EFFICACY OF LISDEXAMFETAMINE IN ADULTS WITH ADHD AND SLUGGISH COGNITIVE TEMPO

A phase II, randomized, double-blind, cross-over, multi-center study of the effects of Vyvanse (LDX) vs. placebo with an intervening single-blind placebo washout period on patients with Adult Attention Deficit Hyperactivity Disorder (ADHD) and Sluggish Cognitive Tempo (SCT)

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Study Product: Lisdexamfetamine Dimesylate (LDX), Vyvanse

Protocol Number: S13-01288

IND Number: IND not required

[SHIRE SCT s13-01288]
Version: 03/03/2016

Table of Contents

List of Abbreviations

Abbreviation	Definition
%	Percentile
ACDS	Adult Clinician Diagnostic Scale
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-C	Attention Deficit Hyperactivity Disorder Combined type
ADHD-HI	Attention Deficit Hyperactivity Disorder-Hyperactive Impulsive type
ADHD-I	Attention Deficit Hyperactivity Disorder-Inattentive type
AE	Adverse Events
ADHD-RS	ADHD Rating Scale
AMP	Amphetamine
AST	Attention Switching Task
BARRS	Barkley SCT Scale
BFIS	Barkley Functional Impairment Scale
BP	Blood Pressure
bpm	Beats per minute
BRIEF-A	Behavior Rating Inventory of Executive Function®–Adult Version
CANTAB	Cambridge Neuropsychological Testing Automated Battery
CRF	Case Report Form
CGI-IS	Clinical Global Impressions-Impairment scale
CI	Confidence Interval

Abbreviation	Definition
C-SSRS	Columbia-Suicide Severity Rating Scale
CM	Concomitant Medications
CT	Clinical Trial
CPOE	Computerized Physician Order Entry system
d/c'd	Discontinued
DEA	Drug Enforcement Administration
DR	Dose Related
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
ECG	Electrocardiograph
EPIC	Electronic Medical Health Records
f/u	Follow up
FDA	Food & Drug Administration
freq	Frequency
GEE	Generalized Estimating Equation
GLM	General Linear Model
HIPAA	Health Insurance Portability and Accountability Act of 1996
IR	Immediate Release
IDS	Investigational Drug Service
kg	Kilogram
LDX	Lisdexamfetamine Dimesylate
LT	Long-term
MAO	Monoamine Oxidase

Abbreviation	Definition
MAOI	Monoamine Oxidase Inhibitors
MAS	Mixed Amphetamine Salts
MAS XR	Mixed Amphetamine Salts Extended Release
MI	Myocardial Infarction
MINI	Mini International Neuropsychiatric Interview
mg	Milligram
mmHg	Millimeters of Mercury
MPH	Methylphenidate
ON-TOP	On Time Management, Organization, and Planning ON-TOP
QTc	Q T Interval
RCT	Randomized Controlled Trial
SCT	Sluggish Cognitive Tempo
stim	Stimulant
WAIS-IV	Wechsler Adult Intelligence Scale-IV

Study Summary

Title	EFFICACY OF LISDEXAMFETAMINE IN ADULTS WITH ADHD AND SLUGGISH COGNITIVE TEMPO
Short Title	Shire SCT
Protocol Number	S13-01288
Phase	Clinical study phase 2
Methodology	A phase II, randomized, double-blind, cross-over, multi-center study of the effects of Vyvanse (LDX) vs. placebo with an intervening single-blind placebo washout period on patients with Adult Deficit Hyperactivity Disorder (ADHD) and Sluggish Cognitive Tempo (SCT).
Study Duration	13 weeks
Study Center(s)	Multi-center; NYU and Mount Sinai
Objectives	To examine the effects of Vyvanse (LDX) vs. placebo with an intervening single-blind placebo washout period on patients with Adult Deficit Hyperactivity Disorder(ADHD) and Sluggish Cognitive Tempo(SCT).
Number of Subjects	120 adults (20% screen fail rate), will be recruited to evaluate at the screening visit approximately 100 adults with ADHD at two sites (NYU and Mount Sinai) to identify 50 SCT+ and 50 SCT-.
Diagnosis and Main Inclusion Criteria	The study population will consist of male and female outpatients between 18 and 60 years of age, inclusive, with a Primary diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) 16 criteria as determined by the Adult Clinician Diagnostic Scale version 1.2 (ACDS v1.2).

Study Product, Dose, Route, Regimen	Lisdexamfetamine Dimesylate (LDX), Vyvanse. Placebo controlled cross-over study of oral, LDX 30-70 mg/day in SCT+ adults. Participants taking prohibited concomitant medications, including ADHD medications, will be required to washout of their medication during the screening phase. The washout period will be one week for psychostimulants and three weeks for non-stimulants.
Duration of administration	Patients will be assigned either LDX/Placebo for 10 weeks with a two week placebo washout period.
Reference therapy	Reference is a placebo.
Statistical Methodology	During the phenotype phase: Comparisons between the adult ADHD patients cohorts with SCT and without SCT in terms of ADHD symptoms will be examine via One Way ANOVA . Treatment Phase: Changes in outcome ratings in the patients in the treatment phase with LDX and placebo will be modeled with longitudinal generalized estimating equation (GEE) mixed regression models using STATA 12.0 [StataCorp, 2011 #25856] within the framework of the general linear model (GLM).

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

SCT describes individuals who are "dreamy", "spacey", slow moving, hypoactive, have difficulty initiating tasks, and often seem under-motivated and under-aroused. In a population sample of 1,249 adults with and without ADHD, and with and without SCT, Barkley identified nine cardinal symptoms of SCT: 1) prone to daydreaming instead of concentrating; 2) trouble staying alert/awake in boring situations; 3) being easily confused; 4) being easily bored; 5) feeling spacey/in a fog; 6) frequently feeling lethargic; 7) being underactive/having less energy than others; 8) being slow moving; 9) not processing information quickly/accurately [1]. Individuals were identified as SCT if they had at least 5 of 9 symptoms rated often or very often on the 9-item SCT subscale from the Barkley Adult ADHD Rating Scale-IV: Self-Report (BAARS-IV; hereafter called the Barkley SCT Scale) [2]. The prevalence rate of SCT in this sample was 5.8%, approximately half of whom had ADHD. These results indicate that SCT is common in a large subgroup of adults with ADHD, but is not restricted to ADHD.

