NYU Langone Health

Official Title:	Study of the Duration and Efficacy of MYDAYIS on Adult ADHD Symptoms and Executive Function Throughout the Day Into the Early Evening
NCT Number:	NCT03945175
Study Number:	19-00046
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• September 2, 2021

CLINICAL STUDY PROTOCOL

Study of the Duration and Efficacy of Mydayis on Adult ADHD Symptoms and Executive Function Throughout the Day into the Early Evening

Protocol Number

Shire # IIR-USA-002255 IRB#s19-00046

Clinical Phase

Phase III

Sponsor

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Protocol Version

July 17 2020 Version
August 12, 2021 Version

Confidentiality Statement:

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Synopsis

Primary Objective

The primary objective of this proposal is to examine the efficacy of Mydayis on ADHD symptoms and executive function throughout the day into early evening, about 14-15 hours after first morning dosing. The primary measure of ADHD symptoms will be the total score on the AISRS, the Adult ADHD Investigator Symptom Rating Scale.

Secondary Objectives

The secondary objectives of this study are to examine the changes after Mydayis treatment in:

1. Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS and overall impairment via the Clinical Global Impression-Severity (CGI-S) scale.

2. Total ADHD symptoms fourteen to fifteen hours after morning dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and the Inattentive (IA) and hyperactive- impulsive (HI) ADHD symptom TASS subsets.

3. Neuropsychological measurement of executive function in the early evening (fourteen to fifteen hours after morning dosing) as measured by the WebNeuro Assessment Battery(Verbal Interference/Stroop, Go/No-Go, Continuous Performance Test/Test of Variables of Attention, or TOVA)

4. Clinical symptoms of executive function, as measured by the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A).

Study Duration

The estimated total study duration is approximately 15-18 months. Each subject's participation will last about seven weeks, depending on the amount of time spent in the screening phase of the study.

It will take 12 months to recruit the initial 50 subjects (consented subjects). The last subject will be in the study for approximately 7 weeks. The final months are for data entry, data analysis and manuscript preparation.

Study Design

This is an outpatient study for subjects between the ages of 18-55, inclusive, who have an Attention Deficit/Hyperactivity Disorder (ADHD) diagnosis meeting all inclusion criteria while also not meeting any of the exclusion criteria.

Number and Description of Each Treatment Arm/Group

This six-week, treatment/placebo trial will be conducted after thorough screening has occurred and subjects are deemed eligible to move to the treatment/placebo portion of the study. After a two-week, subject, single–blinded, placebo lead-in, all patients will receive four weeks of order-fixed treatment with Mydayis (12.5mg — 37.5mg/day).

Doses per Subject per Treatment

During the two-week, placebo lead-in, all subjects will receive 12.5mg of placebo at Visit 1 and Visit 2. During the four-week, subject single-blind treatment phase, Mydayis will be initiated at a dose of 12.5mg/day at Visit 3 and can be titrated up (in the judgment of the investigator) in increments of 12.5mg, based upon clinical response and tolerability, up to 25mg at Visit 4, up 37.5mg at Visit 5 and holding at the dose from visit 5 of up to 37.5mg at Visit 6.

Subjects will return study medication not taken along with any medication bottles, including empty medication bottles.

Of Note

Hybrid Study Visits will consist of remote and in clinic visits. Patients will be seen weekly, remotely and in the clinic throughout the trial. One week after dosing has been completed, subjects will receive a follow up safety telephone call. We will ask about adverse events start and resolution. We will also ask about integration into regular treatment in the community.

This makes the subject's participation in the study approximately 7 weeks or more depending on the length of time the subject spent in screening.

Completers are defined as subjects who have completed Visit 7.

Study Population

Inclusion Criteria

1. Male or female between the ages of 18-55, inclusive, of all races and ethnicity.
2. Meets DSM 5-TR criteria for a primary diagnosis of ADHD (including predominantly inattentive presentation or combined presentation) as diagnosed via the Adult ADHD Clinician Diagnostic Scale version 1.2 (ACDS v1.2)
3. Current diagnosis of comorbid major depressive disorder, anxiety disorder or dysthymia comorbid diagnoses in remission and stable on medications for three weeks. Medication to treat these comorbid disorders will be held constant for the duration of the protocol.

