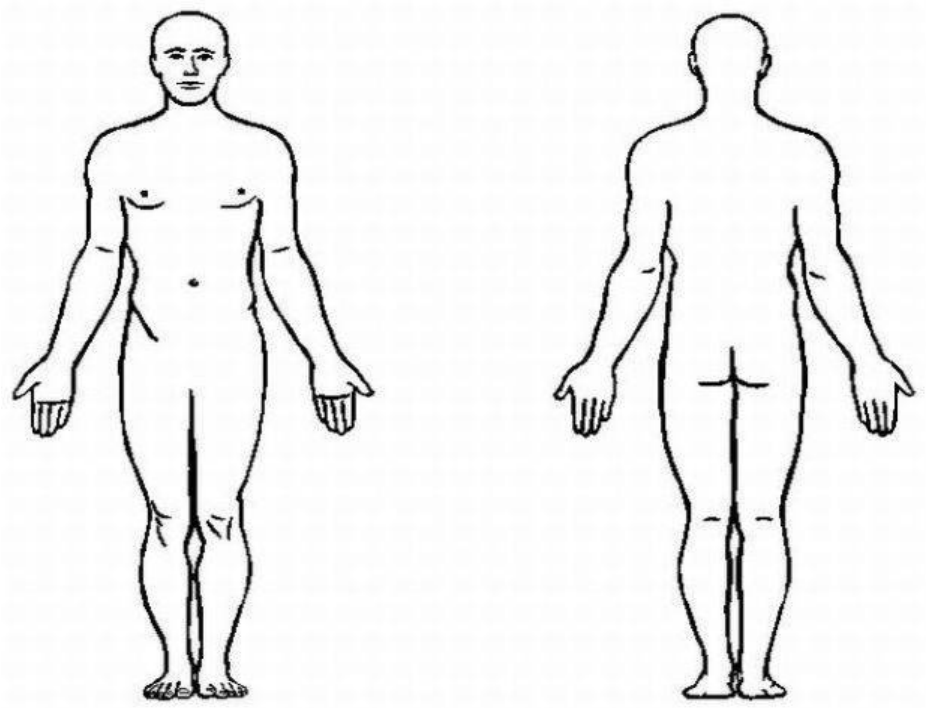
Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Date of Consultation: (dd/mmm/yyyy)	Subject No./ Subject Initials:

Mark location(s) of the rash, including any urticarial lesions or swelling/edema, on the figures below. If the subject has any visible skin rash that predates the trial onset, be sure to identify such rash separately on the figures below.



Please note any of the following:

Oral mucosal involvement and lip involvement ☐ No ☐ Yes – details:

Conjunctival involvement ☐ No ☐ Yes – details:

Genital involvement ☐ No ☐ Yes – details:

Scalp involvement ☐ No ☐ Yes – details:

Palmar lesions ☐ No ☐ Yes – details:

Plantar lesions ☐ No ☐ Yes – details:

Targetoid lesions ☐ No ☐ Yes – details:

Urticarial lesions ☐ No ☐ Yes – details:

Swelling/edema ☐ No ☐ Yes – details:

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Date of Consultation: (dd/mmm/yyyy)	Subject No./ Subject Initials:

Please take pictures of the rash per the standard photography procedures at your office. ***NOTE: Ensure rash location(s) is clearly photographed. If rash location is generalized, the torso, back, abdomen, and extremities should be photographed. *Do not photograph any personal identifiers.***

Were pictures taken? ☐ Yes ☐ No If No, please explain why not:

_____

Please provide narrative description of rash, as follows:

- Occupation
- Exposure to dyes or toxins
- Prodromal symptoms
- Recent contact with anyone else who had a rash
- Changes in the environment: inhalants, foods, new clothing, new skin care products, new detergent
- Itching, burning/stinging, tenderness, color (eg, pink, red, or brown), texture (raised or flat), pattern (small lesions, grouped large plaques), unusual characteristics (scaly, peeling, follicles), size (eg, pea-sized, dime-sized, 10 mm), starting location (eg, nails, feet/soles, hands/palms, scalp, mouth, genitalia, symmetric)
- Did it move or spread? Time course?
- Any signs by physical examination or subject report of associated symptoms (eg, respiratory, fever, systemic symptoms)

Please insert the narrative below:

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist

Version 2.0 dated 18 Aug 2017

Trial Protocol: 277-201-00001	
Date of Consultation: (dd/mmm/yyyy)	Subject No./ Subject Initials:

For skin eruptions that are classified as **SEVERE** (defined as the inability to perform normal daily activities) or **SERIOUS** (life threatening, causing hospitalization, requiring medical/surgical intervention, medically significant), **a biopsy of a representative lesion is encouraged.**

Was a biopsy performed? ☐ Yes ☐ No

Please mark location of biopsy on body by placing 'Bx' on the map above. Please forward a copy of the pathology report from the biopsy to your trial contact when it becomes available.

Final causality assessment (choose one):

☐ Definite drug eruption due to IMP

☐ Probably drug eruption due to IMP (the etiology of the rash has a ≥ 50% chance of being related to the IMP)

☐ Possible drug eruption due to IMP (the etiology of the rash has a < 50% chance of being related to the IMP)

☐ Not related

☐ Other Diagnosis (specify): _____

Dermatologist Disposition (choose one):

Is the rash considered to be IMP-related?

☐ Yes

☐ No (if it is determined that the rash is not related to the IMP and further treatment with the IMP is in the subject's best interest, the IMP may be restarted at the same dose provided no more than 7 days have elapsed since the IMP was stopped)

_____ _____

Signature of Local Dermatologist **Date (dd/mmm/yyyy)**

Protocol 277-201-00001

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist

Version 2.0 dated 18 Aug 2017

Post Subject-Assessment Instructions and Reminders for Local Dermatologist

1) As soon as possible but within 24 hours following your assessment of the subject, please contact the central dermatologist assigned to the trial to discuss your findings and review lab results (if applicable).

Central Dermatologist Contact Info

TBD

2) If a biopsy sample was obtained, please ship the sample per standard procedures to the histopathology laboratory noted below:

Histopathology Laboratory Info

TBD

3) REMINDER: Please scan and email the above completed forms and any supporting documents to your contact at the trial site as soon as possible following the visit. If the subject is seen more than once, the forms above should be completed for each visit. Forward any laboratory tests or pathology results to your contact at the trial site, as soon as they become available.

Protocol 277-201-00001

Appendix 14 OPC-64005 Skin AESI Worksheet for Central Dermatologist

277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Central Dermatologist

Version 2.0 dated 18 Aug 2017

To be completed by the Central Dermatologist

Trial Protocol: 277-201-00001	
Date: (dd/mmm/yyyy)	Subject No./ Subject Initials

Narrative / Comments (including pathology results, if applicable):

Final causality assessment (choose one):

☐ Definite drug eruption due to IMP

☐ Probably drug eruption due to IMP (the etiology of the rash has a ≥ 50% chance of being related to the IMP)

☐ Possible drug eruption due to IMP (the etiology of the rash has a < 50% chance of being related to the IMP)

☐ Not related

☐ Other Diagnosis (specify): _____

Reminder: Please scan and email completed form(s) to the Local Dermatologist and trial site contacts.

_____ _____

Signature of Central Dermatologist **Date (dd/mmm/yyyy)**

Protocol 277-201-00001

Appendix 15 Protocol Amendment(s)/Administrative Change(s)

Administrative Change Number: 1

Issue Date: 25 Apr 2017

PURPOSE:

The purpose of this administrative change is to update the IND number for the protocol and the approximate number of trial sites.

BACKGROUND:

Due to the change in indication, a new IND is being submitted for this compound and a revised IND number has been provided.

Also, based on further analysis of enrollment rates in similar trials, it was determined that additional sites are required in order to meet enrollment objectives and timelines.

GENERAL CHANGES:

Description of Change	Rationale for Change	Section Affected by Change
Changed IND number	Change in indication	Cover page; and Protocol Synopsis (page 2)
Updated number of US trial sites	Increased number from 21 to approximately 40 US trial sites	Protocol Synopsis (page 3)

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 277-201-00001

Amendment Number: 1

Issue Date: 29 Jun 2017

PURPOSE:

The purpose of this protocol amendment is to:

- Replace 1 of the scales used for diagnosis and 2 of the scales used for efficacy assessments
- Modify the investigator-administered CAARS-O:SV so that only the 18 DSM-relevant items are administered to the subject
- Modify the CAARS-S:SV so that only the 18 items that comprise the ADHD Symptoms Total Score will be administered to the subjects
- Add a ± 1-day window around the Day 7 through Day 56 trial visits to allow for flexibility around the trial visits
- Add IMP administration details to the schedule of assessments for clarity
- Clarify that the first follow-up takes place 3 days after the last dose for subjects who complete the trial and for subjects who terminate early from the trial
- Add how to handle missed trial visits/doses and clarify contact with the medical monitor in such cases
- Add that subjects are permitted to titrate back up one time to allow subjects to return to their maintenance dose
- Modify the steps required for subjects with a rash and add that any instances of rash must be reported to the CRO medical monitor
- Clarify and modify the inclusion and exclusion criteria
- Change the trial duration from 11 to 9 months based on when the first subject will be enrolled to when the last subject will complete the trial
- Add details around the timing of PK blood sampling for clarity
- Add a pregnancy test at Day 28 to assess pregnancy at the midpoint of the trial
- Clarify that any rash, regardless of severity or seriousness, will lead to discontinuation of IMP
- Clarify that normal consumption of caffeine is permitted
- Clarify adverse events of special interest (ie, newly acquired skin eruptions that are nontraumatic)
- Clarify IMP storage details
- Clarify safety analyses for standard safety variables and the C-SSRS
- Add that CYP2D6 substrates with a narrow therapeutic index are prohibited, as requested by the FDA
- Reduce the number of trial sites from 40 to approximately 25

Protocol 277-201-00001

- Add the IRB, CRO, and central laboratory information to Appendix 2
- Add all of the efficacy scales as appendices
- Add appendices for follow-up activities if rash is detected to clarify the process to be followed for rash evaluation

BACKGROUND:

The rationale for the changes in this protocol amendment is as follows:

- The ADHD RS-5 was replaced with the AISRS as the AISRS already has language built in for adults and has been validated in multiple adult ADHD treatment trials.
- The CAADID was replaced with the ACDS (version 1.2) as the ACDS v1.2 is specifically designed to generate DSM-5 ADHD diagnoses and may be faster for the clinic staff to administer.
- The POMS 2-A was replaced with the POMS-Brief as the POMS-Brief contains items sufficient to capture symptoms often viewed as residual after ADHD treatment. Additionally, the POMS 2-A contained an adolescent scale, which is not relevant to this trial.
- The text regarding rash was modified to be consistent with the informed consent form and to add clarity around the process of rash review.
- Inclusion criterion #4 was modified to replace the CAADID with the ACDS v1.2 and was revised for clarity.
- Inclusion criterion #5 was modified to replace the ADHD RS-5 with the AISRS and to clarify the ADHD treatment.
- Inclusion criterion #7 was revised for clarification only.
- Inclusion criterion #8 was modified to replace the ADHD RS-5 with the AISRS.
- Exclusion criterion #3 was modified to add that subjects with suboptimal tolerability to atomoxetine are also excluded and to remove “after 18 years of age”.
- Exclusion criterion #6 was modified to remove intolerability (lifetime treatment history) to stimulant or nonstimulant ADHD medications.
- Exclusion criteria #8 was modified to remove Axis I/II terminology and specify that current or lifetime bipolar disorder is excluded.
- Exclusion criterion #9 was modified to add additional DSM-5 diagnoses for clarification to the investigator.
- Exclusion criteria #10, #11, #12, and #27 were revised for clarification only.
- Exclusion criterion #14 was modified to include dermatological disorders and active hepatitis B or C.
- Exclusion criterion #20 was modified to be consistent with DSM-5 terminology and requirements for diagnosis.

Protocol 277-201-00001

- Exclusion criterion #21 was modified to allow retesting or rescreening based on the opinion of the investigator.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Old Text	Updated Text
Synopsis, Trial Design	The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur at Day 59 or discontinuation (± 1 day), and a follow-up telephone contact to occur 30 (+ 2) days after the last treatment.	The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur at **3** (± 1) **days after the last dose**, and a follow-up telephone contact to occur 30 (+ 2) days after the last **dose**.
Synopsis, Subject Population	Approximately 201 adult male and female subjects with ADHD will be randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo (50 completers per arm).	Approximately 201 adult male and female subjects with ADHD will be randomized (1:1:1) to be administered OPC-64005, atomoxetine, or placebo.
Synopsis, Inclusion Criteria	• Subjects with a primary *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) diagnosis of ADHD (including inattentive, hyperactive, and combined subtypes) as confirmed by the Conners' Adult ADHD Diagnostic Interview for *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) (CAADID) (The CAADID will be adapted to be consistent with the DSM-5). Subjects may have received prior treatment for adult ADHD or may be currently receiving treatment for adult ADHD at screening.	• Subjects with a primary *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) diagnosis of ADHD (including **predominantly** inattentive **presentation**, hyperactive **presentation**, and combined **presentations**) as confirmed by the **Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2)**. Subjects **must** have received prior **successful** treatment **(pharmacotherapy)** for adult ADHD **based on medical records and the principal investigator's judgment. Subjects** may be currently receiving treatment for adult ADHD at screening**, but it is not necessary that they are currently receiving treatment**. **The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Synopsis, Inclusion Criteria	• Subjects who are not currently receiving treatment for ADHD who have an ADHD Rating Scale based on DSM-5 criteria (ADHD RS-5) with Adult Prompts score of ≥ 26 and subjects who are receiving any treatment for ADHD at screening who have an ADHD RS-5 with Adult Prompts score of ≥ 22.	• Subjects who are not currently receiving **an approved pharmacological** treatment for ADHD who have an **Adult ADHD Investigator Symptom Rating Scale (AISRS)** with Adult Prompts score of ≥ 26 and subjects who are receiving any **pharmacological** treatment for ADHD at screening who have an **AISRS** with Adult Prompts score of ≥ 22.
Synopsis, Trial Site(s)	Approximately 40 trial sites in the United States	Approximately **25** trial sites in the United States
Synopsis, Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	During the Titration Period (Days 1 - 4), subjects randomized to the OPC-64005 arm will receive 20 mg OPC-64005 daily (ie, two 10 mg OPC-64005 tablets); subjects randomized to the atomoxetine arm will receive 40 mg of atomoxetine daily, and subjects randomized to the placebo arm will receive daily placebo only.	During the Titration Period (Days 1 - 4), subjects randomized to the OPC-64005 arm will receive 20 mg OPC-64005 (ie, two 10 mg OPC-64005 tablets) **and atomoxetine placebo** daily**,** subjects randomized to the atomoxetine arm will receive 40 mg of atomoxetine **and OPC-64005 placebo** daily, and subjects randomized to the placebo arm will receive **both OPC-64005** placebo **and atomoxetine placebo** daily.
Synopsis, Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	During the Treatment Period (Days 5 - 56), subjects randomized to the OPC-64005 arm will receive 30 mg OPC-64005 daily; subjects randomized to the atomoxetine arm will receive 80 mg of atomoxetine daily, and subjects randomized to the placebo arm will receive daily placebo only. If a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period.	During the Treatment Period (Days 5 - 56), subjects randomized to the OPC-64005 arm will receive 30 mg OPC-64005 **and atomoxetine placebo** daily**,** subjects randomized to the atomoxetine arm will receive 80 mg of atomoxetine **and OPC-64005 placebo** daily, and subjects randomized to the placebo arm will receive **both OPC-64005 placebo and atomoxetine placebo** daily. If a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. **Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Synopsis, Trial Assessments	**Efficacy:** Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV), Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV), ADHD RS-5 with Adult Prompts, CGI-S, Global Clinical Impression-Improvement (CGI-I), Adult ADHD Quality of Life Scale (AAQoL), and Profile of Mood States 2nd Edition™ (POMS 2-A).	**Efficacy: 18-item, investigator-administered** Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV), **18-item** Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV), **AISRS** with Adult Prompts, CGI-S, Global Clinical Impression-Improvement (CGI-I), Adult ADHD Quality of Life Scale (AAQoL), and Profile of Mood States-**Brief Form™** (**POMS**).
Synopsis, Trial Assessments	**Screening/Other:** Demographic information; medical, medication, and psychiatric history; identification of comorbidities; HIV, hepatitis B surface antigen (HBsAg), and anti hepatitis C virus (HCV) status; urine alcohol and drug screen; urine pregnancy test.	**Screening/Other:** Demographic information; medical, medication, and psychiatric history; identification of comorbidities **(in part, using the Mini International Neuropsychiatric Interview)**; HIV, hepatitis B surface antigen (HBsAg), and anti hepatitis C virus (HCV) status; urine alcohol and drug screen; urine pregnancy test.
Synopsis, Criteria for Evaluation	**Primary Endpoint:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit in the CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.	**Primary Endpoint:** The primary efficacy endpoint is the change from baseline to the Day 56 **(± 1 day)** Visit in the **investigator-administered** CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.