SCT may represent a clinically meaningful condition with distinct underlying pathophysiology and treatment response. Several investigators have posited the existence of neurobiologically distinct subtypes of ADHD that are differentially characterized by deficits in executive/inhibitory control, reward-related motivational processes, and state regulation [3-8]. This proposal to investigate treatment response of adults with ADHD and SCT is proposed in that context. To date, there has only been one naturalistic treatment trial of methylphenidate (MPH) in children with ADHD and SCT, which found that the response for SCT was lower than core ADHD symptoms [9].

However, that study was done with MPH. A controlled, clinical trial of LDX in adult ADHD with and without SCT is of critical importance for several reasons:

1) SCT is highly co-morbid and impairing in adult ADHD but there have been no controlled treatment studies of SCT in adults.

2) The magnitude of response in adults with ADHD and SCT is not known, but it is presumed (possibly incorrectly) from preliminary pediatric data that it may be less robust [9].

3) There have been no treatment trials of amphetamines (AMP) in SCT and ADHD.

Examining the efficacy of AMP in SCT is important as the AMP stimulant class is more potent than the MPH class through a dual effect on adrenergic/dopaminergic pathways, which may be important for effects on SCT.

1.2 Investigational Agent

Vyvanse (Lisdexamfetamine Dimesylate) manufactured by Shire, is a DEA class two, sympathomimetic amine. Its indications are for treatment of attention-deficit hyperactivity disorder. The initial adult dosage is 30mg with allowed adjustments in increments of 10mg or 20mg at weekly intervals. The maximum dosage is 70mg/day. Pediatric dosage will not be discussed as we will only recruit adults for this study. Vyvanse is supplied in 20mg, 30mg, 40mg, 50mg, 60mg, and 70mg capsules.

Drug interactions with Vyvanse (Lisdexamfetamine Dimesylate)

Urinary acidifying agents (e.g., ascorbic acid) increase urinary excretion and decrease the T1/2 of the amphetamine, while urinary alkalinizing agents (e.g., sodium bicarbonate) decrease urinary excretion and extend the T1/2 of the amphetamine; adjust dose accordingly. There can be possible contraindications with Vyvanse if used with an MAOI or used within 14 days of the last MAOI dosage.

Pregnancy with Vyvanse (Lisdexamfetamine Dimesylate)

Vyvanse is a Category C and is not for use while pregnant or nursing. There are no adequate and well-controlled studies with Vyvanse in pregnant women. Vyvanse is an amphetamine and its sympathomimetic effects on placental perfusion and fetal blood flow are unknown. Adverse pregnancy outcomes, including premature delivery and low birth weight have been seen in infants born to mothers dependent on amphetamines. Animal reproduction studies performed with lisdexamfetamine dimesylate showed no effects on embryofetal morphological development and survival. Long-term neurochemical and behavioral effects have been seen in animal developmental studies using clinically relevant doses of amphetamine (d- or d,l-). Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [28].

Vyvanse (Lisdexamfetamine Dimesylate) mechanism of action

Sympathomimetic amine; CNS stimulant. Product of dextroamphetamine. Blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the releases of these monoamines into the extraneuronal space.

Vyvanse (Lisdexamfetamine Dimesylate) Pharmacokinetics

Absorption: Rapid; Tmax=1 hr (Lisdexamfetamine), 3.5 hrs (Dextroamphetamine). Distribution: Found in breast milk. Metabolism: Hydrolysis by RBC; Dextroamphetamine (active metabolite). Elimination: Urine (96%; 42% amphetamine, 2% unchanged), feces (0.3%); T1/2=<1 hr. (www.nlm.nih.gov).

1.3 Preclinical Data

Vyvanse is approved by the Food and Drug Administration (FDA) for the treatment of ADHD in adults and children. SCT describes individuals who are “dreamy,” “spacey,” slow moving, hypoactive, have difficulty initiating tasks, and often seem under-motivated and under-aroused. This study will determine similarities and differences between adults with ADHD with SCT and adults with ADHD without SCT. This important study will investigate the treatment response of Adults with ADHD

and SCT using Vyvanse verses Placebo (sugar pill). Information regarding the clinical presentation of adults with ADHD (those with and without SCT) will establish the potential utility of LDX in the population of adults with ADHD and SCT. As such, this study will address important gaps in the existing treatment literature.

1.4 Clinical Data to Date

To date, there has only been one naturalistic treatment trial of methylphenidate (MPH) in children with ADHD and SCT, which found that the response for SCT was lower than core ADHD symptoms [9]. However, that study was done with MPH.

A controlled, clinical trial of LDX in adult ADHD with and without SCT is of critical importance for several reasons:

1) SCT is highly co-morbid and impairing in adult ADHD but there have been no controlled treatment studies of SCT in adults.

2) The magnitude of response in adults with ADHD and SCT is not known, but it is presumed (possibly incorrectly) from preliminary pediatric data that it may be less robust [9].

3) There have been no treatment trials of amphetamines (AMP) in SCT and ADHD.

Examining the efficacy of AMP in SCT is important as the AMP stimulant class is more potent than the MPH class through a dual effect on adrenergic/dopaminergic pathways, which may be important for effects on SCT.

1.5 Dose Rationale

FDA data on adult short term dosing information from clinical trials show that doses of Vyvanse are 30 mg, 50mg or 70mg. The patients were initiated on these doses and then they were titrated up by 20mg with a maximum dose of 70mg.

1.6 Research Risks & Benefits

1.6.1 Risk of Study Drug

Study drug risks with Vyvanse (Lisdexamfetamine Dimesylate) are decreased appetite, insomnia, upper abdominal pain, irritability, nausea and vomiting, weight decreased, dry mouth, dizziness, affect lability, rash, diarrhea, anxiety, anorexia, jittery feeling, and agitation. Patients will be told to take medication once daily in the morning and report if they have any of these effects at each visit [10].