Exclusion Criteria

1. Meets DSM 5-TR criteria for a primary diagnosis of ADHD (including predominantly inattentive presentation or combined presentation) as diagnosed via the Adult ADHD Clinician Diagnostic Scale version 1.2 (ACDS v1.2)
2. Any other current psychiatric disorder, determined via the M.I.N.I, which requires pharmacotherapy treatment; exception for major depression, dysthymia and anxiety disorders in remission but stable on psychiatric medications for three weeks or more at the discretion of the principal investigator
3. Current suicidal ideation or history of suicide attempts, based on the Columbia-Suicide Severity Rating Scale(C-SSRS)
4. Lifetime history of bipolar disorder or any psychotic disorder as per the M.I.N.I; exception for major depression, dysthymia and anxiety disorders in remission, but stable on psychiatric medications for three weeks or more at the discretion of the principal investigator.
5. Pregnant or breastfeeding women, or women planning to become pregnant.
6. Positive urine drug toxicology is excluded.
7. Any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromises the subject's safety.

Number of Participants

In this study, approximately 100 subjects will be phone prescreened, which will give us at least 50 participants coming in for screening and consenting for participation. Up to 50 patients will be enrolled, to ensure that 32 evaluable patients reach the end of treatment at week seven.

There will be screen failures in this study. Subjects can fail the phone prescreen or those that passed the phone prescreen can fail during the in-clinic screening during the

MINI (psychiatric interview), ACDS (ADHD diagnostic interview) or upon notice of abnormal safety test results.

The remaining 34 subjects will be randomized/enrolled into the treatment/placebo part of the study. During the two-week, placebo lead-in, if the subject has a 30% decrease in the AISRS, they will not move into the 4-week treatment period of the study.

We are aiming to have at least 32 subjects complete the study. The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 32 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size: it is half of the 1.2 effect size reported by Spencer et al. 2008 and thus is at the lower end of what we should expect to see in this study.

Number of Study Sites

This is an investigator-initiated protocol with funding from Shire. Shire will provide the investigational product MYDAYIS and PLACEBO in addition to some funding. This is a single site study, where all subjects are consented and all study activities are conducted remotely and/or at the address below.

NYU Langone Medical Center- Adult ADHD program

One Park Ave, 8th floor

New York NY 10016

Primary Outcome Variables

We will explore correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day into the early evening.

Secondary and Exploratory Outcome Variable

Exploratory Objectives: This study will explore correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day into early evening. The study will also explore correlations of changes in

neuropsychological assessments of executive function (WebNeuro: Verbal Interference/Stroop, Go/No-Go, Continuous Performance Test (CPT)/TOVA) versus changes in BRIEF-A measures. Furthermore, it will examine potential differential effects of Mydayis in the sample of patients who have defined executive dysfunctions (defined by a Global Executive Composite (GEC) score on BRIEF-A ≥ 65 at placebo-baseline). The study will also examine correlations in self-report of ADHD symptoms on the ASRS versus clinician report on the AISRS and also changes in self report measures of executive function and emotional dyscontrol on the ASRS versus these measures on the BRIEF-A.

Visit Schedule Table

Description	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	TC
	Week -3-0 Screen	**Week -3-0 Screen/BL**	**Week 1 PbO Lead in**	**Week 2 PbO Lead in**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	
Consent	X								
Demographics	X								
MINI	X								
ACDS v1.2	X								

AISRS	X		X	X	X	X	X	X	
CGI S	X		X	X	X	X	X	X	
WEBNEURO; STROOP, GO/NO-GO, CONTINUOUS PERFORMANCE TEST CPT	X			X				X	
BRIEF A	X			X				X	
EXPANDED ASRS	X		X	X	X	X	X	X	
TASS		x	X	X	X	X	X	X	
Medical History		X							
Psychiatric History		X							
Physical Exam		X							

Hematology Chem, UA	X								
Drug Toxicology	X								
Urine Pregnancy Test	X								
ECG /EKG Reading	X								
Review Eligibility		X							
Vital Signs w/ HT/WT	X		X	X	X	X	X	X	
C-SSRS		X	X	X	X	X	X	X	
Prior/Con Meds		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X

Dose adjustment		X	X	X	X	X			
Dispense/High Intensity		X	X	X	X	X	X		
Returns/Drug Account		X	X	X	X	X	X	X	
Subject reimbursement		X	X	X	X	X	X	X	

Study Flow Chart

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1 - Introduction

1.1 Introductory Statement

One purpose of this trial is to extend the evidence basis for Mydayis in adult ADHD to include efficacy with a clinical ADHD symptom measure validated for DSM-5 adult ADHD. *Spencer et al. (2008)* and *Weisler et al. (2017)* used the ADHD-RS scale; the former also used DSM-4 adult ADHD criteria and training for adult ADHD prompts. *Weiser et al. (2017)* embedded adult ADHD prompts into the ADHD-RS. Although the ADHD-RS with prompts has been widely utilized in ADHD trials, it not yet been fully validated for DSM-5. The Adult ADHD Investigator Symptom Rating Scale (AISRS) is a similar scale to the ADHD-RS with adult prompts, but it employs adult stem questions (as compared to the ADHD-RS using childhood stem questions), rates the 18 DSM symptoms of ADHD and has been validated for the DSM-5 (*Silverstein MJ et al. 2018*).