Protocol 277-201-00001

Location	Old Text	Updated Text
Synopsis, Criteria for Evaluation	**Other Endpoint(s):** • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/early termination [ET]) in the CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 and Day 56 Visits for the ADHD RS-5 with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups • CGI-I score at each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CAARS–S:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 and Day 56 Visits in the AAQoL score in the OPC-64005, atomoxetine, and placebo groups • OPC-64005 potential for abuse liability and dependence as assessed by the DEQ at baseline and each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET).	**Other Endpoint(s):** • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/early termination [ET]**; all visits have a ± 1-day window**) in the **18-item, investigator-administered** CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits for the **AISRS** with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups • CGI-I score at each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the **18-item** CAARS–S:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits in the AAQoL score in the OPC-64005, atomoxetine, and placebo groups • OPC-64005 potential for abuse liability and dependence as assessed by the DEQ at baseline and each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**).

Protocol 277-201-00001

Location	Old Text	Updated Text
Synopsis, Statistical Methods	**Primary:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit in the CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group. Bayesian posterior probability of true baseline corrected difference at Day 56 between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on CAARS-O:SV given estimates of means and SD in the treatment arms will be calculated. ... The change from baseline in CAARS-O:SV will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week, an interaction term of treatment by visit week, and baseline CAARS-O:SV as covariate. ...	**Primary:** The primary efficacy endpoint is the change from baseline to the Day 56 **(± 1 day)** Visit in the **investigator-administered** CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group. Bayesian posterior probability of true baseline corrected difference at Day 56 **(± 1 day)** between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on **the 18-item, investigator-administered** CAARS-O:SV given estimates of means and SD in the treatment arms will be calculated. ... The change from baseline in **the 18-item, investigator-administered** CAARS-O:SV will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week, an interaction term of treatment by visit week, and baseline **18-item, investigator-administered** CAARS-O:SV as covariate. ...
Synopsis, Trial Duration	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 11 months. The duration of the trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a safety follow-up phone call at Day 59 or discontinuation (± 1 day), and a 30 (+ 2)-day safety follow-up phone call).	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately **9** months. The duration of the trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a **3** [± 1]-day safety follow-up phone call, and a 30 [+ 2]-day safety follow-up phone call).

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 1.1.1, Efficacy Pharmacology	OPC-64005 also shows selective affinities for human 5-HT, NE, and DA transporters (inhibition constant values = 1.62, 6.57, and 123.06 nmol/L, respectively).[2,3] In addition, OPC-64005 has the potential to modulate monoamine systems. An in vivo microdialysis study demonstrated that extracellular 5-HT, NE, and DA levels in the rat medial prefrontal cortex were dose dependent and simultaneously increased by OPC-64005 from lower doses than paroxetine, sertraline, duloxetine, and bupropion.[4,5] In addition, OPC-64005, orally administered at doses of 0.2 mg/kg and greater, produced statistically significant increases in extracellular 5-HT, NE, and DA (area under the curve as an integrated measurement of percent of basal values during 0 to 360 minutes after administration) to 206.7%, 176.5%, and 164.8%, respectively, of the vehicle group. In the medial prefrontal cortex, where there is a low density of dopamine transporter (DAT), extracellular DA levels are thought to be regulated by norepinephrine transporter (NET).[6] The effects of DAT inhibition on the extracellular DA level were therefore evaluated in the striatum, where there is a high density of DAT. OPC-64005 significantly increased extracellular DA levels in the rat striatum at 2.5 mg/kg and greater.[7]	OPC-64005 shows selective affinities for human 5-HT, NE, and DA transporters (inhibition constant values = 1.62, 6.57, and 123.06 nmol/L, respectively).[2,3] In addition, OPC-64005 has **demonstrated** the potential to modulate monoamine systems. In vivo microdialysis demonstrated that extracellular 5-HT, NE, and DA levels in the rat medial prefrontal cortex were dose dependent and simultaneously increased by OPC-64005 **with greater potency relative to** paroxetine, sertraline, duloxetine, and bupropion.[4,5] In addition, OPC-64005, orally administered at doses of 0.2 mg/kg and greater, produced statistically significant increases in extracellular 5-HT, NE, and DA (area under the curve as an integrated measurement of percent of basal values during 0 to 360 minutes after administration) to 206.7%, 176.5%, and 164.8%, respectively, **compared to** the vehicle group. In the medial prefrontal cortex, where there is a low density of dopamine transporter (DAT), extracellular DA levels are thought to be regulated by norepinephrine transporter (NET).[6] The effects of DAT inhibition on the extracellular DA level were therefore evaluated in the striatum, where there is a high density of DAT. OPC-64005 significantly increased extracellular DA levels in the rat striatum at 2.5 mg/kg and **higher doses**.[7]
Section 1.1.1, Efficacy Pharmacology	From the results of these nonclinical pharmacology studies, OPC-64005 may have the potential to improve depression related to monoamine dysfunction.	From the results of these nonclinical pharmacology studies, OPC-64005 may have the potential to improve **depressive symptoms** related to monoamine **imbalance**.
Section 1.1.4.2, Repeated-dose Toxicity	Limb tremor in both sexes and decreased body weight or suppressed body weight gain in females were observed at 10 mg/kg/day.	Limb tremor **(males and females),** decreased body weight**,** or suppressed body weight gain in females were observed at 10 mg/kg/day.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 1.2.2, Phase 1 Single-Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-10-001)	This trial was designed to administer a single dose of OPC-64005 at doses of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, or placebo to healthy adult males, and to randomize 8 subjects each (6 subjects for OPC-64005 and 2 subject for placebo) and 9 subjects each (6 subjects for OPC-64005 and 3 subjects for placebo) to the 1 to 20 mg groups and the 25 to 70 mg groups, respectively. However, only up to the 60 mg dose was used.	This trial was designed to **assess the pharmacokinetics (PK), safety, and tolerability of** a single dose of OPC-64005 at doses of 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, or placebo to healthy adult males, and to randomize 8 subjects each (6 subjects for OPC-64005 and 2 subject for placebo) and 9 subjects each (6 subjects for OPC-64005 and 3 subjects for placebo) to the 1 to 20 mg groups and the 25 to 70 mg groups, respectively. However, 60 mg was **the highest** dose **assessed in this trial**.
Section 1.2.2, Phase 1 Single-Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-10-001)	Therefore, another cohort for 60 mg OPC-64005 was established again for further assessment to determine the maximum tolerated dose (MTD). As a result, the MTD was considered hardly possible to determine in this trial for the following reasons: The dosage in this cohort did not violate the MTD defined in the protocol; supraventricular tachycardia observed in this subject was difficult to assess; and the investigator and subinvestigator did not change the assessment of 'nonserious' for supraventricular tachycardia even after the Sponsor had assessed the event as serious. Although the result suggested the possibility to proceed to the next dose step of 70 mg, the dose escalation in this trial was terminated at a dose of 60 mg.	The MTD was **not determined** in this trial for the following reasons: this cohort did not **meet** the **definition of** MTD **as** defined in the protocol; supraventricular tachycardia observed in this subject was difficult to assess; and the investigator and subinvestigator did not change the assessment of 'nonserious' for supraventricular tachycardia even after the Sponsor had assessed the event as **'**serious**'**. Although the result suggested the possibility to proceed to the next dose step of 70 mg, dose escalation in this trial was terminated at a dose of 60 mg.
Section 1.2.3, Phase 1 Multiple-Dose Trial to Evaluate Pharmacokinetics, Safety, and Pharmacodynamics in Healthy Adult Male and Female Subjects (United States, 277-10-206)	The 30-mg dose of OPC-64005 demonstrated significant effects in cerebrospinal fluid (CSF) reuptake in NE and 5-HT, but no statistically significant effect on DA. Plasma monoamine changes for OPC-64005 in the NE and 5-HT systems were consistent with those found in CSF. Bupropion, which was believed to be a comparator for DA activity, showed no statistically significant activity on any of the monoamine transmitters or their metabolites in CSF.	**Assays to detect the presence of neurotransmitter metabolites** in cerebrospinal fluid (CSF) **suggested that** the 30 mg dose of OPC-64005 **had a** significant **impact on** reuptake **inhibition for** NE and 5-HT. **However, there was no clear evidence of** DA **related metabolites** in CSF i**n either OPC-64005 samples or in those collected from subjects who received** bupropion **(positive control)**.

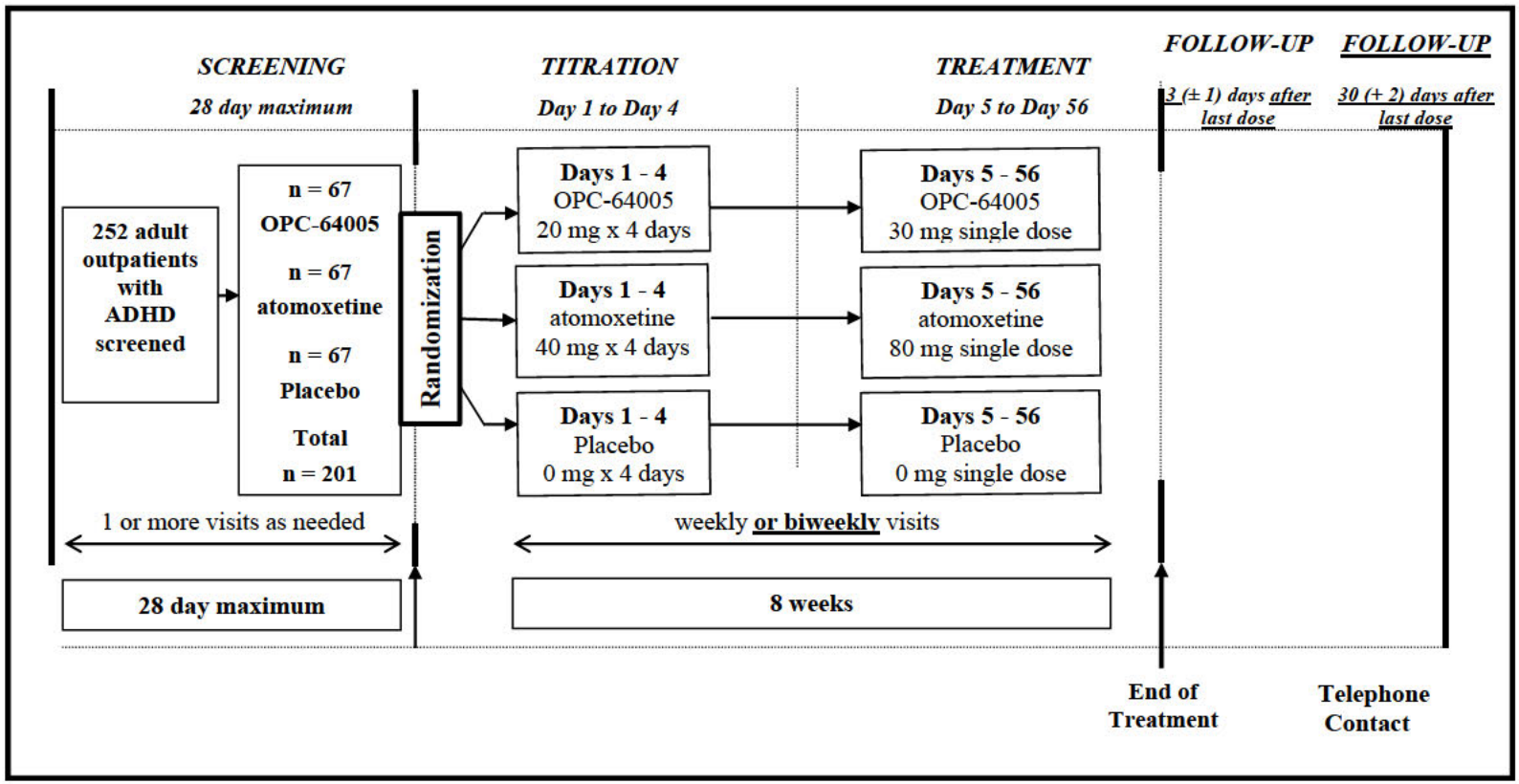
Protocol 277-201-00001

Location	Old Text	Updated Text
Section 1.2.4, Phase 1, Multiple Ascending Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-12-001)	After the completion of Cohort 2 (30 mg), it was decided not to proceed with Cohort 3 (60 mg), because sufficient data for pharmacokinetic (PK) and safety were obtained from Cohorts 1 and 2.	After the completion of Cohort 2 (30 mg), **the decision** was **made** not to proceed with Cohort 3 (60 mg) because sufficient data for PK and safety were obtained from Cohorts 1 and 2.
Section 1.2.4, Phase 1, Multiple Ascending Dose Trial in Healthy Adult Male Subjects (Japan, Trial 277-12-001)	The TEAEs observed during the trial were nausea, somnolence, and rash pruritic and all were reported in the OPC-64005 group: rash pruritic, 1 subject (1/6) in the 20 mg OPC-64005 group: nausea, 2 subjects (2/6) in the 30 mg OPC-64005 group: somnolence, 1 subject (1/6) in the 30 mg OPC-64005 group.	The TEAEs observed during the trial were nausea, somnolence, and **pruritic rash** and all were reported in the OPC-64005 group: **pruritic rash**, 1 subject (1/6) in the 20 mg OPC-64005 group: nausea, 2 subjects (2/6) in the 30 mg OPC-64005 group: somnolence, 1 subject (1/6) in the 30 mg OPC-64005 group.
Section 1.2.5, Phase 1 Trial to Evaluate Serotonin, Norepinephrine, and Dopamine Transporter Occupancy in Healthy Adult Male Subjects (United States, 277-10-205)	The times of postdose scans were to be at approximately 3 hours and at 16 to 24 hours postdose, as feasible.	The times of postdose scans **occurred** at approximately 3 hours and at 16 to 24 hours postdose, as feasible.
Section 1.3, Known and Potential Risks and Benefits	The subjects will not derive any benefit from this trial.	The subjects **may or may** not derive any benefit from this trial.
Section 3.1, Type/Design of Trial	The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur at Day 59 or discontinuation (± 1 day), and a follow-up telephone contact to occur 30 (+ 2) days after the last treatment.	The trial includes a Screening Period (≤ 28 days), a 4-day titration period, a 52-day treatment period, a follow-up telephone contact to occur **3** (± 1) **days after the last dose**, and a follow-up telephone contact to occur 30 (+ 2) days after the last **dose**.
Section 3.1, Type/Design of Trial	During the Treatment Period (Days 5 - 56), subjects who were randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. ... During the 8-week Titration/Treatment Period, subjects will have visits to the clinical site. Critical and non-standard trial assessments to be performed during the trial are listed in Table 3.7-1.	During the Treatment Period (Days 5 - 56), subjects who **are** randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. ... During the 8-week Titration/Treatment Period, subjects will have weekly **or biweekly** visits to the clinical site. Assessments to be performed during the trial are listed in Table 3.7-1.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.1, Type/Design of Trial	If any subject discontinues the trial early, every effort should be made to complete the Day 56/early termination (ET) evaluations. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or clinic visit at Day 59 or discontinuation (± 1 day) and 30 (+ 2) days after the last dose of OPC-64005, atomoxetine, or placebo. The total duration of this trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a safety follow-up phone call at Day 59 or discontinuation (± 1 day), and a 30 (+ 2)-day safety follow-up phone call).	If any subject discontinues the trial early, every effort should be made to complete the Day 56 **(± 1 day)**/early termination (ET) evaluations. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone at **3** (± 1) days and 30 (+ 2) days after the last dose of OPC-64005, atomoxetine, or placebo. The total duration of this trial for each subject is estimated to be up to 16 weeks (Screening Period of up to 28 days, 56 days of dosing, a **3** [± 1]-day safety follow-up phone call, and a 30 [+ 2]-day safety follow-up phone call).
Figure 3.1-1, Trial Design Schematic	Changes to Figure 3.1-1 are summarized on the next page and are indicated by **bold, underlined** text.	