Warnings and Precautions with Vyvanse (Lisdexamfetamine Dimesylate) are sudden death, stroke, and myocardial infarction (MI) reported in adults. Sudden death reported in children and adolescents with structural cardiac abnormalities and other serious heart problems [10]. Patients will have an electrocardiograph (EKG) prior to induction on Vyvanse (Lisdexamfetamine Dimesylate). Subjects will be monitored weekly for hypertension, tachycardia and any cardiac abnormalities. People with heart abnormalities will not be treated with amphetamines. These serious but uncommon side effects were reported by people who took Vyvanse. The following cardiovascular side effects (involving the heart and/or blood vessels) have been reported with the use of amphetamines:

- Sudden death
- Cardiomyopathy (enlargement of the heart or muscle weakness)
- Myocardial infarction (heart attack)
- Increased blood pressure
- Tachycardia (rapid heart rate)
- Palpitations (forceful, sometimes irregular heartbeats)

Vyvanse (Lisdexamfetamine Dimesylate) may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Vyvanse may induce a mixed/manic episode in patients with bipolar disorder. Patients will be screened for any preexisting Axis 1 diagnosis, which would exclude them from the study.

The following uncommon central nervous system side effects involving the brain and/or spinal cord have been reported with the use of amphetamine: stroke, psychotic episodes, mania, euphoria, depression, dysphoria, overstimulation, aggressive behavior, hostility, seizures, tremor, dyskinesia, exacerbation of phonic tics including Tourette's syndrome or motor tics, blurry vision, dizziness, restlessness, and headache. If during the course of the study patient develops any of these side effects including changes in mood, the study doctor will discontinue patient from the study and refer the patient to regular treatment.

Vyvanse (Lisdexamfetamine Dimesylate) is associated with decreased weight and growth in pediatric patients which will not be studied in this clinical trial. There are also these uncommon gastrointestinal side effects: diarrhea, constipation, urticaria, skin rashes, unpleasant taste, and other allergic reactions.

Vyvanse (Lisdexamfetamine Dimesylate) is also associated with peripheral vasculopathy, including Raynaud's phenomenon, which generally improves after dose reduction or discontinuation. Observe carefully for digital changes during treatment.

Sometimes people have allergic reactions to drugs. Allergic reactions can be mild or severe, but they should always be taken seriously. In rare cases, severe allergic reactions can be life-threatening.

Some things that happen during an allergic reaction are:

- A rash
- Having a hard time breathing
- Wheezing when you breathe
- Sudden drop in blood pressure
- Swelling around the mouth, throat, or eyes
- Fast pulse
- Sweating

1.6.2 Other Risks of Study Participation

There are other potential risks associated with participating in this study. Patients will be made aware of these risks. There is a minimal risk when obtaining blood samples, which include slight bruising, swelling, pain, blood clots, and a small risk of infection or a temporary feeling of faintness. Only experienced trained staff will perform phlebotomy on these patients. A minimal risk is associated with an EKG, which include an initial feeling of coldness when the test material touches your skin and a localized rash or skin irritation from the test material.

There is the risk associated with taking a placebo, which is similar to not taking medication for ADHD. When patients take placebo during the study, it is possible that their ADHD symptoms may return or get worse. The study doctor and the study staff will monitor these ADHD symptoms while the patient is taking the placebo. There is a risk if patients stop their regular medication to be in the study; their ADHD symptoms may return or get worse. It would be vital to inform the patients to tell the study doctor or study staff right away if they have any problems.
The risk associated with stopping current ADHD medications before starting the study include: dizziness, nausea, headache, abnormal sensations in arms and legs, fatigue, vomiting, irritability, sleeplessness, diarrhea, anxiety, fainting, excessive sweating. These side-effects with similar drugs were temporary and usually resolved by themselves.

There is a possible risk of loss of confidentiality related to urine screens and clinical data obtained during this study. As a guard against the loss of confidentiality, all information will be stored in locked files which can be accessed only by members of the research staff for this project.

1.6.3 Potential benefits

This research study includes procedures that may change the treatment patients with ADHD would otherwise receive. We hope knowledge gained will be of benefit to the patients. While there may not be a direct benefit to the patients, it is hoped that the knowledge gained will benefit others in the future.

2 Study Objectives

Primary Objective: The primary objective is to examine changes in ratings of ADHD symptoms and SCT. The primary measure of ADHD symptoms will be the total score on the ADHD Rating Scale (ADHD-RS) with prompts [16]. The primary measure of SCT will be the Barkley SCT Scale.

Secondary Objectives:

1) Examine changes in the BRIEF-A Metacognition Index and Motivation Subscales as these subscales are more closely related to measures of arousal and motivation than other subscales of the BRIEF-A.

2) Examine changes in ratings of functional impairment via the B Barkley Functional Impairment Scale (BFIS).

3) Examine changes in a battery of neuropsychological tests of arousal and alerting, including:
    i. The Cambridge Neuropsychological Testing Automated Battery (CANTAB) ADHD battery: A validated battery of 4 tests which assess motor speed (Motor Control Task), spatial working memory (Spatial Working Memory), response inhibition (Stop Signal Task), and sustained attention (Rapid Visual Information Processing) [17]. In addition, we have included the Attention Switching Task (AST), an useful test in defining the cognitive phenotype in individuals with ADHD + high IQ. Measures of reaction time and reaction time variability will be

examined.

ii. The Wechsler Adult Intelligence Scale-IV (WAIS-IV): Coding and Symbol Search subtests will be used to evaluate processing speed [18].

4) Examine potential differences in nature and severity of ADHD symptoms (total, inattentive, and hyperactive-impulsive), symptoms of executive function (BRIEF GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), neuropsychological test performance on the CANTAB and WAIS subtests listed above, and impairment (Barkley Functional Impairment Scale (BFIS)) [27]
5) The On-Top scale will be used on treatment outcome in adult ADHD to measure executive functions in daily life.[29][30]

3 Study Design

3.1 General Design

1) Total number of subjects/Total sample size: Approximately 120 patients with ADHD (with the final number of subjects depending on the proportion of ADHD subjects who have SCT; we have based our projections on an estimated 50% prevalence) in the phenotype phase (screening visit); 50 adults with ADHD and SCT+ will enter the treatment phase with LDX and placebo. We will analyze data from all subjects who take at least one dose of medication in both blocks. Using a 20% drop-out rate to occur throughout the trial, we estimate that approximately 50 subjects will enroll in the trial; 46 patients will complete the first phase of treatment, 44 patients will complete the intervening placebo washout, and 40 patients will complete each treatment phase.
2) Justification for sample size: We will enroll a sufficient number of subjects to recruit 80 patients with ADHD and SCT to enter the treatment study. The 50% prevalence of SCT in adult ADHD has been established in community samples [1, 2]. Power for this study was calculated using PASS [22] based on the primary outcome, i.e. change between baseline and week 4 of treatment on the Barkley SCT scale. Previous studies suggest that the upper bound of the effect size for the comparison of ADHD

medications vs. placebo for ADHD symptoms varies between 1.2 and 1.5 standard deviations. Using a conservative estimate of effect that is half as robust for SCT as ADHD we based on our calculations on a 0.6 ES for SCT symptoms. The primary comparison will be a reduction in SCT symptoms on LDX vs. placebo. With 45 evaluable patients with SCT we will have 80% power to detect an effect size (ES) of 0.6 using a two-sided test with a type I error of 0.05.