The AISRS has also been used in multiple adult ADHD clinical treatment trials evaluating atomoxetine, droxidopa, and OROS methylphenidate (see section on scales) and its use in a Mydayis trial will further the comparison of Mydayis results with these agents. Another purpose of this trial is to reexamine the clinical efficacy of Mydayis later in the day on ADHD symptoms; the data on ADHD symptoms via the TASS (*Spencer et al. 2008*) is a decade old and has not been examined in subsequent trials. This study will specifically examine TASS ratings 14-15 hours after morning dosing. We have chosen 14-15 hours to allow comparison to neuropsychological assessments completed later in the day. A third purpose is extend the data on the effects of Mydayis on executive function to include neuropsychological measures of executive function and specific clinical scales of executive function.

2 - Background

2.1.1 Preclinical Experience

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by problems with sustaining attention, organization, planning, procrastination, daydreaming, restlessness, impulsivity and hyperactivity. Adult ADHD is a common and highly impairing disorder affecting 4.4% of the US population *(Kessler RC et al. 2006*). Recent factor analyses *(Adler et al. 2017*) have highlighted the importance of co-travelling symptoms of executive function deficits (organization, planning, time management and working memory) in addition to the core symptoms of inattention and hyperactivity-impulsivity noted in the DSM (DSM —5) (*American Psychiatric Association 2013*). Furthermore, it has been posited that executive function deficits (organization, planning, time management and working memory) define the impairment in ADHD *(Barkley and Murphy 2010*). Psychostimulants are a mainstay of pharmacotherapy for adult ADHD and five sustained release preparations have been FDA approved for adult ADHD.

The recommended starting dose of Mydayis is 12.5 mg once daily in the morning upon awakening. Initial doses of 25 mg once daily may be considered for some patients. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly, up to a maximum dose of 50 mg once daily, based on the therapeutic needs and response of the patient. Doses above 50 mg daily have shown no additional clinically meaningful benefit. (FDA 2017 Reference ID: 4114154).

2.1.2 Clinical Experience

Mydayis is a triple-beaded preparation of mixed amphetamine salts which in early studies *(Spencer et al. 2008)* has been shown to have a clinical duration of up to 16 hours via the TASS scale and a documented efficacy on adult ADHD DSM-4 symptoms via the ADHD-RS (where training on use of adult ADHD prompts was given but not utilized with scale administration). Data from this study also supported some efficacy of Mydayis on co-travelling symptoms on executive function as measured by subsets of the Brown ADD Scale (*Bron et al. 2014*). However, specific executive function clinical scales and neuropsychological tests of executive function were not utilized, and executive function was not assessed later in the day.

MYDAYIS was studied in adults between the ages of 18 to 55 using the Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th editions (DSM-IV-TR and DSM-5) criteria for ADHD. The safety data for adults were pooled from three randomized, double-blind, placebo-controlled studies in doses of 12.5 mg to 75 mg per day (1.5 times the maximum recommended dosage). Doses higher than 50 mg per day did not demonstrate additional clinical benefit and are not recommended. (*FDA 2017, Reference ID: 4114154*).

The decision for the dosage amount in this study was made based on the results from former studies on the efficacy of Mydayis in treating adult ADHD.

In the proposed study, subjects can receive Mydayis in doses of 12.5mg to 37.5mg per day. Subjects will receive Mydayis at an initial dose of 12.5mg per day after the two-week, placebo, lead-in phase. Dosage can be titrated up in increments of 12.5mg at the approval and opinion of the investigator. At Visit 4, dosage can be increased to 25mg per day for some subjects based upon clinical response and tolerability. At Visit 5, dosage can be increased to 37.5mg per day for some subjects. At Visit 6, the decision to stay at the maximum dosage of 37.5mg per day or decrease dosage in increments of 12.5mg for the remainder of the study will be made. The decision for dosage amount was made based on the results from former studies on the efficacy of Mydayis in treating adult ADHD.