Protocol 277-201-00001



Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.2, Trial Treatments	During the Treatment Period, subjects in the OPC-64005 group will receive daily 30-mg oral doses of OPC-64005. During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. Subjects in the atomoxetine group will receive daily 80-mg oral doses of atomoxetine. During the Treatment Period, if a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects in the placebo group will receive daily oral doses of both OPC-64005 and atomoxetine placebo. All tablets/capsules are to be taken together orally once daily and can be taken without regard to meals. Every effort should be made to take the IMP at the same time every day.	During the Treatment Period, subjects in the OPC-64005 group will receive daily 30-mg oral doses of OPC-64005 **and atomoxetine placebo**. During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. Subjects in the atomoxetine group will receive daily 80-mg oral doses of atomoxetine **and OPC-64005 placebo**. During the Treatment Period, if a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. **Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial.** Subjects in the placebo group will receive daily oral doses of both OPC-64005 **placebo** and atomoxetine placebo. All tablets/capsules are to be taken together orally once daily and can be taken without regard to meals. Every effort should be made to take the IMP at the same time **every morning,** every day.
Table 3.2-1, Dosing Schedule	Time 8:00am	Time 8:00 am **(AM dosing)**

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.2-1, Dosing Schedule	[a]Blood samples for PK analyses will be collected predose and at 1 and 3 hours postdose at the Baseline (Day 1) Visit, predose and at 2 hours postdose at the Day 7 Visit, predose and at 3 hours postdose at the Day 14 Visit, and predose at the Day 21 Visit. [b]May be reduced to 20 mg if 40 mg dose is not tolerable. [c]May be reduced to 40 mg if 80 mg dose is not tolerable.	[a]Blood samples for PK analyses will be collected predose and at 1 and 3 hours postdose at the Baseline (Day 1) Visit, predose and at 2 hours postdose at the Day 7 **(± 1 day)** Visit, predose and at 3 hours postdose at the Day 14 **(± 1 day)** Visit, and predose at the Day 21 **(± 1 day)** Visit. [b]May be reduced to 20 mg if **the 30** mg dose is not tolerable. **Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005) during the trial.** [c]May be reduced to 40 mg if **the** 80 mg dose is not tolerable. **Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 80 mg for atomoxetine) during the trial.**
Section 3.3.1, Number of Subjects and Description of Population	Approximately 252 adult (18 - 55 years) subjects with a diagnosis of ADHD will be screened to randomize approximately 201 subjects to have approximately 150 completers (50 completers per arm).	Approximately 252 adult (18 - 55 years) subjects with a diagnosis of ADHD will be screened to randomize approximately 201 subjects to **yield** approximately 150 completers.
Section 3.3.1, Number of Subjects and Description of Population	Subjects must meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria for ADHD (any type) as confirmed by the Conners' Adult ADHD Diagnostic Interview for *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) (CAADID) (The CAADID will be adapted to be consistent with the DSM-5) to be considered for enrollment.[49]	Subjects must meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria for ADHD (any **presentation**) as confirmed by the **Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2)**.[49]
Section 3.3.1, Number of Subjects and Description of Population	Subjects identified with bipolar disorder, schizophrenia, or other psychotic disorder or current Axis II personality disorder will not be eligible for enrollment. Subjects must have a history of successful treatment with stimulants or nonstimulant ADHD medication.	Subjects identified with **a current or lifetime history of** bipolar disorder, schizophrenia, other psychotic disorder, or personality disorder will not be eligible for enrollment. Subjects must have a history of **adequate symptom reduction** with stimulants or nonstimulant ADHD medication.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.3.1, Number of Subjects and Description of Population	At screening, subjects not currently receiving treatment for ADHD must have an ADHD Rating Scale based on DSM-5 criteria (ADHD RS-5) with Adult Prompts score of ≥ 26. Subjects receiving any treatment for ADHD at screening must have an ADHD RS-5 with Adult Prompts score of ≥ 22 and will wash out from their current ADHD therapy prior to the baseline (ie, Day 1) evaluations for a period equivalent to 5 half-lives. At baseline, all subjects must have an ADHD RS-5 with Adult Prompts score of ≥ 26 to be enrolled.	At screening, subjects not currently receiving **an approved pharmacological** treatment for ADHD must have an **Adult ADHD Investigator Symptom Rating Scale (AISRS)** with Adult Prompts score of ≥ 26. Subjects receiving any **pharmacological** treatment for ADHD at screening must have an **AISRS** with Adult Prompts score of ≥ 22 and will wash out from their current ADHD therapy prior to the baseline (ie, Day 1) evaluations for a period equivalent to 5 half-lives. At baseline, all subjects must have an **AISRS** with Adult Prompts score of ≥ 26 to be enrolled.
Section 3.3.2, Subject Selection and Numbering	Subjects will be assigned a unique subject number upon enrollment, prior to dosing on Day 1.	Subjects will be assigned a unique subject number upon **randomization**, prior to dosing on Day 1.
Table 3.4.2-1, Inclusion Criteria	4. Subjects with a primary DSM-5 diagnosis of ADHD (including inattentive, hyperactive, and combined subtypes) as confirmed by the CAADID (The CAADID will be adapted to be consistent with the DSM-5). Subjects may have received prior treatment for adult ADHD or may be currently receiving treatment for adult ADHD at screening.	4. Subjects with a primary DSM-5 diagnosis of ADHD (including **predominantly** inattentive **presentation**, hyperactive **presentation**, and combined **presentations**) as confirmed by the **ACDS v1.2**. Subjects **must** have received prior **successful** treatment **(pharmacotherapy)** for adult ADHD **based on medical records and the principal investigator's judgment. Subjects** may be currently receiving treatment for adult ADHD at screening**, but it is not necessary that they are currently receiving treatment**. **The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability.**
Table 3.4.2-1, Inclusion Criteria	5. Subjects who are not currently receiving treatment for ADHD who have an ADHD RS-5 with Adult Prompts score of ≥ 26 and subjects who are receiving any treatment for ADHD at screening who have an ADHD RS-5 with Adult Prompts score of ≥ 22.	5. Subjects who are not currently receiving **an approved pharmacological** treatment for ADHD who have an **AISRS** with Adult Prompts score of ≥ 26 and subjects who are receiving any **pharmacological** treatment for ADHD at screening who have an **AISRS** with Adult Prompts score of ≥ 22.
Table 3.4.2-1, Inclusion Criteria	7. Subjects willing to discontinue all prohibited psychotropic medication starting from the time of signing the informed consent and during the trial period.	7. Subjects willing to discontinue all prohibited psychotropic medication starting from the time of signing the informed consent and **up to the 30 (+ 2)-day follow-up** period.
Table 3.4.2-1, Inclusion Criteria	8. Subjects who have an ADHD RS-5 with Adult Prompts score of ≥ 26.	8. Subjects who have an **AISRS** with Adult Prompts score of ≥ 26.

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.4.3-1, Exclusion Criteria	3. Subjects with an inadequate response to atomoxetine taken after 18 years of age (ie, in the investigator's opinion, the subject was treated with an adequate dose for an adequate period of time, yet failed to show satisfactory response).	3. Subjects with **a history of** inadequate response **or suboptimal tolerability** to atomoxetine**.** (In the investigator's opinion, the subject was treated with an adequate dose for an adequate period of time, yet failed to show satisfactory response.)
Table 3.4.3-1, Exclusion Criteria	6. Subjects who report allergies or an intolerability (lifetime treatment history) to stimulant or nonstimulant ADHD medications.	6. Subjects who report allergies (lifetime treatment history) to stimulant or nonstimulant ADHD medications.
Table 3.4.3-1, Exclusion Criteria	8. Subjects with other DSM-5 Axis I disorders including history of psychosis (current or lifetime), current bipolar disorder, current major depressive disorder, or current panic disorder; or subject has a controlled (requiring a prohibited medication) or uncontrolled comorbid psychiatric condition with significant symptoms such as any severe DSM-5 Axis I or II disorders or other psychopathological or abnormal behavioral manifestations that, in the opinion of the principal investigator, will confound efficacy or safety assessments of the trial, or interfere with participation in the trial otherwise. Psychiatric diagnosis will be established using the M.I.N.I.	8. Subjects with other DSM-5 disorders including psychosis (current or lifetime), bipolar disorder **(current or lifetime)**, current major depressive disorder, or current panic disorder; or **another** psychiatric **diagnosis** that the investigator **believes is primary or that** will confound efficacy or safety assessments of the trial or interfere with participation in the trial otherwise. Psychiatric diagnosis will be established using the M.I.N.I.
Table 3.4.3-1, Exclusion Criteria	9. Subjects with a clinically significant current Axis II (DSM-5) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder.	9. Subjects with a clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, **narcissistic, avoidant, obsessive compulsive,** or **dependent** personality disorder**s**.
Table 3.4.3-1, Exclusion Criteria	10. Subjects receiving new onset psychotherapy (individual, group, marriage, or family therapy) within 42 days of screening or at any time during participation in the trial.	10. Subjects receiving new onset psychotherapy (**eg,** individual, group, marriage, or family therapy) within 42 days of screening or **who will initiate psychotherapy** at any time during participation in the trial. **Those who are receiving ongoing psychotherapy for over 42 days are permitted to enroll. Psychotherapy should not be started or changed during a subject's participation in the trial.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.4.3-1, Exclusion Criteria	11. Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months, OR Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months OR Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, OR Subjects who, in the opinion of the investigator, present a serious risk of suicide.	11. Subjects who **meet criteria for** C-SSRS Suicidal Ideation Item**s** 4 **or 5** within the last 6 months or subjects who **meet criteria for** any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, OR Subjects who, in the opinion of the investigator, present a serious risk of suicide.
Table 3.4.3-1, Exclusion Criteria	12. Subjects who have met DSM-5 criteria for substance use disorder within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.	12. Subjects who have met DSM-5 criteria for substance use disorder within the past 180 days; including **all substances of potential abuse**, excluding caffeine and nicotine.
Table 3.4.3-1, Exclusion Criteria	14. Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C.	14. Subjects who currently have clinically significant **dermatological,** neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, **or active or** chronic hepatitis B or C.
Table 3.4.3-1, Exclusion Criteria	20. Subjects with known mental retardation defined as an IQ less than 75, or clinical evidence of mental retardation based on the opinion of the investigator.	20. Subjects with known **intellectual disability (intellectual developmental disorder), including mild adaptive functioning impairment**, or clinical evidence of **intellectual disability** based on the opinion of the investigator.

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.4.3-1, Exclusion Criteria	21. Subjects with a positive drug screen for cocaine or other illicit drugs will be excluded and may not be retested or re-screened. Subjects with a positive urine drug screen resulting from use of prescription or OTC medications.	21. Subjects with a positive drug screen for cocaine or other illicit drugs will be excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or OTC medications **may be retested or rescreened, at the discretion of the investigator**.
Table 3.4.3-1, Exclusion Criteria	27. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.	27. Prisoners or subjects who are compulsorily detained (involuntarily **hospitalized or** incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
Section 3.5.1, Primary Endpoint	The primary efficacy endpoint is the change from baseline to the Day 56 Visit in the Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.	The primary efficacy endpoint is the change from baseline to the Day 56 **(± 1 day)** Visit in the **investigator-administered** Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.5.2, Other Endpoint(s)	Other efficacy endpoints are • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 and Day 56 Visits for the ADHD RS-5 with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups • CGI-I score at each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the OPC-64005 group relative to the atomoxetine, and placebo groups • Change from baseline to each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) in the Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV) score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 and Day 56 Visits in the Adult ADHD Quality of Life Scale (AAQoL) score in the OPC-64005 group relative to the atomoxetine and placebo groups • OPC-64005 potential for abuse liability and dependence as assessed by the Drug Effects Questionnaire (DEQ) at baseline and each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET)	Other efficacy endpoints are • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the **18-item, investigator-administered** CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits for the **AISRS** with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups • CGI-I score at each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the OPC-64005 group relative to the atomoxetine, and placebo groups • Change from baseline to each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) in the **18-item** Conners' Adult ADHD Rating Scales–Self-Report: Screening Version (CAARS-S:SV) score in the OPC-64005 group relative to the atomoxetine and placebo groups • Change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits in the Adult ADHD Quality of Life Scale (AAQoL) score in the OPC-64005 group relative to the atomoxetine and placebo groups • OPC-64005 potential for abuse liability and dependence as assessed by the Drug Effects Questionnaire (DEQ) at baseline and each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**)

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.6, Measures to Minimize/Avoid Bias	Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the interactive voice response system/interactive web response system (IVRS/IWRS), and reporting SAEs to regulatory agencies.	Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the interactive voice response system/interactive web response system (IVRS/IWRS), and reporting SAEs to regulatory agencies. **The interim analysis will be conducted by an independent biostatistician from the OPDC Data Sciences Department and the treatment code will remain blinded for all others until the unblinding at the final analysis after trial completion.**
Table 3.7-1, Schedule of Assessments	Changes to Table 3.7-1 are summarized on the next page and are indicated by **bold, underlined** text.	

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
ENTRANCE CRITERIA										
Inclusion/exclusion criteria	X	X								
Demographic information	X									
Medical history	X									
Psychiatric history to confirm DSM-5 ADHD diagnosis using **the ACDS v1.2**	X									
Identification of comorbidities using **the** M.I.N.I.	X									
Investigator assessment of **previous and** current ADHD treatment	X	X								
HIV, HBsAg, and anti-HCV	X									
Urine pregnancy test[a]	X	X				**X**		X		
SAFETY										
Physical examination[b]	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X		X	X	X		
Clinical laboratory	X	X				X		X		
Urine alcohol and drug screen	X							X		
C-SSRS	X	X	X	X	X	X	X	X		

Protocol 277-201-00001

Table 3.7-1 Schedule of Assessments										
Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
EFFICACY										
18-item, investigator-administered CAARS-O:SV[c]	X	X	X	X	X	X	X	X		
AISRS with Adult Prompts	X	X				X		X		
CGI-S	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X		
18-item CAARS-S:SV[c]		X	X	X	X	X	X	X		
AAQoL		X				X		X		
POMS	X	X	X	X	X	X	X	X		
CLINIC PROCEDURES										
IMP administration[d]		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
PK blood samples		X[e]	X[f]	X[g]	X[h]					
Pharmacogenomic sample for CYP2D6 testing		X								
FBR blood sample[i]		X								
DEQ		X	X	X	X	X	X	X		
Record AEs	X	X	X	X	X	X	X	X	X	X
Record concomitant medication	X	X	X	X	X	X	X	X	X	X
Telephone contact									X	X

FBR = future biospecimen research; **POMS** = Profile of Mood States**-Brief Form**™.