Study Phases

Recruitment and Selection of SCT cases (Phenotype phase)

We plan to recruit 120 adults (20% screen fail rate), to evaluate at the screening visit approximately 100 adults with ADHD at two sites (NYU and Mount Sinai) to identify 50 SCT+ and 50 SCT-. These patients will be evaluated with clinical measures of SCT (Barkley SCT Scale), ADHD (ADHD-RS with prompts), executive function (BRIEF-A), assessment of other psychiatric disorders (M.I.N.I.), global impairment (CGI), functional impairment (Barkley Functional Impairment Scale (BFIS)), suicidality (C-SSRS), and neuropsychological function (neuropsychological battery). Only patients in the SCT+ cohort will enter the treatment phase of the protocol.

LDX Treatment Phase

We are proposing a 2-site (NYU and Mount Sinai) study of LDX in 50 adults with ADHD + SCT. The study will be a double-blind, 10-week, cross-over treatment trial of LDX (4 weeks; 30 – 70 mg/day) vs. placebo (4 weeks) with an intervening single-blind placebo washout period (2 weeks). During the LDX treatment epoch, LDX treatment will be initiated at a dose of 30mg/day at Visit 2 and can be titrated up (in the judgment of the investigator) in increments of 20mg, based upon clinical response and tolerability, to 50mg/day at Visit 1 and 70mg/day at Visit 3. Subjects receiving daily doses of 50mg or 70mg of LDX will be allowed to down titrate one dosage step of 20mg during Visits 3-5 if (in the judgment of the investigator) they are having issues in tolerability. The highest effective dose of LDX will then be maintained until Visit 6. Patients will be seen weekly throughout the trial except during placebo washout. The same schedule will occur during Phase 2 of the study.

During the Phase 2 LDX treatment epoch, LDX treatment will be initiated at a dose of 30mg/day at Visit 7 and can be titrated up (in the judgment of the investigator) in increments of 20mg, based upon clinical response and tolerability, to 50mg/day at Visit 1 and 70mg/day at Visit 8. The titration procedure will follow that of phase 1.

3.2 Primary Study Endpoints

The primary study endpoint is to examine the efficacy of lisdexamfetamine dimesylate (LDX) versus placebo on symptoms of sluggish cognitive tempo (SCT) in adults with ADHD and SCT.

3.3 Secondary Study Endpoints

The secondary study endpoints are to define the SCT phenotype and determine similarities and differences between adults with ADHD with and without SCT on SCT symptoms, executive function symptoms, nature and severity of ADHD symptoms, and neuropsychological profile

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1) Male or female between the ages of 18-60 of all races and ethnicity.
2) Meets DSM-IV-TR criteria for a primary diagnosis of inattentive or combined type ADHD as diagnosed via the Adult ADHD Clinician Diagnostic Scale version 1.2 (ACDS v1.2) [10].
3) If SCT+ group, ≥ 5 items on the Barkley SCT Scale must be rated 3 (“often”) or 4 (“very often”) and total SCT symptom score ≥ 26; must have a T-score ≥ 65 on the Metacognition Index Subscale of the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A) [11].
4) If SCT+ group, Impairment: must have a total score > 95th percentile on the Barkley Functional Impairment Rating Screen (Barkley Functional Impairment Scale (BFIS) [13].
5) If SCT- group, < 5 items on the Barkley SCT Scale must be rated 3 (“often”) or 4 (“very often”) and total SCT symptom score < 26; must have a T-score < 65 on the Metacognition Index and Motivation Subscales of the BRIEF-A.

4.2 Exclusion Criteria

1) Meets DSM-IV-TR criteria for a primary diagnosis of hyperactive-impulsive type ADHD as diagnosed via the ACDS v1.2.
2) Any other current psychiatric disorder, determined via the M.I.N.I , which requires pharmacotherapy treatment.
3) Current suicidal ideation or history of suicide attempts, based on the Columbia-Suicide Severity Rating Scale(C-SSRS) [15].
4) Lifetime history of bipolar disorder or any psychotic disorder as per the M.I.N.I
5) Pregnant, breastfeeding or women planning to become pregnant.
6) Positive urine drug toxicology are excluded.
7) Any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromise the subject safety.

4.3 Subject Recruitment and Screening

We plan to recruit 120 adults (20% screen fail rate) to evaluate at the screening visit; approximately 100 adults with ADHD at two sites (NYU and Mount Sinai) to identify 50 SCT+ and 50 SCT-. We will accept referrals from other clinicians provided that the patients have given their clinicians permission to be contacted by the study team or the clinician has provided our contact information to the patient. We will advertise within and outside New York Langone Medical Center. There are flyers, radio and print advertisement created and approved for help with recruitment.
New York University Langone Medical Center and Mount Sinai will submit to their own IRBs. Subjects will be seen only at location consented. Mount Sinai will provide NYU with their IRB approvals for submission to the NYU IRB. Both locations will have their own staff and pharmacy.

Patients will be evaluated with clinical measures of SCT (Barkley SCT Scale), ADHD (ADHD-RS with prompts), executive function (BRIEF- A), assessment of other psychiatric disorders (M.I.N.I) global impairment (CGI), functional impairment (BFIRS), suicidality (C-SSRS), and neuropsychological function (neuropsychological battery). Only patients in the SCT+ cohort will enter the treatment phase of the protocol.

Intended age for this study will require participants to be within 18 years to 60 years of age. There is no restriction as to gender, race or ethnic origin of patients.