Efficacy of MYDAYIS in the treatment of ADHD was established in the following trials:

Three short-term trials in adults (18 to 55 years, Studies 1, 2, and 3)

Two short-term trials in pediatric patients (13 to 17 years, Studies 4 and 5)

Adult patients (18 to 55 years) with ADHD

The approved adult doses, 12.5 mg, 25 mg, and 37.5 mg are based on Studies 1 and 3 and the 50 mg dose efficacy is based on Study 2. Doses up to 75 mg per day (1.5 times the maximum recommended adult dosage) were evaluated, but demonstrated no additional clinical benefit.

A 4-week, randomized, double-blind, multi-center, placebo-controlled, forced-dose titration, safety and efficacy study (Study 1) was conducted in adults aged 18 to 55 years (N=275) who met DSM-5 criteria for ADHD. Patients were randomized in a 1:1:1 ratio, to two MYDAYIS treatment groups and a placebo group. Group 1 received a dose of 12.5 mg/day throughout the study. Group 2 were titrated on a weekly basis from the initial dose 12.5 mg until target dose of 37.5 mg/day was reached by Week 3 and were maintained at 37.5 mg throughout the study. Group 3 received placebo.

The primary efficacy endpoint was defined as the change from baseline of the adult ADHD-Rating Scale (RS) with prompts total score at Week 4. Baseline adult ADHD-RS with prompts total score was defined as the last valid adult ADHD-RS with prompts total score assessment prior to taking the first dose of double-blind investigational product, usually at Visit 2. The primary comparison of interest was at Week 4 for each MYDAYIS dose compared with placebo.

MYDAYIS demonstrated a statistically significant treatment effect compared with placebo on change of ADHD-RS total score from baseline at visit 6 (Week 4), for both 12.5 mg and 37.5 mg doses respectively (Study 1 in Table 4). Patients on MYDAYIS also showed statistically significantly greater improvement on the Clinical Global Impression of Improvement (CGI-I) score compared with placebo treatment.

Two multi-center, randomized, double-blind, placebo-controlled, crossover studies of MYDAYIS 25 mg/day (Study 3) and 50 mg/day (Study 2) were conducted in adult patients who met DSM-IV TR criteria for ADHD. The efficacy was determined using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. Efficacy assessments were conducted at 2, 4, 8, 12, 14, and 16 hours post-dose using the PERMP. MYDAYIS treatment, compared to placebo, reached statistical significance at either 2 hours (Study 2) or 4 hours (Study 3) post-dose to 16 hours post-dose in both studies. In a pre-specified supplementary analysis for Study 2, the maximum approved dose of MYDAYIS (50 mg) demonstrated a statistically significant treatment effect compared with placebo beginning at 2 to 16 hours post-dose(FDA 2017, Reference ID: 4114154).

2.2 Background/prevalence of research topic

Recent factor analyses (*Adler et al. 2017*) have highlighted the importance of co-travelling symptoms of executive function deficits (organization, planning, time management and working memory) in addition to the core symptoms of inattention and hyperactivity-impulsivity noted in the DSM (DSM-5). (*American Psychiatric Association 201*3). Furthermore, it has been posited that executive function deficits define the impairment in ADHD (*Barkley and Murphy 2010*). Psychostimulants are a mainstay of pharmacotherapy and five sustained-release preparations have been FDA approved for adult ADHD.

This proposal specifically addresses these issues by using Mydayis, a triple-beaded preparation of mixed amphetamine salts, which in early studies (*Spencer et al. 2008*) has been shown to have a clinical duration of up to 16 hours via the TASS scale and a documented efficacy on adult ADHD DSM-4 symptoms. We propose to assess ADHD symptoms with the AISRS, an ADHD symptoms scale validated for the DSM-5 then re-assess ADHD clinical symptoms later in the day via the TASS. We will also assess executive function throughout the day with the clinical scale BRIEF-A and neuropsychological tests (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA). Psychostimulants are a mainstay of pharmacotherapy for adult ADHD and five sustained release preparations have been FDA approved for adult ADHD

3 - Rationale/Significance

3.1 Problem Statement

One purpose of this trial is to extend the evidence basis for Mydayis in adult ADHD to include efficacy with a clinical ADHD symptom measure validated for DSM-5 adult ADHD. The *Spencer et al. (2008)* and *Weisler et al. (2017)* studies used the ADHD-RS scale; the former using DSM-IV adult ADHD criteria and training for adult ADHD prompts. The *Weisler et al. (2017)* study embedded adult ADHD prompts into the ADHD-RS. Although the ADHD-RS with prompts has been widely utilized in ADHD trials, it not yet been fully validated for DSM-5. The Adult ADHD Investigator Symptom Rating Scale (AISRS) is a similar scale to the ADHD-RS with adult prompts, but it employs adult-stem questions (as compared to the ADHD-RS using childhood stem questions), rates the 18 DSM symptoms of ADHD and has been validated for the DSM-5 (*Silverstein MJ et al. 2018).* It has also been used in multiple adult ADHD clinical treatment trials studying atomoxetine, droxidopa, and OROS methylphenidate (see section on scales) and its use in a Mydayis trial will further the comparison of Mydayis results with these agents.