...

[b] A physical examination will be performed at the Screening, Baseline, and Day 56 **(± 1 day)**/ET Visits. Weight, height, and waist circumference will be recorded at **the** Screening Visit. A focused examination for **the** detection of rash will be performed at the Day 7, 14, 21, 28, and 42 Visits**; all visits have a ± 1-day window**. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged.

Protocol 277-201-00001

[c]The **18-item** CAARS-S:SV should be conducted before the **18-item, investigator-administered** CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.

[d]**Subjects will receive daily doses of IMP starting on Day 1. At the baseline visit, subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to 7. During the treatment period, subjects will receive a treatment card(s) for dosing on scheduled visits.**

[e]Day 1 samples collected predose and 1 and 3 hours postdose.

[f]Day 7 **(± 1 day)** samples collected predose and 2 hours postdose.

[g]Day 14**(± 1 day)** samples collected predose and 3 hours postdose.

[h]Day 21 **(± 1 day)** samples collected predose.

[i]**FBR sample will be collected once the subject has provided consent for FBR.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.1, Screening	• Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ADHD using the CAADID (The CAADID will be adapted to be consistent with the DSM-5).	• Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ADHD using the **ACDS v1.2**.
Section 3.7.1.1, Screening	• The investigator will assess and record previous ADHD medications. Subjects must have a history of successful treatment with stimulants or nonstimulant ADHD medication.	• The investigator will assess and record previous ADHD medications. Subjects must have a history of **adequate symptom reduction** with stimulants or nonstimulant ADHD medication.
Section 3.7.1.1, Screening	• A complete physical examination will be performed.	• A physical examination will be performed.
Section 3.7.1.1, Screening	• Vital sign measurements (including blood pressure and pulse) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes.	• Vital sign measurements (including **body temperature,** blood pressure, pulse, **and respiratory rate**) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
Section 3.7.1.1, Screening	• The ADHD RS-5 with Adult Prompts will be administered. Subjects not currently receiving treatment for ADHD must have an ADHD RS-5 with Adult Prompts score of ≥ 26. Subjects receiving any treatment for ADHD at screening must have an ADHD RS-5 with Adult Prompts score of ≥ 22.	• The **AISRS** with Adult Prompts will be administered. Subjects not currently receiving **an approved pharmacological** treatment for ADHD must have an **AISRS** with Adult Prompts score of ≥ 26. Subjects receiving any **pharmacological** treatment for ADHD at screening must have an **AISRS** with Adult Prompts score of ≥ 22.
Section 3.7.1.1, Screening	• A qualified and certified rater will administer the investigator-rated CAARS-O:SV.	• A qualified and certified rater will administer the investigator-rated **18-item** CAARS-O:SV.
Section 3.7.1.1, Screening	• The Profile of Mood States 2nd Edition™ (POMS 2-A) will be administered.	• The Profile of Mood States-**Brief Form™** (**POMS**) will be administered.
Section 3.7.1.2, Baseline (Day 1)	• A complete physical examination will be performed.	• A physical examination will be performed.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.2, Baseline (Day 1)	• Vital sign measurements (including blood pressure and pulse) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes.	• Vital sign measurements (including **body temperature,** blood pressure, pulse, **and respiratory rate**) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
Section 3.7.1.2, Baseline (Day 1)	• The ADHD RS-5 with Adult Prompts will be administered. Subjects must have an ADHD RS-5 with Adult Prompts score of ≥ 26.	• The **AISRS** with Adult Prompts will be administered. Subjects must have an **AISRS** with Adult Prompts score of ≥ 26.
Section 3.7.1.2, Baseline (Day 1)	• The subject will complete the CAARS-S:SV. The CAARS-S:SV should be conducted before the CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.	• The subject will complete the **18-item** CAARS-S:SV. The **18-item** CAARS-S:SV should be conducted before the **18-item, investigator-administered** CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.
Section 3.7.1.2, Baseline (Day 1)	• A qualified and certified rater will administer the investigator-rated CAARS-O:SV.	• A qualified and certified rater will administer the investigator-rated **18-item** CAARS-O:SV.
Section 3.7.1.2, Baseline (Day 1)	• Blood samples for FBR will be collected.	• Blood samples for FBR will be collected (**once the subject has provided consent for FBR)**.
Section 3.7.1.2, Baseline (Day 1)	• The POMS 2-A will be administered.	• The **POMS** will be administered.
Section 3.7.1.2, Baseline (Day 1)	Not applicable (newly added text)	• **Subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to 7.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At each visit, a focused physical examination for the presence of rash will be performed. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged. A complete physical examination will be performed at the Day 56/ET Visit. See Section 3.7.3.3 for a description of follow-up activities to be completed if rash is detected.	• At each visit, a focused physical examination for the presence of rash will be performed. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged. A complete physical examination will be performed at the Day 56 **(± 1 day)**/ET Visit. See Section 3.7.3.3 for a description of follow-up activities to be completed if rash is detected. **The investigator must immediately report any instances of rash to the Clinical Research Organization (CRO) medical monitor.**
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At each visit, vital sign measurements (including blood pressure and pulse) will be recorded. Blood pressure and pulse are to be measured after the subject has been in the sitting position at least 5 minutes. At the Day 14, 28, 42, and 56 Visits, a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes.	• At each visit, vital sign measurements (including **body temperature**, blood pressure, pulse, **and respiratory rate**) will be recorded. Blood pressure and pulse are to be measured after the subject has been in the sitting position at least 5 minutes. Respiratory rate at each visit will be performed after the subject has been in the sitting position for at least 5 minutes. At the Day 14, 28, 42, and 56 Visits **(all visits have a ± 1-day window)**, a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At the Day 28 and 56 Visits, blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1).	• At the Day 28 **(± 1 day)** and **Day** 56 **(± 1 day)** Visits, blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1).
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• A urine pregnancy test will be performed for all WOCBP at the Day 56/ET Visit. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.	• A urine pregnancy test will be performed for all WOCBP at the **Day 28 (± 1 day) and** Day 56 **(± 1 day)**/ET Visit**s**. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	Not applicable (newly added text)	• **Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and marijuana at the Day 56 (± 1 day)/ET Visit.**
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At the Day 28 and 56 Visits, the ADHD RS-5 with Adult Prompts will be administered.	• At the Day 28 **(± 1 day)** and **Day** 56 **(± 1 day)** Visits, the **AISRS** with Adult Prompts will be administered.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• The subject will complete the CAARS-S:SV. The CAARS-S:SV should be conducted before the CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.	• The subject will complete the **18-item** CAARS-S:SV. The **18-item** CAARS-S:SV should be conducted before the **18-item, investigator-administered** CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At each visit, a qualified and certified rater will administer the investigator-rated CAARS-O:SV.	• At each visit, a qualified and certified rater will administer the investigator-rated **18-item** CAARS-O:SV.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At each visit, the POMS 2-A will be administered.	• At each visit, the **POMS** will be administered.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• Blood samples for PK analyses will be collected predose and at 2 hours postdose at the Day 7 Visit, predose and at 3 hours postdose at the Day 14 Visit, and predose at the Day 21 Visit.	• Blood samples for PK analyses will be collected predose and at 2 hours postdose at the Day 7 **(± 1 day)** Visit, predose and at 3 hours postdose at the Day 14 **(± 1 day)** Visit, and predose at the Day 21 **(± 1 day)** Visit.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	• At the Day 28 and 56 Visits, the subject will complete the AAQoL.	• At the Day 28 **(± 1 day)** and **Day** 56 **(± 1 day)** Visits, the subject will complete the AAQoL.
Section 3.7.1.3, Treatment Period Visits (Day 7 through Day 56 Visits)	Not applicable (newly added text)	• **Subjects will receive a treatment card(s) for dosing on scheduled visits.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.4, Safety Follow-up Period	A follow-up telephone contact will occur at Day 59 or discontinuation (± 1 day). A follow-up telephone contact will occur 30 (+ 2) days after the last dose of IMP for all subjects (completers and early withdrawals).	A follow-up telephone contact will occur **3** (± 1) **days and** 30 (+ 2) days after the last dose of IMP for all subjects (completers and early withdrawals).
Section 3.7.2.1, Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV)	3.7.2.1 Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV) The CAARS-O:SV is designed to measure a cross-section of ADHD-related symptoms and behaviors in adults using observer scales.[52] The screening version of the CAARS that is being used to monitor ADHD symptoms in this trial can be administered by an appropriately trained and qualified clinician in approximately 10 minutes. The CAARS-O:SV consists of 30 items that are each scored on a 4-point scale as follows: 0 = not at all, never; 1 = just a little, once in a while; 2 = pretty much, often; and 3 = very much, very frequently based on the extent to which the item is applicable to the individual being evaluated. For analysis purposes, the 30 items of the scale are grouped into 3 subscales: Inattentive Symptoms (9 items), Hyperactive/Impulsive Symptoms (9 items), and ADHD Index (12 items). The primary evaluation of ADHD will be based on the 18-item ADHD Symptoms Total Score, which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales.	3.7.2.1 Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV; **Investigator-Administered**) The **investigator-administered** CAARS-O:SV **(Appendix 4)** is designed to measure a cross-section of ADHD-related symptoms and behaviors in adults using observer scales.[52] The **investigator-administered** CAARS-O:SV consists of 30 items grouped into 3 subscales: Inattentive Symptoms (9 items), Hyperactive/Impulsive Symptoms (9 items), and ADHD Index (12 items). **As is frequently done in adult ADHD trials, items will be modified using the Adler adult prompts and only the 18 DSM-5 criteria relevant items (9 Inattentive and 9 Hyperactive/Impulsive) will be administered.** The primary **efficacy assessment** of ADHD **symptoms is** the ADHD Symptoms Total Score, which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales. The **18-item scale** can be administered by an appropriately trained and qualified clinician in approximately **20 to 30** minutes.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.2.2, Conners' Adult ADHD Rating Scale-Self Report: Screening Version (CAARS-S:SV)	The CAARS-S:SV includes the same 30 items used for the CAARS-O:SV, worded in the first person for the subject's impressions of ADHD behaviors (eg, "I talk too much," "I am always on the go..."etc). The subjects will score each of the items on a 4-point scale as follows: 0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; and 3 = Very much, very frequently.[52] For analysis purposes, the 30 items of the scale are grouped into 3 subscales: Inattentive Symptoms (9 items), Hyperactive/Impulsive Symptoms (9 items), and ADHD Index (12 items). The evaluation of ADHD will be based on the 18-item ADHD Symptoms Total Score which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales. The screening version of the CAARS-S:SV that is being used to monitor self-reported ADHD symptoms in this trial can be completed in approximately 10 minutes.	The CAARS-S:SV **(Appendix 5)** includes the same 30 items **as** the **investigator-administered CAARS-O:SV**, worded in the first person for the subject's impressions of **their own** ADHD behaviors (eg, "I talk too much," "I am always on the go...").[52] **As with the investigator-administered CAARS-O:SV, administration of the CAARS-S:SV in the current trial will be limited to the 18 DSM-5 criteria relevant items (9 Inattentive Symptoms and 9 Hyperactive/Impulsive Symptoms subscales).** The evaluation of ADHD **symptoms** will be based on the 18-item ADHD Symptoms Total Score, which consists of the combined score for the Inattentive Symptoms and Hyperactive/Impulsive Symptoms subscales. The CAARS-S:SV can be completed in approximately 10 minutes.
Section 3.7.2.3, ADHD Rating Scale based on DSM-5 Criteria (ADHD RS-5 with Adult Prompts)	3.7.2.3 ADHD Rating Scale based on DSM-5 Criteria (ADHD RS-5 with Adult Prompts The ADHD RS-5 with Adult Prompts is an 18-item scale based on the DSM-5 criteria for ADHD that provides a rating of the severity of symptoms.[53] The first 9 items assess inattentive symptoms, and the last 9 items assess hyperactive-impulsive symptoms. Scoring is based on a 4-point severity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.	3.7.2.3 **Adult** ADHD **Investigator Symptom** Rating Scale (**AISRS** With Adult Prompts **The AISRS (Appendix 6) was published in 2010 by Drs. Lenard Adler, Thomas Spencer, and Joseph Biederman of New York University and Massachusetts General Hospital.[53] The AISRS consists of the 18 DSM ADHD symptoms with adult-relevant wording. It has been validated for use as a primary efficacy scale in adult ADHD treatment trials.**
Section 3.7.2.4, Clinical Global Impression - Severity of Illness Scale (CGI-S)	To perform this assessment, the investigator or rater will respond to the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.	To perform this assessment, the investigator or rater will respond to the following question: "Considering your total clinical experience with **the ADHD** population, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. **Suggested anchor guidance is provided in Appendix 7.[55]**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.2.5, Clinical Global Impression - Improvement Scale (CGI-I)	The rater or investigator will rate whether the subject's total improvement relative to baseline is due entirely to drug treatment. Response choices include: 0 = not assessed; 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.	The rater or investigator will rate whether the subject's total improvement relative to baseline is due entirely to drug treatment. Response choices include: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. **Suggested anchor guidance is provided in Appendix 8.**[55]
Section 3.7.2.6, Adult ADHD Quality of Life Scale (AAQoL)	The AAQoL is a validated, 29-item instrument for measuring the impact of ADHD symptoms on quality of life.[55]	The AAQoL **(Appendix 9)** is a validated, 29-item instrument for measuring the impact of ADHD symptoms on quality of life.[56]
Section 3.7.2.7, Profile of Mood States 2nd Edition (POMS 2-A)	3.7.2.7 Profile of Mood States 2nd Edition (POMS 2-A) The Profile of Mood States™ (POMS) self-report scales are a collection of tools that allow for the quick assessment of transient, fluctuating feelings, and enduring affect states. The tool is applicable in clinical, medical, research, and athletic settings, where its sensitivity to change makes the assessment ideal for treatment monitoring and evaluation, as well as clinical trials. The POMS 2-A is comprised of 65 items. This full length version yields several scale scores: Anger-Hostility, Confusion Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Vigor-Activity. Total Mood Disturbance is a function of these 6 scale scores. The Friendliness scale is scored separately. These comprehensive versions are recommended for use when a thorough evaluation of mood is desired.	3.7.2.7 Profile of Mood States-**Brief Form** (POMS) **The POMS (Appendix 10) is a 30-item self-report scale that generates the following subscales: Tension or Anxiety, Anger - Hostility, Vigor - Activity, Fatigue - Inertia, Depression - Dejection, and Confusion - Bewilderment.**[57] **These subscales yield an overall total mood score. It will be used in the trial as an exploratory measure to assess potential changes in symptoms often associated with ADHD. The time period of interest for this trial is "during the past week".**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.3.3, Physical Examination and Vital Signs	A physical examination will be performed at screening and at each weekly visit. ... In addition, at each visit during the Treatment Period (ie, beginning with the Day 7 Visit), the physical examination will include a focused examination for the presence of rash. ... The subject should be evaluated by a dermatologist. The rash should be photographed and a punch biopsy performed. At the appearance of or discovery of the rash, vital signs (specifically, body temperature), symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine), a discussion of other possible causes of the rash (eg, allergic, contact dermatitis), and specific location(s) of the rash should be recorded.	A physical examination will be performed at screening**, baseline,** and at **Day 56 (± 1 day)**. ... **A focused examination for the detection of rash, defined as any type of newly acquired skin eruptions that are nontraumatic, will be performed at the** Day 7**, 14, 21, 28, and 42** Visit**s; all visits have a ± 1-day window.** ... **Any rash, regardless of severity or seriousness, will lead to the discontinuation of IMP. Any** subject **who experiences a rash will** be evaluated by a **board-certified or board-eligible** dermatologist. **Depending on the severity, the subject will be asked to have a skin** biopsy performed **of the rash area(s)**. At the appearance of or discovery of the rash, the rash **will** be photographed **by the investigator** and vital signs (specifically, body temperature), symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine), a discussion of other possible causes of the rash (eg, allergic, contact dermatitis), and specific location(s) of the rash should be recorded. **The investigator must immediately report any instances of rash to the CRO medical monitor. Refer to Appendix 11 through Appendix 14 for follow-up activities if rash is detected.**
Section 3.7.3.3, Physical Examination and Vital Signs	Vital signs will be measured and recorded at screening, baseline, and at each weekly visit.	Vital signs will be measured and recorded at screening, baseline, and at each **scheduled** visit.
Section 3.7.3.4, Electrocardiogram Assessments	At Screening, Baseline, and the Day 14, 28, 42, and 56 Visits, a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.	At Screening, Baseline, and the Day 14 **(± 1 day)**, 28 **(± 1 day)**, 42 **(± 1 day)**, and 56 **(± 1 day)** Visits, a standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
Section 3.7.3.5, Columbia-Suicide Severity Rating Scale (C-SSRS)	The since-last-visit version of the C-SSRS will be administered at the Baseline Visit and at each subsequent weekly visit.	The since-last-visit version of the C-SSRS will be administered at the Baseline Visit and at each subsequent **scheduled** visit.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.4.1.1, Pharmacokinetic Blood Samples	Blood samples for the determination of OPC-64005 and its metabolite(s) will be collected at Baseline (Day 1) predose and at 1 and 3 hours postdose, at the Day 7 Visit predose and at 2 hours postdose, at the Day 14 Visit predose and at 3 hours postdose, and at the Day 21 Visit predose. In addition, every effort will be made to obtain a PK blood sample from any subject who experiences an SAE. This sample should be obtained as soon as is practical after the onset of the SAE.	Blood samples for the determination of OPC-64005 and its metabolite(s) will be collected at Baseline (Day 1) predose **(within 15 minutes of dosing)** and at 1 and 3 hours postdose, at the Day 7 **(± 1 day)** Visit predose **(within 5 minutes of dosing)** and at 2 hours postdose, at the Day 14 **(± 1 day)** Visit predose **(within 5 minutes of dosing)** and at 3 hours postdose, and at the Day 21 **(± 1 day)** Visit predose **(within 5 minutes of dosing)**. In addition, every effort will be made to obtain a PK blood sample from any subject who experiences an SAE. This sample should be obtained as soon as is practical after the onset of the SAE. **Every effort should be made to draw the sample at the appropriate time. If a sample cannot be drawn at the designated time, a window of ± 3 minutes for each blood draw is acceptable, provided the exact time of the draw is recorded.**
Section 3.8.3.1, Down Titration of Treatment	During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg for the duration of the Treatment Period.	During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg for the duration of the Treatment Period. **Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial.**
Section 3.8.3.2, Treatment Discontinuation	Not applicable (newly added text)	**If a subject will miss/misses a trial visit, the investigator should contact the medical monitor to discuss the potential to retain the subject. Depending on how many doses of IMP the subject will miss/misses, the sponsor, medical monitor, and investigator will determine if the subject is able to continue in the trial and at which dose the subject will resume, taking into consideration any scheduled and unscheduled dose adjustments.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.8.3.3, Documenting Reasons for Treatment Discontinuation	A subject may discontinue IMP for a number of reasons including those listed below: ... • Rash (see Section 5.3).	A subject may discontinue IMP for a number of reasons including those listed below: ... • Rash **(regardless of severity or seriousness)** (see Section 5.**4**)
Section 3.8.3.4, Withdrawal of Consent	A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.	A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. **If a subject will miss/misses a trial visit, the investigator should contact the medical monitor to discuss the potential to retain the subject. Depending on how many doses of IMP the subject will miss/misses, the sponsor, medical monitor, and investigator will determine if the subject is able to continue in the trial and at which dose the subject will resume, taking into consideration any scheduled and unscheduled dose adjustments.** Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.
Section 3.10, Definition of Completed Subjects	For purposes of this trial, subjects who complete Day 56 Visit will be defined as trial completers.	For purposes of this trial, subjects who complete Day 56 **(± 1 day)** Visit will be defined as trial completers.
Table 4.1-1, List of Medications Prohibited Before the Trial	6. CYP2B6 inhibitors, CYP2D6 inhibitors, and CYP3A4 inhibitors and inducers	6. CYP2B6 inhibitors, CYP2D6 inhibitors, **CYP2D6 substrates with a narrow therapeutic index,** and CYP3A4 inhibitors and inducers