We will contact patients from clinician referrals who have provided permission to be contacted or patients will call us from either a clinician referral or advertisement. They will be asked to provide verbal consent to see if they would be a possible candidate by completing a pre-screening questionnaire over the phone. After the pre-screen, a 5 minute general questionnaire about their mental or physical health, they will be asked to come in to the clinic at One Park Avenue for screening. An application for waiver of documentation of consent will be submitted as consent is obtained over the telephone and the questionnaire is minimal risk. All collected PHI from anyone who does not pass the pre-screening questionnaire or who decides not to participate will be immediately withdrawn.

At the study site, research staff will have patients read the consent form and opt to discuss with their private doctor and family. When the patient is ready, research staff will read and review each page of consent form. The research staff will ask if the patient understands and allow the patient to ask questions. After the patient has completed the inform consent process and has given consent by signing the consent document screening will begin. The patient is given a copy of the signed consent form. The original consent form will be filed in the patient's source documentation for the study. The research staff will document the inform consent process and file this with the patient's source documents.

If the patient does not agree to participate in the study the inform consent will be maintained; marked across the signature "declined" with a note to file regarding circumstances of patient's decline. See Consent Process Attachment [7]

4.4 Early Withdrawal of Subjects

Patients can withdraw or take back their permission to use and share his/her health information at any time. When the patient withdraws their permission, they will not be able to take back information that has already been used or shared with others. Patients will be made aware and instructed on how to withdraw their permission by

sending a written notice to the principal investigator for the study noted on page one of their consent form. If patient withdraws their permission, he/she will not be able to stay in this study. Patients will be withdrawn if, in the opinion of the study doctor, is no longer safe for the patient to participate in the study. We can get verbal permission to follow-up the patient in the event they suffer adverse events. We will document three attempts to contact the patient via phone. If unable to contact will send the patient a certified letter. Attachment [4]

4.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects will be followed up after withdrawal for any adverse events and concomitant medications used since last in the research clinic. There will be three documented attempts to contact the patient. In addition we will send a certified letter explaining important to contact us for a follow-up appointment. These contact methods along with any information if obtained will be added to source documentation. See attached letter (Attachment 3)

5 Study Drug

5.1 Description

Vyvanse (Lisdexamfetamine Dimesylate) is manufactured by Shire. Vyvanse is a DEA class two, sympathomimetic amine. Its indications are for treatment of attention-deficit hyperactivity disorder. The initial adult dosage is 30mg with allowed adjustments in increments of 10mg or 20mg at weekly intervals. The maximum dosage is 70mg/day.Vyvanse is supplied in 20mg, 30mg, 40mg, 50mg, 60mg, and 70mg capsules. Contradictions with Vyvanse are use with an MAOI or use within 14 days of the last MAOI dosage. Vyvanse (Lisdexamfetamine Dimesylate) is a Category C and is not for use in nursing. [26]

5.2 Treatment Regimen

Medication will not be dispensed until week 1 of the study. Then for four weeks the dose of LDX or Placebo will be dispensed starting at 30mg up to 70 mg per day with an intervening single-blind placebo washout period (2 weeks).

Block One: During the LDX/epoch, LDX/Placebo treatment will be initiated at a dose of 30mg/day at Visit 2 and can be titrated up (in the judgment of the investigator) in

increments of 20mg, based upon clinical response and tolerability, to 50mg/day at Visit 3 and 70mg/day at Visit 4.

Subjects receiving daily doses of 50mg or 70mg of LDX/Placebo will be allowed to down titrate one dosage step of 20mg during Visits 3-5 if (in the judgment of the investigator) they are having issues in tolerability. The highest effective dose of LDX will then be maintained until Visit 6.

Placebo Washout: At this time the patient are in the washout placebo phase for two weeks.

Block Two: At the end of the Placebo Washout Phase, Visit 7 (week 6), participants will be initiated at a dose of 30mg/day and can be titrated up starting at Visit 8(in the judgment of the investigator) in increments of 20mg, based upon clinical response and tolerability.

Subjects receiving daily doses of 50mg or 70mg of LDX/Placebo will be allowed to down titrate one dosage step of 20mg during Visits 8-10 if (in the judgment of the investigator) they are having issues in tolerability. The highest effective dose of LDX will then be maintained until Visit 11

5.3 Method for Assigning Subjects to Treatment Groups

Due to the study being double blind, an unblinded research assistant will conduct the block randomization of the subjects under the supervision of the NYU pharmacy. The block randomization will choose patients to start either the Vyvanse or placebo phase for four weeks. After these four weeks there will be a two week washout, then again Vyvanse or placebo phase for another four weeks. At the end of the study, the patients will be asked safety questionnaires. The patient and the research staff will not know whether the patient is on Vyvanse or placebo. In case of an emergency, the pharmacy can break the blind with permission from the principal investigator. We will know if the patient is on Vyvanse or placebo after the blind is broken.

5.4 Preparation and Administration of Study Drug

When a patient is consented and prior to enrollment, the research staff will send the investigational pharmacy a copy of the informed consent. On the day of randomization, the research staff will inform the investigational pharmacy of patient status via secure e-mail. The investigational pharmacy will conduct the block randomization as noted in section 5.4. The study doctor will write a prescription for the patient noting that the study drug name is listed as Vyvanse/Placebo. The investigational pharmacist will prepare the study medication for patient dispensation, based on the block randomization and the prescription order. A patient specific label will be generated by the investigational pharmacy and affixed to the study drug bottle. The hard copy of the prescription will be provided to the investigational pharmacy to be filled and dispensed by the research pharmacist to the patient. The contact number of the NYU Investigational Drug Service (IDS) is (212) 263-5039 and the general e-mail address is: investigational.pharmacy@nyumc.org

5.5 Subject Compliance Monitoring

Study team will assess and track subject compliance with the study treatment regimen by asking patient about compliance with daily dosing. Patients will be reminded weekly to take daily dosing at the same time each morning. Patients will be required to bring back their pill bottles at each visit. There will be a pill count at each visit conducted by the study coordinator. Patients who are significantly non-compliant will have their safety assessed by study doctor and withdrawn from the study.

5.6 Prior and Concomitant Therapy

Any medication or non-pharmacological therapy that is taken by or administered to the subject at any point during the course of the study must be recorded in the case report form (CRF).