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 4.1-2, List of Medications Prohibited During the Trial	3. CYP2B6 inhibitors, CYP2D6 inhibitors, or CYP3A4 inhibitors and inducers. Selected CYP2B6 inhibitor is: ticlopidine. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, paroxetine, clomipramine, pyrilamine, diphenhydramine, quinidine, fluoxetine, terbinafine, halofantrine, tripelennamine. Selected CYP3A4 inhibitors are	3. CYP2B6 inhibitors, CYP2D6 inhibitors, **CYP2D6 substrates with a narrow therapeutic index,** or CYP3A4 inhibitors and inducers. Selected CYP2B6 inhibitor is: ticlopidine. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, paroxetine, clomipramine, pyrilamine, diphenhydramine, quinidine, fluoxetine, terbinafine, halofantrine, tripelennamine. **Selected CYP2D6 substrates are: thioridazine, pimozide, desipramine, eliglustat, metoprolol, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine, amitriptyline, encainide, imipramine, propafenone, propranolol, tramadol, trimipramine.** Selected CYP3A4 inhibitors are ....
Section 4.2.1, Restricted Therapies and Precautions	Investigators should discourage the use of caffeine and caffeine-containing products.	Investigators should **inform subjects that normal consumption** of caffeine **is permitted**.
Section 5.1, Definitions	Immediately Reportable Event (IRE): ... • Rash (see Section 5.3).	Immediately Reportable Event (IRE): ... • Rash **(regardless of severity or seriousness)** (see Section 5.**4**).
Section 5.4, Adverse Events of Special Interest	Not applicable (newly added section)	**5.4 Adverse Events of Special Interest** **Newly acquired skin eruptions that are nontraumatic will be considered adverse events of special interest (AESI). These may include, but are not limited to, eruptions such as skin rashes, skin irritations, skin reactions, or acneiform lesions.** **Extra measures that must be performed to characterize any skin AESI of a newly acquired skin eruption that is nontraumatic are specified in Appendix 11 through Appendix 14. The trial site will have a local designated dermatologist available for immediate consultation during the trial for these AESIs.**
Section 7.1, Sample Size	The trial will enroll approximately 201 subjects in expectation to have about 150 completers (50 per arm) at the end of the trial.	The trial will enroll approximately 201 subjects in expectation to have about 150 completers at the end of the trial.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 7.2, Datasets for Analysis	Modified Intent-to-Treat Sample: All subjects in the Randomized Sample who took at least one dose of IMP and have a baseline and at least one post randomization evaluation for the CAARS-O:SV ADHD Symptoms Total Score (18-items).	Modified Intent-to-Treat Sample: All subjects in the Randomized Sample who took at least one dose of IMP and have a baseline and at least one post randomization evaluation for the **investigator-administered** CAARS-O:SV ADHD Symptoms Total Score (18-items).
Section 7.3, Handling of Missing Data	The CAARS-O:SV is utilized as the primary efficacy assessment of a subject's level of ADHD. The CAARS-O:SV is a 30-item scale containing 3 subscales: the 9-item Inattentive Symptoms Subscale (sum of items 1, 9, 13, 14, 19, 21, 26, 29, and 30), the 9-item Hyperactive/Impulsive Symptoms Subscale (sum of items 2, 4, 6, 8, 16, 18, 22, 25, and 27), and the 12-item ADHD Index (sum of items 3, 5, 7, 10, 11, 12, 15, 17, 20, 23, 24, and 28). The 18-item ADHD Symptoms Total Score (sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale) is considered to be the primary efficacy measure.	The **18-item, investigator-administered** CAARS-O:SV is utilized as the primary efficacy assessment of a subject's level of ADHD. The 18-item ADHD Symptoms Total Score (sum of the Inattentive Symptoms Subscale and the Hyperactive/Impulsive Symptoms Subscale) is considered to be the primary efficacy measure.
Section 7.3, Handling of Missing Data	In general, missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed case (OC) data from protocol-specified visits under the assumption of missing at random.	In general, **for primary analysis of efficacy endpoints,** missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed case (OC) data from protocol-specified visits under the assumption of missing at random.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 7.4.1, Primary Endpoint Analysis	The primary efficacy endpoint is the mean change from baseline to the Day 56 Visit in the CAARS-O:SV score in the OPC-64005 group compared with the atomoxetine group. Analysis will be performed using modified intent-to-treat data set. Bayesian posterior probability of true baseline corrected difference at Week 8 between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on CAARS-O:SV given estimates of means and standard deviations (SD) in the treatment arms will be calculated. ... The change from baseline in CAARS-O:SV will be analyzed using an MMRM methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week an interaction term of treatment by visit week, and baseline CAARS-O:SV as a covariate. ...	The primary efficacy endpoint is the mean change from baseline to the Day 56 **(± 1 day)** Visit in the **18-item, investigator-administered** CAARS-O:SV score in the OPC-64005 group compared with the atomoxetine group. Analysis will be performed using modified intent-to-treat data set. Bayesian posterior probability of true baseline corrected difference at Week 8 between treatment arms (OPC-64005 and atomoxetine) being larger than 4 points on **the 18-item, investigator-administered** CAARS-O:SV given estimates of means and standard deviations (SD) in the treatment arms will be calculated. ... The change from baseline in **the 18-item, investigator-administered** CAARS-O:SV will be analyzed using an MMRM methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial site, visit week an interaction term of treatment by visit week, and baseline **18-item, investigator-administered** CAARS-O:SV as a covariate. ...

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 7.4.2, Other Endpoint Analysis	Other key efficacy variables are as follows: 1) Mean change from baseline to each weekly visit (other than Day 56) in the CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups 2) Mean change from baseline to the Day 28 and Day 56 Visits for the ADHD RS-5 with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups 3) Mean change from baseline to each weekly visit in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups 4) Mean CGI-I score at each weekly visit in the OPC-64005 group relative to the atomoxetine and placebo groups 5) Mean change from baseline to each weekly visit in the CAARS-S:SV in the OPC-64005 group relative to the atomoxetine and placebo groups 6) Mean change from baseline to the Day 28 and Day 56 Visits in the AAQoL in the OPC-64005 group relative to the atomoxetine and placebo groups	Other key efficacy variables are as follows: 1) Mean change from baseline to each **scheduled** visit (other than Day 56) in the **18-item, investigator-administered** CAARS-O:SV score in the OPC-64005 group relative to the atomoxetine and placebo groups 2) Mean change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits for the **AISRS** with Adult Prompts score in the OPC-64005 group relative to the atomoxetine and placebo groups 3) Mean change from baseline to each **scheduled** visit in the CGI-S score in the OPC-64005 group relative to the atomoxetine and placebo groups 4) Mean CGI-I score at each **scheduled** visit in the OPC-64005 group relative to the atomoxetine and placebo groups 5) Mean change from baseline to each **scheduled** visit in the **18-item** CAARS-S:SV in the OPC-64005 group relative to the atomoxetine and placebo groups 6) Mean change from baseline to the Day 28 **(± 1 day)** and Day 56 **(± 1 day)** Visits in the AAQoL in the OPC-64005 group relative to the atomoxetine and placebo groups
Section 7.4.2, Other Endpoint Analysis	The placebo group is included in this trial to provide direct estimates of effect for powering a Phase 3 trial.	**Details on other analyses will be provided in the SAP.**
Section 7.6, Safety Analysis	Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and BMI (derived programmatically from body weight and height measurements).	Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, **and** ECGs.
Section 7.6.1, Adverse Events	The incidence of the following events will be summarized by treatment group: • TEAEs • TEAEs by severity ... The above summaries will also be prepared for TEAEs potentially causally related to the IMP.	The incidence of the following events will be summarized by treatment group: • TEAEs • TEAEs by severity • **Potentially drug-related TEAEs** ...

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 7.6.5, Other Safety Data	The DEQ will be completed at each weekly visit (Days 7, 14, 21, 28, 42, and 56/ET) as a measure of abuse potential and will be analyzed via summary statistics. Suicidality data collected on the C-SSRS forms will be summarized as appropriate. The Columbia Classification Algorithm of Suicide Assessment (C-CASA), a standardized, methodical, anchored system for categorizing suicidality, will be used to analyze potential suicide events recorded on the C-SSRS and/or AE forms.	The DEQ will be completed at each **scheduled** visit (Days 7, 14, 21, 28, 42, and 56/ET**; all visits have a ± 1-day window**) as a measure of abuse potential and will be analyzed via summary statistics. Suicidality **will be monitored during the trial using** the C-SSRS. **The incidence of suicidality, suicidal behavior, and suicidal ideation will be calculated from the** potential suicide events recorded on the C-SSRS and **summarized by trial visit.**
Section 8.2, Storage	The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.	**The IMP will be stored according to the storage conditions indicated on the clinical label(s).** The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day. **Temperature excursions, outside of the specific conditions for the IMP (as noted on the label), will be immediately reported to the sponsor.**
Appendix 1, Names of OPDC Personnel	[redacted] Phone: Fax: [redacted]	[redacted] Phone: Fax: [redacted]

Protocol 277-201-00001

Location	Old Text	Updated Text
Appendix 2, Institutions Concerned With the Trial	**Institutional Review Board** TBD **Contract Research Organization** TBD **Central Laboratory** TBD	**Institutional Review Board** [redacted] **USA** **Phone:** [redacted] **Contract Research Organization** **INC Research, LLC** **3201 Beechleaf Court, Suite 600** **Raleigh, NC 27604, USA** **Phone:** [redacted] **Central Laboratory** **Covance Central Laboratory** **8211 SciCor Drive** **Indianapolis, IN 46214, USA** ... **Central Dermatologist** **TBD** **Histopathology Laboratory** **TBD**
Appendix 4, 18-Item, Investigator-Administered Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV)	Not applicable	Newly added appendix
Appendix 5, 18-Item Conners' Adult ADHD Rating Scale-Self Report: Screening Version (CAARS-S:SV)	Not applicable	Newly added appendix
Appendix 6, Adult ADHD Investigator Symptom Rating Scale (AISRS With Adult Prompts)	Not applicable	Newly added appendix
Appendix 7, Clinical Global Impression - Severity of Illness Scale (CGI-S)	Not applicable	Newly added appendix

Protocol 277-201-00001

Location	Old Text	Updated Text
Appendix 8, Clinical Global Impression - Improvement Scale (CGI-I)	Not applicable	Newly added appendix
Appendix 9, Adult ADHD Quality of Life Scale (AAQoL)	Not applicable	Newly added appendix
Appendix 10, Profile of Mood States-Brief Form (POMS)	Not applicable	Newly added appendix
Appendix 11, OPC-64005 Skin AESI Workup Instructions	Not applicable	Newly added appendix
Appendix 12, OPC-64005 Skin AESI Worksheet for Trial Site	Not applicable	Newly added appendix
Appendix 13, OPC-64005 Skin AESI Worksheet for Local Dermatologist	Not applicable	Newly added appendix
Appendix 14, OPC-64005 Skin AESI Worksheet for Central Dermatologist	Not applicable	Newly added appendix

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 277-201-00001

Amendment Number: 2

Issue Date: 28 Aug 2017

PURPOSE:

The purpose of this protocol amendment is to:

- Remove abstinence as a method of birth control
- Add a urine alcohol and drug screen at each scheduled visit
- Add an IMP compliance application (AiCure platform)
- Add the MGH-ATRQ-ADHD
- Modify inclusion criterion #4
- Add inclusion criteria regarding the use of the AiCure platform and a smartphone
- Modify exclusion criterion #2, #3, and #21
- Remove exclusion criteria #4 and #5
- Add an exclusion criterion to note that employees or relatives of employees of the trial site cannot participate in the trial
- Add an exclusion criterion to note that family members or cohabitants of currently enrolled subjects will be excluded
- Add FSH as a laboratory test
- Add additional laboratory tests to Table 3.7.3.2-1
- Add additional analyses for PK blood samples
- Add cannabinoids to the list of prohibited medications

The following additional changes were made for clarification or administrative purposes:

- Updated Appendix 11 through Appendix 14 (skin AESI workup instructions and worksheets)
- Removed “designated” for “local designated dermatologist”
- Added that a subject who is titrated down to a lower dose should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose
- Added that dosing should be held on scheduled visit days until the subject is in the clinic and that subjects will be dosed from a newly dispensed blister card
- Clarified that a treatment card will be issued at baseline for Days 5 to 6
- Removed the specific time required for dosing
- Modified restrictions around psychotherapy
- Corrected a typographical error in reference #39

Protocol 277-201-00001

BACKGROUND:

The rationale for the changes in this protocol amendment is as follows:

- Abstinence was removed as requested by the FDA (given reliability concerns)
- A urine and alcohol drug screen was added at each scheduled visit as requested by the FDA
- The AiCure platform was added to assess compliance with the IMP
- The MGH-ATRQ-ADHD was added to assess medication history, specifically for the treatment of ADHD
- Inclusion criterion #4 was modified to remove prior successful treatment for ADHD
- Inclusion criteria #8 and #9 were added for consistency with the AiCure platform (the previous inclusion criteria #8 and #9 were renumbered to #10 and #11, respectively)
- Exclusion criterion #2 was modified for consistency with the rest of the protocol
- Exclusion criterion #3 was modified to include the MGH-ATRQ-ADHD
- Exclusion criterion #4 was removed as requested by the FDA (newly diagnosed subjects are now permitted to enroll in the trial)
- Exclusion criterion #5 was removed as newly diagnosed subjects are now permitted to enroll in the trial
- Exclusion criterion #21 was modified to replace “cocaine” with “cannabinoids” (which includes marijuana) and add that there are no exceptions
- Exclusion criterion #30 was added to reduce bias in the trial
- Exclusion criterion #31 was added to exclude enrollment of family members or cohabitants of currently enrolled subjects in order to reduce bias and risk of unblinding
- FSH was added as a laboratory test for female subjects who have been postmenopausal for at least 12 consecutive months
- Additional laboratory tests were added to Table 3.7.3.2-1 for consistency with the rest of the protocol
- Added that PK blood samples may be analyzed for atomoxetine and/or other analytes to confirm compliance
- Cannabinoids was added to the list of prohibited medications for consistency

Protocol 277-201-00001

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Old Text	Updated Text
Synopsis, Inclusion Criteria	Subjects with a primary *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2). Subjects must have received prior successful treatment (pharmacotherapy) for adult ADHD based on medical records and the principal investigator's judgment. Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that are currently receiving treatment.	Subjects with a primary *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the Adult ADHD Clinical Diagnostic Scale, version 1.2 (ACDS v1.2). Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that **they** are currently receiving treatment.
Synopsis, Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	During the Treatment Period (Days 5 - 56), subjects randomized to the OPC-64005 arm will receive 30 mg OPC-64005 and atomoxetine placebo daily, subjects randomized to the atomoxetine arm will receive 80 mg of atomoxetine and OPC-64005 placebo daily, and subjects randomized to the placebo arm will receive both OPC-64005 placebo and atomoxetine placebo daily. If a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial.	During the Treatment Period (Days 5 - 56), subjects randomized to the OPC-64005 arm will receive 30 mg OPC-64005 and atomoxetine placebo daily, subjects randomized to the atomoxetine arm will receive 80 mg of atomoxetine and OPC-64005 placebo daily, and subjects randomized to the placebo arm will receive both OPC-64005 placebo and atomoxetine placebo daily. If a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. **When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose. On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Synopsis, Criteria for Evaluation	**Primary Endpoint:** The primary efficacy endpoint is the change from baseline to the Day 56 (± 1 day) Visit in the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.	**Primary Endpoint:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit **on** the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.
Synopsis, Statistical Methods	Details of the planned statistical analysis will be presented in the protocol and in the statistical analysis plan (SAP).	Details of the planned statistical analysis will be presented in the statistical analysis plan (SAP).
Synopsis, Statistical Methods	**Primary:** The primary efficacy endpoint is the change from baseline to the Day 56 (± 1 day) Visit in the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.	**Primary:** The primary efficacy endpoint is the change from baseline to the Day 56 Visit **on** the investigator-administered CAARS-O:SV 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.
Section 3.1, Type/Design of Trial	Treatment Period: During the Treatment Period (Days 5 - 56), subjects who are randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. Subjects randomized to the atomoxetine arm for Titration will continue in the atomoxetine arm for Treatment. Subjects randomized to the placebo arm for Titration will continue in the placebo arm for Treatment. During the 8-week Titration/Treatment Period, subjects will have weekly or biweekly visits to the clinical site. Assessments to be performed during the trial are listed in Table 3.7-1.	Treatment Period: During the Treatment Period (Days 5 - 56), subjects who are randomized to the OPC-64005 arm for Titration will continue in the OPC-64005 arm for Treatment. Subjects randomized to the atomoxetine arm for Titration will continue in the atomoxetine arm for Treatment. Subjects randomized to the placebo arm for Titration will continue in the placebo arm for Treatment. During the 8-week Titration/Treatment Period, subjects will have weekly or biweekly visits to the clinical site. **On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.** Assessments to be performed during the trial are listed in Table 3.7-1.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.2, Trial Treatments	During the Treatment Period, subjects in the OPC-64005 group will receive daily 30-mg oral doses of OPC-64005 and atomoxetine placebo. During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. Subjects in the atomoxetine group will receive daily 80-mg oral doses of atomoxetine and OPC-64005 placebo. During the Treatment Period, if a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. Subjects in the placebo group will receive daily oral doses of both OPC-64005 placebo and atomoxetine placebo.	During the Treatment Period, subjects in the OPC-64005 group will receive daily 30-mg oral doses of OPC-64005 and atomoxetine placebo. During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. Subjects in the atomoxetine group will receive daily 80-mg oral doses of atomoxetine and OPC-64005 placebo. During the Treatment Period, if a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg of atomoxetine for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. **When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.** Subjects in the placebo group will receive daily oral doses of both OPC-64005 placebo and atomoxetine placebo. **On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.**
Table 3.2-1, Dosing Schedule	Time 8:00 am (AM dosing)	Time AM dosing

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.2-1, Dosing Schedule	[b]May be reduced to 20 mg if the 30 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005) during the trial. [c]May be reduced to 40 mg if the 80 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 80 mg for atomoxetine) during the trial.	[b]May be reduced to 20 mg if the 30 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005) during the trial. **When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.** [c]May be reduced to 40 mg if the 80 mg dose is not tolerable. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 80 mg for atomoxetine) during the trial. **When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.**
Section 3.3.1, Number of Subjects and Description of Population	To assure that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (M.I.N.I.) will be used to identify and exclude other psychiatric conditions.[50] Subjects identified with a current or lifetime history of bipolar disorder, schizophrenia, other psychotic disorder, or personality disorder will not be eligible for enrollment. Subjects must have a history of adequate symptom reduction with stimulants or nonstimulant ADHD medication.	To **confirm** that ADHD is the primary diagnosis, the Mini International Neuropsychiatric Interview (M.I.N.I.) will be used to identify and exclude other psychiatric conditions.[50] Subjects identified with a current or lifetime history of bipolar disorder, schizophrenia, other psychotic disorder, or personality disorder will not be eligible for enrollment. **Medication history, specifically for the treatment of ADHD, will be assessed using the Massachusetts General Hospital Treatment Response Questionnaire (ATRQ) - ADHD (MGH-ATRQ-ADHD).[51]**

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.4.2-1, Inclusion Criteria	4. Subjects with a primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the ACDS v1.2. Subjects must have received prior successful treatment (pharmacotherapy) for adult ADHD based on medical records and the principal investigator's judgment. Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that they are currently receiving treatment. The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability.	4. Subjects with a primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, and combined presentations) as confirmed by the ACDS v1.2. Subjects may be currently receiving treatment for adult ADHD at screening, but it is not necessary that they are currently receiving treatment. The rationale to discontinue current ADHD treatment must include either or both suboptimal efficacy response and/or treatment limiting safety/tolerability.
Table 3.4.2-1, Inclusion Criteria	Not applicable (newly added inclusion criterion)	**8. Subjects must be able and willing to utilize the AiCure Platform for each daily dose.**
Table 3.4.2-1, Inclusion Criteria	Not applicable (newly added inclusion criterion)	**9. Subjects likely to possess the capacity to utilize the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone.**
Table 3.4.2-1, Inclusion Criteria	8. Subjects who have an AISRS with Adult Prompts score of ≥ 26.	**10.** Subjects who have an AISRS with Adult Prompts score of ≥ 26.
Table 3.4.2-1, Inclusion Criteria	9. Subjects who have a score of ≥ 4 on the CGI-S.	**11.** Subjects who have a score of ≥ 4 on the CGI-S.
Table 3.4.3-1, Exclusion Criteria	2. Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.	2. **All** males **and** WOCBP who do not agree to practice 2 methods of birth control during the trial and for 30 days after the last dose of IMP. **Two** of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill**s**, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. **This exclusion does not apply for subjects confirmed, by medical record and/or prospective assessment, to be sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months, confirmed by FSH blood level; or men who have had a bilateral orchidectomy).**

Protocol 277-201-00001

Location	Old Text	Updated Text
Table 3.4.3-1, Exclusion Criteria	3. Subjects with a history of inadequate response or suboptimal tolerability to atomoxetine. (In the investigator's opinion, the subject was treated with an adequate dose for an adequate period of time, yet failed to show satisfactory response.)	3. Subjects with a history of inadequate response or suboptimal tolerability to atomoxetine. (The subject was treated with an adequate dose for an adequate period of time, yet failed to show satisfactory response.) **This will be confirmed using the MGH-ATRQ-ADHD.**
Table 3.4.3-1, Exclusion Criteria	4. Subjects who are newly diagnosed, and have not received treatment for ADHD.	4. Criterion deleted by Amendment 2.
Table 3.4.3-1, Exclusion Criteria	5. Subjects who have an existing diagnosis of ADHD, and who have not demonstrated clinical improvement on an approved treatment for ADHD.	5. Criterion deleted by Amendment 2.
Table 3.4.3-1, Exclusion Criteria	21. Subjects with a positive drug screen for cocaine or other illicit drugs will be excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or OTC medications may be retested or rescreened, at the discretion of the investigator.	21. Subjects with a positive drug screen for **cannabinoids** or illicit drugs will be excluded and may not be retested or rescreened. **There will be no exceptions, including subjects from states in which cannabinoids are considered legal.** Subjects with a positive urine drug screen resulting from use of prescription or OTC medications may be retested or rescreened, at the discretion of the investigator.
Table 3.4.3-1, Exclusion Criteria	Not applicable (newly added exclusion criterion)	**30. Employees or relatives of employees of the trial site cannot participate in the trial.**
Table 3.4.3-1, Exclusion Criteria	Not applicable (newly added exclusion criterion)	**31. Siblings and other family members, and those having the same place of residence as another subject, will be excluded. Subjects whose family/household member has completed participation in the trial may be considered for enrollment.**
Section 3.4.3, Exclusion Criteria	Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.	Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months **(confirmed by follicle-stimulating hormone [FSH] blood level)**.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.5.1, Primary Endpoint	The primary efficacy endpoint is the change from baseline to the Day 56 (± 1 day) Visit in the investigator-administered Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.	The primary efficacy endpoint is the change from baseline to the Day 56 Visit **on** the investigator-administered Conners' Adult ADHD Rating Scales–Observer: Screening Version (CAARS-O:SV) 18-item ADHD symptoms total score in the OPC-64005 group relative to the atomoxetine group.
Table 3.7-1, Schedule of Assessments	Changes to Table 3.7-1 are summarized on the next page and are indicated by **bold, underlined** text.	

Protocol 277-201-00001

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
ENTRANCE CRITERIA										
Inclusion/exclusion criteria	X	X								
Demographic information	X									
Medical history	X									
Psychiatric history to confirm DSM-5 ADHD diagnosis using the ACDS v1.2	X									
Diagnosis confirmation and identification of comorbidities using the M.I.N.I.	X									
Investigator assessment of previous and current ADHD treatment **using the MGH-ATRQ-ADHD**	X	X								
HIV, HBsAg, and anti-HCV	X									
Urine pregnancy test[a]	X	X				X		X		
SAFETY										
Physical examination[b]	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X		X	X	X		
Clinical laboratory	X	X				X		X		
Urine alcohol and drug screen	X	**X**	**X**	**X**	**X**	**X**	**X**	X		
C-SSRS	X	X	X	X	X	X	X	X		

Table 3.7-1 Schedule of Assessments

Assessment	Screening (Day −28 to −1)	Baseline (Day 1)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Day 42 (± 1 day)	Day 56 (± 1 day)/ET	Follow-up (3 ± 1 day)	Follow-up (30 + 2 days)
EFFICACY										
18-item, investigator-administered CAARS-O:SV[c]	X	X	X	X	X	X	X	X		
AISRS with Adult Prompts	X	X				X		X		
CGI-S	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X		
18-item CAARS-S:SV[c]		X	X	X	X	X	X	X		
AAQoL		X				X		X		
POMS	X	X	X	X	X	X	X	X		
CLINIC PROCEDURES										
Dispense IMP and download the AiCure platform or receive device with the AiCure platform predownloaded		**X**								
IMP administration[d]		X	X	X	X	X	X	X		
IMP return and accountability / AiCure compliance			**X**	**X**	**X**	**X**	**X**	**X**		
PK blood samples		X[e]	X[f]	X[g]	X[h]					
Pharmacogenomic sample for CYP2D6 testing		X								
FBR blood sample[i]		X								
DEQ		X	X	X	X	X	X	X		
Record AEs	X	X	X	X	X	X	X	X	X	X
Record concomitant medication	X	X	X	X	X	X	X	X	X	X

Table 3.7-1 Schedule of Assessments										
Assessment	**Screening (Day −28 to −1)**	**Baseline (Day 1)**	**Day 7 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 1 day)**	**Day 42 (± 1 day)**	**Day 56 (± 1 day)/ET**	**Follow-up (3 ± 1 day)**	**Follow-up (30 + 2 days)**
Return trial-provided mobile device (if applicable)								**X**		
Telephone contact									X	X

FBR = future biospecimen research; POMS = Profile of Mood States-Brief Form™.

[a]If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test. Additional urine pregnancy testing may be done at the discretion of the investigator.

[b]A physical examination will be performed at the Screening, Baseline, and Day 56 (± 1 day)/ET Visits. Weight, height, and waist circumference will be recorded at the Screening Visit. A focused examination for the detection of rash will be performed at the Day 7, 14, 21, 28, and 42 Visits; all visits have a ± 1-day window. Subjects will be instructed to contact the site if rash is noted at any other time, and an unscheduled visit will be arranged.

[c]The 18-item CAARS-S:SV should be conducted before the 18-item, investigator-administered CAARS-O:SV at each scheduled assessment, giving the investigator a chance to review the self-report before completing their own assessment.