Prior Medications Allowed/Disallowed During Study

Subjects taking stimulant or non-stimulant medications for the treatment of ADHD during screening will be washed out for a period equivalent to 5 half-lives of the medication prior to baseline evaluations.

Disallowed Medications during Study

Use of any of the following medications is not permitted during the study;

1) Antidepressant prescription medication (e.g., paroxetine, sertraline, venlafaxine, monoamine oxidase [MAO] blocker, tricyclic, etc.) and St. John's Wort.
2) Anticonvulsant medications (e.g., phenytoin, carbamazepine, lamotrigine, valproic acid, etc.) and antipsychotic medication.
3) Sedating antihistamines (e.g., doxilamine succinate, diphenhydramine) for use in sedation or aiding with sleep. Subjects routinely use sedating antihistamines for seasonal allergies will be required to switch to non-sedating alternatives for the duration of the study, unless otherwise contraindicated.
4) Other medications that may interfere with the assessment of cognitive function are not permitted during the study.

5.7 Packaging (Pharmacy)

- Study drug and placebo is supplied in 20mg, 30mg, 40mg, 50mg, 60mg, and 70mg capsules in bottles containing #9 pills each. The bottles will be labeled with Patient's name, study identification number, Study name and NYU IRB number, study drug name, study drug dosage, strength, quantity, directions for usage and physician's name and contact information.
- Study drug will be shipped in bulk # 40 bottles at each shipment.

5.8 Blinding of Study Drug

The study drug is double blinded. The research staff; including study doctor and the patient will not know if the patient is receiving Vyvanse or placebo. The study pharmacist will know which study medication either Vyvanse or Placebo the patient is taking and can break the blind in case of an emergency.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Shire pharmaceuticals will ship the study drug quantity for sufficient for patients to be enrolled and treated at NYULMC via the NYU Investigational Drug Service (IDS), contact number (212) 263-5039. Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated

study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

Study medication will be dispensed in a tight, light-resistant container as defined in the USP. The study medication will be stored at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F)

5.9.3 Dispensing of Study Drug

The study doctor will write a prescription for the patient noting that the study drug name is listed as Vyvanse/Placebo. The research coordinator will call pharmacist to prepare the study medication. Study coordinator will fax the prescription to the pharmacist, who will randomize the patient and give the patient a randomization number. The paper prescription will be taken to the investigational pharmacy by study coordinator to be filled and dispensed by research pharmacist, directly to the patient. An electronic record of the order will also be entered into the EPIC system by the research physician and verified by the investigational pharmacist. The study drug will be prepared, labeled and dispensed by the research pharmacist from the NYU Investigational Drug Service (IDS), contact number (212) 263-5039. Used study bottles/pills will be returned to the investigational pharmacist at each dispensing visit. Dispensing/ Return logs will be used and documentation of pills dispensed and pills returned will be documented weekly.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures:

	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit9	Visit 10	Visit 11
Study Procedures and Assessments	Week -3-0		Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 7	Week 8	Week 9	Week 10
	Screening		**Baseline 1**	**Treatment (LDX or PBO) 1**			**EOT 1**	**End of PBO Washout/ Baseline2**	**Treatment (LDX or PBO) 2**			**EOT 2**
SCREENING												
Consent	X											
Demographics	X											
M.I.N.I	X											
ACDS v1.2	X											
Medical History	X											
Psychiatric History	X											
Medical Review of Systems	X											
Physical Exam	X											
Hematology, Chemistry, Urinalysis, and UDS	X											
Urine Pregnancy Test	X											
ECG	X											
Review Eligibility	X	X	X									
EFFICACY												
ADHD-RS		X		X	X	X	X	X	X	X	X	X
Barkley SCT Scale		X		X	X	X	X	X	X	X	X	X
CGI-S		x		X	X	X	X	X	X	X	X	X
SAFETY												
Vital Signs		X	X	X	X	X	X	X	X	X	X	X
C-SSRS		X	X				X	X				X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
NEUROPSYCHOLOGICAL BATTERY/EXECUTIVE FUNCTIONING												
CANTAB ADHD		x					X	X				X
WAIS-CODING & SYMBOL SEARCH		X					X	X				X
BRIEF-A		X					X	X				X
BFIS		X					X	X				X
ON-TOP		X										
OTHER												
Dose Dispense/ Adjustment			X	X	X	X			X	X	X	
Drug Accountability				X	X	X	X	X	X	X	X	X

STUDY VISIT SCHEDULE: This is a two part study. Patients will sign this consent form and be asked to do the following: Visit the study doctor weekly over a 12-week period, communicate over the phone between visits 6 and 7 and approximately 1 week after visit 10, and follow study instructions. In addition, patients who participate in the second part of the study will be asked to take study drug as instructed at the same time each day. Patient will have their blood drawn once in the study about 10mls will be collected for hematology and blood chemistry.

6.1 Visit 1 (Screening) Week -3 to Week 0

Screening (Visit 1) (Phenotype Phase): Informed consent, demographics, medical/psychiatric history, physical exam, review of systems, 12-lead electrocardiogram (ECG), vital signs, ADHD diagnosis via ACDS v1.2, M.I.N.I (assessment of other Axis-I psychiatric diagnosis), laboratory testing (hematology, blood chemistry and urinalysis), urine pregnancy screen (for female participants), urine toxicology screen, Clinical Global Impressions Scale (CGI) [22], C-SSRS, Neuropsychological Battery, and prior and concomitant medications (CM))

6.2 Visit 2 (Baseline 1) Day 0

Baseline visit: During this visit subjects will have all tests/procedures completed and reviewed. We will review medical history, any current of adverse events (AE) and concomitant medications (CM) since screening visit. We will perform vital signs and C-SSRS. We will ensure completion of any assessments not finished during the screening visit. Subjects will be given medication to take the next morning if they are found to have both ADHD and SCT. Study Medication is not dispensed until all assessments and procedure are complete for the baseline visit

Note: If at the end of this baseline visit, the patient is found to have both ADHD and SCT; they will be invited to continue to the second part of the study. If the patient has both ADHD and SCT, he/she will be given Study Medication (Vyvanse or placebo) to take the next morning. Placebo looks just like Vyvanse but has no active ingredients, like a sugar pill. The study medication can be taken with or without food at the same time every day.

6.3 Visits 3, 4, & 5 (Treatment) Day 7±2, Day 14 ±2, and Day 21±2; Weeks 1-3

Visits 3, 4, and 5 will occur at 7, 14, and 21 days (±2 days) from Baseline These visits will consist of ADHD-RS with prompts, Barkley SCT Scale, CGI, vital signs, and assessment of adverse events (AE) and concomitant medications (CM). Study Medication is dispensed.

6.4 Visit 6 (EOT1) Day 28±2; Week 4

Visit 6 will consist of ADHD-RS with prompts, Barkley SCT Scale, BRIEF-A, Barkley Functional Impairment Scale (BFIS), neuropsychological battery, CGI, vital signs, assessment of adverse events (AE) and concomitant medications (CM).Study Medication is dispensed. Drug accountability performed. Patient will receive *two* study medication bottles.

6.5 Telephone Visit- Day 35±2; Week 5

Study Coordinator will call the patient to ask about safety and compliance. We will ask them; how had they been feeling since their last visit. We will document any adverse events, concomitant medications and medication compliance. Study coordinator will go over instructions regarding study medication and remind patient of their next appointment.

6.6 Visit 7 (Baseline 2) Day 42±2; Week 6

Visit 7 will consist of ADHD-RS with prompts, Barkley SCT Scale, BRIEF-A, Barkley Functional Impairment Scale (BFIS), neuropsychological battery, CGI, vital signs, assessment of adverse events (AE) and concomitant medications (CM). Study Medication is dispensed. Drug accountability is performed.

6.7 Visits 8, 9, & 10 (Treatment) Day 49±2, Day 56±2, and Day 63±2; Weeks 7-9

Visits 8 through 10 will consist of the ADHD-RS with prompts, Barkley SCT Scale, CGI, vital signs, assessment of adverse events (AE) and concomitant medications (CM). Study Medication is dispensed. Drug accountability is performed

6.8 Visit 11 End of Treatment 2; Day 70±2 Week 10

End of treatment will consist of ADHD-RS with prompts, Barkley SCT Scale, BRIEF-A, Barkley Functional Impairment Scale (BFIS), C-SSRS, neuropsychological battery, CGI, vital signs, assessment of adverse events (AE) and concomitant medications (CM). Drug accountability is performed.

6.9 Follow-Up Telephone/End of Study- Visit Day 77±2; Week 11

Study Coordinator will call the patient to ask how they been feeling since their last visit. We will document any adverse events, concomitant medications.

7 Statistical Plan

Dr. Farone will conduct the statistical analysis of this study.

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7.1 Sample Size Determination

Phase I: Recruitment and Selection of SCT cases (Phenotype phase)
We plan to recruit 120 adults (20% screen fail rate) to evaluate at the screening visit; approximately 100 adults with ADHD at two sites (NYU and Mount Sinai) to identify 50 SCT+ and 50 SCT-. These patients will be evaluated with clinical measures of SCT (Barkley SCT Scale), ADHD (ADHD-RS with prompts), executive function (BRIEF- A), assessment of other psychiatric disorders (M.I.N.I) global impairment (CGI), functional impairment (FIRS- QS), suicidality (C-SSRS), and neuropsychological function (neuropsychological battery). Only patients in the SCT+ cohort will enter the treatment phase of the protocol.

Phase II: Treatment Phase
We are proposing a 2-site (NYU and Mount Sinai) study of LDX in 50 adults with

ADHD + SCT. The study will be a double-blind, 10-week, cross-over treatment trial of LDX (4 weeks; 30 – 70 mg/day) vs. placebo (4 weeks) with an intervening single-blind placebo washout period (2 weeks). During the LDX treatment epoch, LDX treatment will be initiated at a dose of 30mg/day at Visit 2 and can be titrated up (in the judgment of the investigator) in increments of 20mg, based upon clinical response and tolerability, to 50mg/day at Visit 3 and 70mg/day at Visit 4. Subjects receiving daily doses of 50mg or 70mg of LDX will be allowed to down titrate one dosage step of 20mg during Visits 2-4 if (in the judgment of the investigator) they are having issues in tolerability. The highest effective dose of LDX will then be maintained until Visit 4. Patients will be seen weekly throughout the trial.

7.2 Statistical Methods

Phenotype Phase: Comparisons between the adult ADHD patients cohorts with SCT and without SCT in terms of ADHD symptoms (total, inattentive and hyperactive-impulsive, symptoms of executive function (BRIEF GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), neuropsychological tests (CANTAB ADHD module, WAIS Coding and Symbol Search and Attention Network Test (ANT), and impairment (on Barkley Functional Impairment Scale (BFIS)) will be examine via One Way ANOVA .

Treatment Phase: Changes in outcome ratings in the patients in the treatment phase with LDX and placebo will be modeled with longitudinal generalized estimating equation (GEE) mixed regression models using STATA 12.0 [StataCorp, 2011 #25856] within the framework of the general linear model (GLM). The GLM allows us flexibility in modeling the outcome variable by choosing the appropriate distribution and link function. Each model will predict outcome scores from treatment group (drug vs. placebo), study visit (ordinal predictor), order (drug or placebo first) and the two and three-way interactions among: treatment group, visit, and order. We will first test for order effects and drop effects that are not significant at $p < .05$. The visit by treatment interaction indicates if the reduction in symptoms over time significantly differs between drug and placebo. Our primary analyses will be intention

to treat (ITT) but we will explore the data with less conservative per protocol analyses to assure that we do not miss any signals in the data. Because this is a randomized trial, which follows subjects over a short period of time, missing data is not expected to impact our analyses. Should this become an issue, we will impute data using STATA's impute procedure. Using logistic regression, a responder analysis will be conducted using pre-hoc priori criteria for treatment response (30%) decreases in total ADHD-RS and Barkley SCT scores). These will be last observation carried forward (LOCF) endpoint models that predict responder status (yes/no) from drug group, order and the drug by order interaction. Baseline symptom scores will be included as covariates.