[d]Subjects will receive daily doses of IMP starting on Day 1. At the baseline visit, subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to **6**. During the treatment period, subjects will receive a treatment card(s) for dosing on scheduled visits. **On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.**

[e]Day 1 samples collected predose and 1 and 3 hours postdose.

[f]Day 7 (± 1 day) samples collected predose and 2 hours postdose.

[g]Day 14 (± 1 day) samples collected predose and 3 hours postdose.

[h]Day 21(± 1 day) samples collected predose.

[i]FBR sample will be collected once the subject has provided consent for FBR.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.1, Screening	• The investigator will assess and record previous ADHD medications. Subjects must have a history of adequate symptom reduction with stimulants or nonstimulant ADHD medication. If applicable, washout from ADHD medications will begin. The washout period will be equivalent to 5 half-lives before Baseline (Day 1).	• The investigator will assess and record previous ADHD medications **using the MGH-ATRQ-ADHD**. If applicable, washout from ADHD medications will begin. The washout period will be equivalent to 5 half-lives before Baseline (Day 1).
Section 3.7.1.1, Screening	• Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and marijuana	• Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, **and** phencyclidine
Section 3.7.1.2, Baseline (Day 1)	Not applicable (newly added bullet)	• **Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine.**
Section 3.7.1.2, Baseline (Day 1)	• Subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to 7.	• Subjects will receive a titration card for dosing on Days 1 to 4 and a treatment card for dosing on Days 5 to **6**.
Section 3.7.1.2, Baseline (Day 1)	Not applicable (newly added bullet)	• **The IMP will be dispensed and the subject will download the AiCure platform or receive a provisioned device with the AiCure platform predownloaded and will be trained on IMP compliance using this application. Subjects will be instructed to take their first dose of IMP from the titration card in the clinic.**
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	• At the Day 28 (± 1 day) and Day 56 (± 1 day) Visits, blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1).	• At the Day 28 (± 1 day) and Day 56 (± 1 day)/**ET** Visits, blood and urine samples will be collected for clinical laboratory tests, including hematology, serum chemistry, and urinalysis (see Table 3.7.3.2-1).
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	• Urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and marijuana at the Day 56 (± 1 day)/ET Visit.	• **At each visit,** urine will be collected from all potential subjects for urine screen(s) for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, **and** phencyclidine.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	• At the Day 28 (± 1 day) and Day 56 (± 1 day) Visits, the AISRS with Adult Prompts will be administered.	• At the Day 28 (± 1 day) and Day 56 (± 1 day)/**ET** Visits, the AISRS with Adult Prompts will be administered.
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	• At the Day 28 (± 1 day) and Day 56 (± 1 day) Visits, the subject will complete the AAQoL.	• At the Day 28 (± 1 day) and Day 56 (± 1 day)/**ET** Visits, the subject will complete the AAQoL.
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	• Subjects will receive a treatment card(s) for dosing on scheduled visits.	• Subjects will receive a treatment card(s) for dosing on scheduled visits. **On scheduled visit days (Days 7, 14, 21, 28, 42, and 56), dosing should be held until the subject is in the clinic; subjects will be dosed from a newly dispensed blister card.**
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	Not applicable (newly added bullet)	• **At each visit, IMP returns, accountability, and subject compliance with the IMP will be assessed.**
Section 3.7.1.3, Treatment Period Visits (Day 7 Through Day 56 Visits)	Not applicable (newly added bullet)	• **At the Day 56 (± 1 day)/ET Visit, subjects will return the trial-provided mobile device (if applicable).**
Table 3.7.3.2-1, Clinical Laboratory Assessments	Additional Tests: Urine [or serum] pregnancy for WOCBP Free T4 (free T4 is measured only if result for TSH is abnormal)	Additional Tests: Urine (or serum) pregnancy for WOCBP **FSH (for female subjects who have been postmenopausal for at least 12 consecutive months)** Free T4 (free T4 is measured only if result for TSH is abnormal) **Urine for alcohol and drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine** **C Reactive Protein (CRP) (if rash is detected)** **Human herpes virus 6 (HHV-6) (if rash is detected and the signs and symptoms are suggestive of drug rash with eosinophilia and systemic symptoms [DRESS] or drug-induced hypersensitivity syndrome [DIHS])** **Complete blood count with differential (if rash is detected)**
Section 3.7.3.3, Physical Examination and Vital Signs	A physical examination will be performed at screening, baseline, and at Day 56 (± 1 day).	A physical examination will be performed at screening, baseline, and at Day 56 (± 1 day)/**ET**.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.7.4.1.1, Pharmacokinetic Blood Samples	Blood samples for the determination of OPC-64005 and its metabolite(s) will be collected at Baseline (Day 1) predose (within 15 minutes of dosing) and at 1 and 3 hours postdose, at the Day 7 (± 1 day) Visit predose (within 5 minutes of dosing) and at 2 hours postdose, at the Day 14 (± 1 day) Visit predose (within 5 minutes of dosing) and at 3 hours postdose, and at the Day 21 (± 1 day) Visit predose (within 5 minutes of dosing). In addition, every effort will be made to obtain a PK blood sample from any subject who experiences an SAE.	Blood samples for the determination of OPC-64005 and its metabolite(s) will be collected at Baseline (Day 1) predose (within 15 minutes of dosing) and at 1 and 3 hours postdose, at the Day 7 (± 1 day) Visit predose (within 5 minutes of dosing) and at 2 hours postdose, at the Day 14 (± 1 day) Visit predose (within 5 minutes of dosing) and at 3 hours postdose, and at the Day 21 (± 1 day) Visit predose (within 5 minutes of dosing). **Samples may also be analyzed for atomoxetine and/or other analytes to confirm compliance.** In addition, every effort will be made to obtain a PK blood sample from any subject who experiences an SAE.
Section 3.8.3.1, Down Titration of Treatment	During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial.	During the Treatment Period, if a subject is not able to tolerate the 30-mg dose of OPC-64005, the dose may be reduced to 20 mg for the duration of the Treatment Period. If a subject is not able to tolerate the 80-mg dose of atomoxetine, the dose may be reduced to 40 mg for the duration of the Treatment Period. Subjects are permitted to have one dose reduction and one titration back up to their previous dose (ie, 30 mg for OPC-64005 and 80 mg for atomoxetine) during the trial. **When a subject is titrated down to a lower dose, they should be maintained on that low dose for a minimum of 4 days before being titrated back up to the higher dose.**
Section 3.12, Subject Compliance	Responsible trial personnel will dispense the IMP (ie, OPC-64005, atomoxetine, and placebo) to subjects. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered.	Responsible trial personnel will dispense the IMP (ie, OPC-64005, atomoxetine, and placebo) to subjects. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered. **Details on the AiCure technology to be used in this trial to assess IMP compliance are provided below.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.12.1, IMP Adherence and Reminder System	Not applicable (newly added section)	**This trial will employ an IMP adherence monitoring platform ("AiCure Platform") for all subjects in the trial. The AiCure Platform uses artificial intelligence on smartphones to confirm IMP ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of IMP interruptions.** **Use of this AiCure Platform will in no way supersede or replace the physician and/or prescribed IMP protocol of the subjects. Because the AiCure Platform does not change the IMP protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this AiCure Platform presents minimal risk to the subjects. Use of the AiCure Platform will be required for all subjects in the trial.** **The monitoring AiCure Platform requires that all subjects take each dose of the IMP while using a smartphone. The AiCure Platform will be provided to subjects preloaded on a smartphone, or subjects will download the AiCure Platform onto their own mobile device at baseline (Day 1).**

Protocol 277-201-00001

Location	Old Text	Updated Text
		When at home, subjects will receive an IMP reminder at a time within a predefined window. This notification reminds subjects to take their IMP dose while using the AiCure Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the IMP. The application on the smartphone will make an automated determination of whether the subject has properly taken their IMP at the prescribed time. There is no need for the trial site staff to review the administration, nor would the trial site staff need to be available at the time the subject takes their IMP. The amount of guidance that the device provides to the subjects is automatically reduced as the subject becomes more proficient at using the application. **After the device confirms proper IMP ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured data and video are reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.** **Phone numbers of the subjects may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with subjects, including automated messaging from the AiCure Platform device and contact by the trial site staff or other monitoring personnel. At no time is the phone number visible to the trial site staff or monitoring personnel on the AiCure Platform. Individuals outside the trial sites will not be provided with subject names, nor will they be given access to subject medical records.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.12.2, Subject Risk	Not applicable (newly added section)	**The AiCure Platform provides no more than minimal risk to subjects. This protocol only introduces a smartphone-based monitoring application that prompts the user to take their IMP, verifies ingestion, and stores encrypted data securely for analysis. When functioning properly, use of the AiCure Platform does not affect titration, dosage, route of administration, or treatment duration, conforming to any trial requirements as noted by trial site staff.** **It is possible, though very unlikely, that the AiCure application can fail to remind subjects to take the IMP or tell them to take their IMP when not required. To date, AiCure has not encountered such a malfunction.** **All trial data, including any identifiable subject information, will be obtained and encrypted by the application. Subjects will be coded according to the protocol and their identity will not be stored with the trial data obtained. After the subject has taken the IMP and confirmation of proper ingestion has been completed, the encrypted data will be automatically forwarded to a secure server. The server is compliant with the HIPAA, which protects the privacy and security of healthcare information. The data will be securely stored and only accessible to the trial site staff and other authorized personnel through two-way authentication.** **The data may also be retained in a secure manner beyond the term of the trial and utilized to improve the operation of the AiCure Platform, categorize adherence activity by disease state or other useful categories, and/or for regulatory filings by the AiCure Platform Provider to support future applications for the AiCure Platform Provider's product. Individuals who are not associated with the care and treatment of subjects will not have access to subject identity or any medical records.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 3.12.3, Subject Confidentiality	Not applicable (newly added section)	**The AiCure Platform Provider will protect subjects' personal information to the full extent required by law. However, information from this trial, including de-identified video recording(s) of subject performance of various actions, may be submitted to the trial site, and potentially to the FDA. Both information obtained by the application, and information in the subject Informed Consent, may be examined by the trial site or the trial site's representatives, and may also be reviewed by the FDA and other regulatory agencies, IRBs, and or Ethics Committee(s). All of these parties are bound to safeguard the rights, safety, and well-being of all clinical trial subjects, and to maintain all information in confidence, with special consideration given to trials that may include vulnerable subjects.** **The results of this trial may be presented at meetings or in publications; however, specific subjects will not be identified by name in these presentations and/or publications. Information from this trial may also be retained by the AiCure Platform Provider for the purpose of improving the AiCure Platform, to allow for future analysis of various facial and other parameters, the reporting of high level statistical analysis of the AiCure Platform, to improve the internal workings of the system running on the smartphone device, or for regulatory filings by the AiCure Platform Provider to support future applications for the Provider's product.**
Table 4.1-2, List of Medications Prohibited During the Trial	All psychotropic agents including, but not limited to, the following: ... i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements, etc)	All psychotropic agents including, but not limited to, the following: i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements, etc) **j) Cannabinoids**

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 4.2.2.2, Restrictions	Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they have been participating in the therapy regularly (ie, weekly) for at least 6 weeks (42 days) prior to screening and commit to maintain their participation during the course of the trial at the current frequency or unless permission is obtained from the medical monitor. Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial.	Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they have been participating in the therapy regularly (ie, **at consistent intervals**) for at least 6 weeks (42 days) prior to screening and commit to maintain their participation during the course of the trial **with no changes** or unless permission is obtained from the medical monitor. Subjects will be instructed to refrain from drinking alcoholic beverages or using **cannabinoids or** illicit drugs during participation in the trial.
Section 5.4, Adverse Events of Special Interest	The trial site will have a local designated dermatologist available for immediate consultation during the trial for these AESIs.	The trial site will have a local dermatologist available for immediate consultation during the trial for these AESIs.
Section 5.6, Pregnancy	Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months. ... Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide.	Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months **[confirmed by FSH blood level]**). ... Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months **[confirmed by FSH blood level]**; or men who have had a bilateral orchidectomy), 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide.
Section 7.4.1, Primary Endpoint Analysis	The primary efficacy endpoint is the mean change from baseline to the Day 56 (± 1 day) Visit in the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group compared with the atomoxetine group. Analysis will be performed using modified intent-to-treat data set.	The primary efficacy endpoint is the mean change from baseline to the Day 56 Visit **on** the 18-item, investigator-administered CAARS-O:SV score in the OPC-64005 group compared with the atomoxetine group. Analysis will be performed using modified intent-to-treat data set.

Protocol 277-201-00001

Location	Old Text	Updated Text
Section 15, References	39. [redacted] Study for effects of OPC-266 on fertility and early embryonic development to implantation by oral administration in female rats. Otsuka Study No. 029621, Otsuka Report No. 024131, 2009.	39. [redacted] Study for effects of OPC-**277** on fertility and early embryonic development to implantation by oral administration in female rats. Otsuka Study No. 029621, Otsuka Report No. 024131, 2009.
Section 15, References	Not applicable (newly added reference - note that all subsequent references were automatically renumbered accordingly)	**51. Fava M. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire x ADHD-Adult Version. Massachusetts General Hospital. 2014.**

Protocol 277-201-00001

Location	Old Text	Updated Text
Appendix 11, OPC-64005 Skin AESI Workup Instructions	277-201-00001 Skin Adverse Event of Special Interest (AESI) Instructions Version 1.0 dated 25 Jun 2017 At any point during the study, upon the report by the subject or upon the observation by site personnel of any type of newly acquired skin eruptions that are non-traumatic (considered adverse events of special interest [AESIs]), and the Investigator or medical professional designee will take the following steps: 1. Discontinue administration of IMP regardless of the severity and seriousness of rash. 2. Collect a detailed history, including specific questioning for symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine) or other possible causes of the rash (eg, allergic, contact dermatitis); perform a physical examination of the area affected by the skin rash, **including** vital signs (specifically, body temperature); record all concomitant medications and nutritional supplements and compare them with the use of investigational medicinal product (IMP) and the onset and resolution of skin eruptions. 3. Take a picture of the area(s) of the rash using the Clinical Ink tablet. If the rash area is generalized, torso, back, abdomen and extremities should be photographed. NOTE: Photographs should not contain any personal identifiers or other parts of the body. 4. Contact the CRO Medical Monitor for the study.	277-201-00001 Skin Adverse Event of Special Interest (AESI) **Workup** Instructions Version **2**.0 dated **18 Aug** 2017 At any point during the **trial**, upon the report by the subject or upon the observation by site personnel of any type of newly acquired skin eruptions that are non-traumatic**, they will be considered** adverse events of special interest (AESIs), and the investigator or medical professional designee will take the following steps: 1. Discontinue administration of IMP regardless of the severity and seriousness of rash. 2. Collect a detailed history, including specific questioning for symptoms of hepatitis (eg, weight loss, right upper quadrant tenderness, malaise, jaundice, hepatomegaly, dark urine) or other possible causes of the rash (eg, allergic, contact dermatitis). **3.** Perform a physical examination of the area affected by the skin rash**, listing all body parts affected (eg, left or right hand, forearm, upper arm, etc.)**. **4. Obtain** vital signs (**including** body temperature). **5.** Record all concomitant medications and nutritional supplements and compare them with the use of IMP and the onset and resolution of skin eruptions. **6.** Take a picture of the area(s) of the rash using the Clinical Ink **SureSource** tablet. If the rash area is generalized, **the** torso, back, abdomen**,** and extremities should be photographed. NOTE: Photographs should not contain any personal identifiers or parts of the body **that would identify the subject (such as unusual tattoos, full-face views, etc.)**. 7. Contact **Otsuka's and INC's** Medical Monitor for the **trial**.

Protocol 277-201-00001

Location	Old Text	Updated Text
	5. Collect blood samples for laboratory testing, including a complete blood count with differential to detect lymphocytosis, atypical lymphocytes, and absolute (total) eosinophil count and chemistry with liver enzyme tests and C-reactive protein (CRP) testing [to rule out cases of systemic hypersensitivity]. • (Note: If the signs and symptoms are suggestive of drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), human herpes virus 6 (HHV-6) infection should be ruled out.) 6. Complete Skin AESI Worksheet for study site (Appendix 12). 7. Refer the subject to the local dermatologist assigned to the study site as soon as possible for consultation. a. For rash that is classified as SEVERE (defined as the inability to perform normal daily activities) or meets the definition of an SAE: If subject agrees, have the local dermatologist obtain a biopsy for histopathological examination by a dermatopathologist. Consider direct immunofluorescence evaluation, particularly if the eruption is characterized by vesicles, bullae, or pustules. b. Have the local dermatologist complete Skin AESI Worksheet (see Appendix 13) when the subject is evaluated. i. The local dermatologist will contact the study Central Dermatologist for consultation (see Appendix 14) 8. Monitor the subject daily via telephone contact or in-clinic visits (per the PI's discretion) to evaluate if the event is improving, unchanging, or worsening. When the event resolves, record the last day as the end date of the AE. 9. Repeat steps 3-7 as required.	**8.** Collect blood samples for laboratory testing, including a complete blood count with differential to detect lymphocytosis, atypical lymphocytes, and absolute (total) eosinophil count and chemistry with liver enzyme tests and C-reactive protein (CRP) testing **(**to rule out cases of systemic hypersensitivity**)**. • (Note: If the signs and symptoms are suggestive of drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), human herpes virus 6 (HHV-6) infection should be ruled out. **9.** Complete **the** Skin AESI Worksheet for **the trial** site (Appendix 12). **10.** Refer the subject to **a** local dermatologist assigned **by** the **trial** site **for a consultation** as soon as possible **(Note that after 7 days without IMP, the subject may not continue in the trial regardless of the outcome of the investigation of the rash)**. a. For rash that is classified as SEVERE (defined as the inability to perform normal daily activities) or meets the definition of an SAE: If **the** subject agrees, have the local dermatologist obtain a biopsy for histopathological examination by a dermatopathologist. Consider direct immunofluorescence evaluation, particularly if the eruption is characterized by vesicles, bullae, or pustules. b. Have the local dermatologist complete **the** Skin AESI Worksheet (see Appendix 13) when the subject is evaluated. i. The local dermatologist will contact the **trial** Central Dermatologist for consultation (see Appendix 14) **11.** Monitor the subject daily via telephone contact or in-clinic visits (per the **investigator**'s discretion) to evaluate if the event is improving, unchanging, or worsening. When the event resolves, record the last day as the end date of the AE. **12.** Repeat steps 3-**11** as required.

Protocol 277-201-00001

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td>Appendix 12, OPC-64005 Skin AESI Worksheet for Trial Site</td><td>
277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site
Version 1.0 dated 25 Jun 2017

To be completed by the study site
<table>
<tr><td colspan="2">Study Protocol: 277-201-00001</td></tr>
<tr><td>Site No.</td><td>Investigator:</td></tr>
<tr><td>Subject No.</td><td>Subject Initials:</td></tr>
</table>
<table>
<tr><th></th><th>Date: (dd/mmm/yyyy)</th><th>Time: (hh mm)</th></tr>
<tr><td>Date and time of first dose (Day 1) of study drug</td><td></td><td></td></tr>
<tr><td>Date and time of last study drug dose</td><td></td><td></td></tr>
<tr><td>Date and time of rash onset</td><td></td><td></td></tr>
<tr><td>Date and time of blood sample collected</td><td></td><td></td></tr>
<tr><td>Date and time of blood sample results</td><td></td><td></td></tr>
</table>
Blood pressure: _____ / _____ mmHg
Heart Rate: _____ BPM
Temperature: _____ °F or °C (circle one)
Respiration: _____BPM
</td><td>
277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Trial Site
Version 2.0 dated 18 Aug 2017

To be completed by the trial site
<table>
<tr><td colspan="2">Trial Protocol: 277-201-00001</td></tr>
<tr><td colspan="2">Adverse Event # (in SureSource):</td></tr>
<tr><td>Site No.</td><td>Investigator:</td></tr>
<tr><td>Subject No.</td><td>Subject Initials:</td></tr>
</table>
<table>
<tr><th></th><th>Date: (dd/mmm/yyyy)</th><th>Time: (hh:mm)</th></tr>
<tr><td>Date and time of rash onset</td><td></td><td></td></tr>
<tr><td>Date and time of first dose (Day 1) of IMP</td><td></td><td></td></tr>
<tr><td>Date and time of last IMP dose (before the rash)</td><td></td><td></td></tr>
</table>
<u>Vital Signs – Sitting Position</u>
Time subject was placed into sitting position: _____ : _____
Time of sitting vitals assessment:
_____ : _____

Temperature: _____ . _____ °F / °C

Heart rate: _____ _____ _____ bpm
Blood pressure: _____ _____ _____ / _____ _____ _____ mmHg
Respiration: _____ _____ bpm

Vital signs collected by:
Initials
</td></tr>
</table>

Protocol 277-201-00001

Location	Old Text	Updated Text
	Description of Rash: Location(s) of Rash: ***If rash location is generalized, torso, back, abdomen and extremities should be photographed.*** ***Do not photograph any personal identifiers or other parts of the body.*** **Were pictures taken?** ☐ Yes ☐ No If no, please explain why: *Note: Attach copies of Adverse Events, Demographics, Concomitant Medications (including herbal and dietary supplements), and Medical History source document records to this worksheet before forwarding to the dermatologist.* **Final review and disposition by the Investigator (to be completed AFTER receipt of any pertinent laboratory tests or pathology results):** **After review of the dermatologic consultation and subject history, does the Investigator consider the rash to be study drug-related?**	Description of Rash: Location(s) of Rash: **Locations of Adenopathy (if applicable):** ***NOTE: Ensure rash location(s) is clearly specified and photographed. If the body location is not obvious, label the photo or include a label with the body location in the photo, or take a "staging" shot of the body part and then a closer shot of the rash. Make sure all photos are in precise focus; some cameras will focus on items in the background behind the subject's skin.*** ***If rash location is generalized, the torso, back, abdomen, and extremities should be photographed.*** ***Do not photograph any personal identifiers or other parts of the body.*** **Were pictures taken?** ☐ Yes ☐ No If no, please explain why **not**: *Note: Attach copies of adverse events, demographics, concomitant medications (including herbal and dietary supplements), medical history,* ***lab reports, and vital signs*** *source document records to this worksheet before forwarding to the dermatologists.* ***Please upload the completed Skin AESI Worksheets from the local and central dermatologists to the SureSource portal (ie, Appendix 13 and Appendix 14).*** **Final review and disposition by the investigator (to be completed AFTER receipt of any pertinent laboratory tests or pathology results):** **After review of the dermatologic consultation and subject history, does the investigator consider the rash to be IMP-related?**

Protocol 277-201-00001

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td>☐ Yes

☐ No (if it is determined that the rash is not related to the study drug and further treatment with the study drug is in the subject's best interest, the study drug may be restarted at the same dose provided no more than 7 days have elapsed since the study drug was stopped)</td><td>☐ Yes

☐ No (if it is determined that the rash is not related to the IMP and further treatment with the IMP is in the subject's best interest, the IMP may be restarted at the same dose provided no more than 7 days have elapsed since the IMP was stopped)</td></tr>
<tr><td>Appendix 13, OPC-64005 Skin AESI Worksheet for Local Dermatologist</td><td>277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist
Version 1.0 dated 25 Jun 2017

To be completed by the Local Dermatologist assigned to study site
<table><tr><td colspan="2">Study Protocol: 277-201-00001</td></tr><tr><td>Date of Consultation: (dd/mm/yyyy)</td><td>Subject No./ Subject Initials</td></tr></table>
...

Mark location(s) of the rash, including any urticarial lesions or swelling/edema, on the figures below:

Oral Mucosal involvement ☐ No ☐ Yes – details:
Palmar lesions ☐ No ☐ Yes – details:
Plantar lesions ☐ No ☐ Yes – details:
Targetoid lesions ☐ No ☐ Yes – details:
Urticarial lesions ☐ No ☐ Yes – details:
Swelling/edema ☐ No ☐ Yes – details:</td><td>277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Local Dermatologist
Version 2.0 dated 18 Aug 2017

To be completed by the Local Dermatologist assigned by the trial site
<table><tr><td colspan="2">Trial Protocol: 277-201-00001</td></tr><tr><td>Date of Consultation: (dd/mmm/yyyy)</td><td>Subject No./ Subject Initials</td></tr></table>
...

Mark location(s) of the rash, including any urticarial lesions or swelling/edema, on the figures below. If the subject has any visible skin rash that predates the trial onset, be sure to identify such rash separately on the figures below.

Oral mucosal involvement and lip involvement ☐ No ☐ Yes – details:
Conjunctival involvement ☐ No ☐ Yes – details:
Genital involvement ☐ No ☐ Yes – details:
Scalp involvement ☐ No ☐ Yes – details:
Palmar lesions ☐ No ☐ Yes – details:
Plantar lesions ☐ No ☐ Yes – details:
Targetoid lesions ☐ No ☐ Yes – details:
Urticarial lesions ☐ No ☐ Yes – details:
Swelling/edema ☐ No ☐ Yes – details:</td></tr>
</table>

Protocol 277-201-00001

Location	Old Text	Updated Text
	Please take pictures of the rash per the standard photography procedures at your office. ***NOTE: Ensure rash location(s) is clearly photographed. If rash location is generalized, torso, back, abdomen and extremities should be photographed. *Do not photograph any personal identifiers or other parts of the body*** **Were pictures taken?** ☐ Yes ☐ No If No, please explain why: **Please provide narrative description of rash, as follows:** • Occupation • prodromal symptoms • Recent contact with anyone else who had a rash • Changes in the environment: inhalants, foods, new clothing, new skin care products, new detergent • Itching, burning/stinging, tenderness, color (eg, pink, red, or brown), texture (raised or flat), pattern (small lesions, grouped large plaques), unusual characteristics (scaly, peeling, follicles), size (eg, pea-sized, dime-sized, 10mm), starting location (eg, nails, feet/soles hands/palms, scalp, mouth, genitalia, symmetric) • Did it move or spread? Time course? • Any signs by physical examination, associated symptoms (eg, respiratory, fever, systemic symptoms) ...	**Please take pictures of the rash per the standard photography procedures at your office.** ***NOTE: Ensure rash location(s) is clearly photographed. If rash location is generalized, the torso, back, abdomen, and extremities should be photographed. *Do not photograph any personal identifiers.*** **Were pictures taken?** ☐ Yes ☐ No If No, please explain why **not**: **Please provide narrative description of rash, as follows:** • Occupation • **Exposure to dyes or toxins** • Prodromal symptoms • Recent contact with anyone else who had a rash • Changes in the environment: inhalants, foods, new clothing, new skin care products, new detergent • Itching, burning/stinging, tenderness, color (eg, pink, red, or brown), texture (raised or flat), pattern (small lesions, grouped large plaques), unusual characteristics (scaly, peeling, follicles), size (eg, pea-sized, dime-sized, 10 mm), starting location (eg, nails, feet/soles, hands/palms, scalp, mouth, genitalia, symmetric) • Did it move or spread? Time course? • Any signs by physical examination **or subject report of** associated symptoms (eg, respiratory, fever, systemic symptoms) ...

Protocol 277-201-00001

Location	Old Text	Updated Text
	Please mark location of biopsy on body by placing an 'X' on the map above. Please forward a copy of the pathology report from the biopsy to your study contact when it becomes available. **Final causality assessment (choose one):** ☐ Definite drug eruption due to study drug ☐ Probably drug eruption due to study drug (the etiology of the rash has a ≥50% chance of being related to the drug) ☐ Possible drug eruption due to study drug (the etiology of the rash has a <50% chance of being related to the drug) ☐ Other Diagnosis: **Dermatologist Disposition (choose one):** **Is the rash considered to be study drug-related?** ☐ Yes ☐ No (if it is determined that the rash is not related to the study drug and further treatment with the study drug is in the subject's best interest, the study drug may be restarted at the same dose provided no more than 7 days have elapsed since the study drug was stopped) **Post Subject-Assessment Instructions and Reminders for Local Dermatologist** 1) As soon as possible but within 24 hours following your assessment of the subject, please contact the central dermatologist assigned to the study to discuss your findings and review lab results (if applicable). ... 3) REMINDER: Please scan and email the above completed forms and any supporting documents to your contact at the Study Site as soon as possible following the visit. The forms above should be completed for each visit (if subject is seen more than once). Forward any laboratory tests or pathology results, as soon as they become available.	**Please mark location of biopsy on body by placing 'Bx' on the map above. Please forward a copy of the pathology report from the biopsy to your trial contact when it becomes available.** **Final causality assessment (choose one):** ☐ Definite drug eruption due to **IMP** ☐ Probably drug eruption due to **IMP** (the etiology of the rash has a ≥ 50% chance of being related to the **IMP**) ☐ Possible drug eruption due to **IMP** (the etiology of the rash has a < 50% chance of being related to the **IMP**) ☐ **Not related** ☐ Other Diagnosis **(specify)**: **Dermatologist Disposition (choose one):** **Is the rash considered to be IMP-related?** ☐ Yes ☐ No (if it is determined that the rash is not related to the **IMP** and further treatment with the **IMP** is in the subject's best interest, the **IMP** may be restarted at the same dose provided no more than 7 days have elapsed since the **IMP** was stopped) **Post Subject-Assessment Instructions and Reminders for Local Dermatologist** 1) As soon as possible but within 24 hours following your assessment of the subject, please contact the central dermatologist assigned to the **trial** to discuss your findings and review lab results (if applicable). ... 3) REMINDER: Please scan and email the above completed forms and any supporting documents to your contact at the **trial site** as soon as possible following the visit. **If the subject is seen more than once,** the forms above should be completed for each visit. Forward any laboratory tests or pathology results **to your contact at the trial site**, as soon as they become available.

Protocol 277-201-00001

Location	Old Text	Updated Text
Appendix 14, OPC-64005 Skin AESI Worksheet for Central Dermatologist	277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Central Dermatologist Version 1.0 dated 25 Jun 2017 **To be completed by the Central Dermatologist** Study Protocol: 277-201-00001 Date of Consultation: (dd/mm/yyyy) | Subject No./ Subject Initials ... **Final causality assessment (choose one):** ☐ Definite drug eruption due to study drug ☐ Probably drug eruption due to study drug (the etiology of the rash has a ≥50% chance of being related to the drug) ☐ Possible drug eruption due to study drug (the etiology of the rash has a <50% chance of being related to the drug)☐ ☐ Other Diagnosis: Reminder: Please scan and email completed form(s) to the Local Dermatologist and Study Site contacts.	277-201-00001 Skin Adverse Event of Special Interest (AESI) Worksheet for Central Dermatologist Version **2**.0 dated **18 Aug** 2017 **To be completed by the Central Dermatologist** **Trial** Protocol: 277-201-00001 Date of Consultation: (dd/mm**m**/yyyy) | Subject No./ Subject Initials ... **Final causality assessment (choose one):** ☐ Definite drug eruption due to **IMP** ☐ Probably drug eruption due to **IMP** (the etiology of the rash has a ≥ 50% chance of being related to the **IMP**) ☐ Possible drug eruption due to **IMP** (the etiology of the rash has a < 50% chance of being related to the **IMP**) ☐ **Not related** ☐ Other Diagnosis **(specify)**: Reminder: Please scan and email completed form(s) to the Local Dermatologist and **trial site** contacts.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 277-201-00001

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-64005, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where OPC-64005 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on electronic case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

Principal Investigator Print Name	Signature	Date

Otsuka Pharmaceutical Development & Commercialization, Inc.
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