Safety Analysis: Variables to be summarized and listed include vital signs, adverse events, clinical laboratory results, ECG readings, and the C-SSRS. All adverse events results will be tabulated in manuscripts along with significance testing using the appropriate general linear model. These models will use LOCF endpoint analyses with terms for drug, order and the drug by order interaction

7.3 Subject Population(s) for Analysis

All subjects will be entered into the analysis including:

All-randomized population: Any subject randomized into the study, regardless of whether they received study drug

All-treated population: Any subject randomized into the study that received at least one dose of study drug

Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any

subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document (though should be grouped under one diagnosis).

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important events

Unexpected and related SAE will be reported to the IRB and within 5 days after study personnel become aware of the event. Serious adverse events (SAE) occurring after a participant is discontinued from the study will only be reported if the Principal Investigator believes that the event may have been caused by the study medication or a protocol procedure.

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:

The following events must be reported to Shire by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Additionally, an FDA Form 3500A (MEDWATCH Form; see Attachment [5]) must be completed by the investigator and faxed to the studyShire within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

Joe Kerkering- jkerkering@shire.com
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16
Wayne, PA 19087

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse events shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**

  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but **no later than 5 working days** of the protocol deviation.

- **Withdrawal of IRB approval**

  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but **no later than 5 working days** of the IRB notification of withdrawal of approval.

8.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- **Unanticipated problems including adverse events that are unexpected and related**
  - Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:

The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3.3 Sponsor reporting: Notifying the FDA

Shire is required to report certain study events in an expedited fashion to the FDA. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days** (via telephone or facsimile report)

  Any study event that is:

  – associated with the use of the study drug
  – unexpected,
  – fatal or life-threatening

- **Within 15 calendar days** (via written report)

  Any study event that is:

  – associated with the use of the study drug,
  – unexpected, and
  – serious, but not fatal or life-threatening

  -or-

  – A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

  – Suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form; see Attachment [5]), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting reports is noted below:

Mitchell V. Mathis, M.D. CAPT USPHS Director Division of Psychiatry Products *or* CAPT Paul A. David, Chief Project Management Staff, at (30 I) 796-1058.

8.3.4 Sponsor reporting: Notifying participating investigators

It is the responsibility of Lead Principal Investigator Dr. Adler to notify Shire and Dr. Jeffery Newcorn, Principal Investigator at Mount Sinai of all and any adverse event that meets the FDA 15-day reporting requirement criteria as note above in section 8.3.4. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

8.4 Unblinding Procedures

While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study follow-up and referral is necessary to ensure a subject's safety. Patients will be unblinded if in the opinion of the investigator subjects adverse events or continued participation will be unsafe to the subjects. If subjects are experiencing a decline of 30% per the clinical assessments conducted they will be withdrawn. Patient will be unblinded by our investigational pharmacist to ensure safety. We will manage the patient and report these finding to our medical monitor. In the case subject is unblinded not due to an adverse event we will notify shire within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.

8.5 Stopping Rules

If subjects are experiencing a decline of 30% per the clinical assessments conducted they will be withdrawn. Patient experiencing adverse events that in the opinion of the investigator the subject can no longer participate due to a change in medical status (e.g. experiences from adverse events becomes pregnant the subject will be discontinued from the study).

<u>These are the possible reasons for termination from the study:</u>

- Adverse events
- Lack of efficacy
- Lost to follow-up

- Pregnancy
- Withdrawal by subject
- Noncompliance
- Protocol violation
- Other

8.6 Medical Monitoring

Dr. Adler as the lead principal investigator will oversee safety for both NYU and MSSM. It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site and communicate safety issues as per the monitoring plan. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan; Attachment [6] .Medical monitoring will include a regular assessment of the number and type of serious adverse events and a report to be submitted to the IRB. Dr. Vatsal G. Thakkar, M.D. is a Clinical Assistant Professor of Psychiatry at the NYU School of Medicine. Dr. Thakkar is board certified in psychiatry and licensed to practice medicine in the states of New York and Connecticut.

Medical Monitor: Vatsal Thakkar M.D.

304 Park Avenue, 11th floor

New York, NY 10010

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Study Monitoring Plan:
Dr. Adler, as PI, will be responsible for review of all aspects of the study at our site, and will review subject progress weekly, including:

- Recruitment procedures
- Informed consent
- Recruitment procedures
- Protocol violations
- Occurrence and handling of adverse effects
- Patient Outcomes
- Participants' safety, privacy and confidentiality

- Protocol violations
- Occurrence and handling of adverse effects
- Patient Outcomes
- Participants' safety, privacy and confidentiality
- Study progress toward recruitment goals and participant retention/attrition rates
- Review of new scientific literature pertinent to the safety of participants

All subject charts will be reviewed for accuracy and completeness on a weekly basis. Also electronic data will be entered twice for verification purposes. Dr. Adler, in collaboration with the subcontracting site PI, Lenard Adler, MD, will determine whether risk/benefit ratios have changed to the extent that the trial should be modified or discontinued. Specific recommendations for protocol modifications, should they be necessary, will be elaborated, with accompanying rationale for each. This will be reported to sponsor, IRB and manufacturers who will donate the study drug (Shire Pharmaceuticals Group plc.)
Dr. Adler will provide Dr. Thakkar (medical monitor) information on a monthly basis for the medical monitor report. The medical monitors report will be submitted to the IRB at each continuation. Unless, there are serious adverse events and those will be reported immediately Data Monitoring Committee- Not Required

9 Data Handling and Record Keeping

9.1 Confidentiality

Any identifying information collected in the course of the study, such as study records and evaluations (including those stored on computer), will be securely locked and will only be accessible to authorized study staff. If the results of this study are reported in medical journals or at meetings, the participant will not be identified by name or other identifying information.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above

the item, then initial and date it.

9.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the **monitoring plan** in Attachment [6]. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment [2] for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.
Research coordinator will obtain consent as noted in the standard operating procedure for the consent process. See Attachment [1]

It will not be necessary to use 'Auditor/Witness' and/or translator because persons who consent must be able to read English well enough to understand informed consent and study materials. Patient must be able to pass the short quiz given at the end of the consent prior to signing consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from Shire Pharma.

12.2 Conflict of Interest

Dr. Adler, who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) had the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

Patients will not be paid for participation in this study. They will receive a twenty five dollar voucher for their travel at each study visit. By the end of the study the patient would have received a combined amount of three hundred dollars for travel. We will give patients vouchers which they would redeem for cash at each attended visit.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

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