3.2 Purpose of Study/Potential Impact

Another purpose of this trial is to re-examine the clinical efficacy of Mydayis later in the day on ADHD symptoms; the data on ADHD symptoms via the TASS *(Spencer et al. 2008)* is a decade old and has not been examined in subsequent trials. This study will specifically examine TASS ratings 14-15 hours after morning dosing. We have chosen 14-15 hours to allow comparison to neuropsychological measures which could not be completed later in the day in the clinic. A third purpose is extending the data on the effects of Mydayis on executive function to include neuropsychological measures of executive function and specific clinical scales of executive function.

The impact this research will have on ADHD would be more knowledge regarding effects of Mydayis and its effects on executive function would improve the quality of life for people with ADHD.

3.3.1 Potential Risks

MYDAYIS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older. The most common adverse reactions reported in adults were insomnia, decreased appetite, dry mouth, decreased weight, increased heart rate, and anxiety.

The following adverse reactions have been associated with the use of amphetamines.

Cardiovascular: Dyspnea, sudden death. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, euphoria, dyskinesia, dysphoria, headache, tics, fatigue, aggression, anger, logorrhea, dermatillomania, and paresthesia (including formication).

Eye Disorders: Mydriasis.

Gastrointestinal: Unpleasant taste, constipation.

Allergic: Urticaria, rash, hypersensitivity reactions, including angioedema and anaphylaxis. Serious skin rashes, including Stevens - Johnson syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido, frequent or prolonged erections. Skin: Alopecia.

Vascular Disorders: Raynaud's phenomenon.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Risk of taking a placebo

The subject will have periods of taking a placebo and during this time, their symptoms may return and or get worse.

Risk of Safety Clinical assessments

Potential risks associated with obtaining blood samples are minimal but include: slight bruising, swelling, pain, blood clots, and a small risk of infection or a temporary feeling of faintness.

Potential risks associated with an EKG include an initial feeling of coldness when the test material (sticky pads and gel) touches the skin, localized rash or skin irritation from the test material.

Risk of loss of Confidentiality

Possible loss of confidentiality related to urine screens and clinical data obtained during this study is recognized. 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.

Patients will be told to take medication once daily in the morning and report if they have any of these effects at each visit.

3.3.2 Potential Benefits

This research study includes procedures that may change the treatment patients with ADHD would otherwise receive. We hope the 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.

4 - Study Objectives

4.1 Hypothesis

In subjects with adult ADHD after Mydayis treatment (from end of single-blind placebo lead-in) there will be significant improvement in:

1) Overall symptoms of adult ADHD as measured by the total score on the Adult ADHD Investigator Symptom Rating Scale (AISRS) (primary effect).

2) Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS and overall impairment via the Clinical Global Impression-Severity (CGI-S) scale.

3) Total ADHD symptoms fourteen hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS); Inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets (TASS) subsets.

4) In neuropsychological measurement of Executive Function in the early evening (fourteen to fifteen hours after morning dosing) as measured by (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA)

5) In clinical symptoms of Executive Function in the early evening, as measured by the BRIEF-A.

4.2 Primary Objective

The primary objective of this proposal is to examine the efficacy of Mydayis on ADHD symptoms and executive function throughout the day into early evening, about 14-15 hours after first morning dosing. The primary measure of ADHD symptoms will be the total score on the AISRS, the Adult ADHD Investigator Symptom Rating Scale.

4.3 Secondary Objectives

The secondary objectives of this study are to examine the changes after Mydayis treatment in:

1. Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS and overall impairment via the Clinical Global Impression-Severity (CGI-S) scale.

2. Total ADHD symptoms fourteen to fifteen hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and the Inattentive (IA) and hyperactive- impulsive (HI) ADHD symptom TASS subsets.

3. Neuropsychological measurement of executive function in the early evening (fourteen to fifteen hours after morning dosing) as measured by (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA)

4. Clinical symptoms of executive function, as measured by the BRIEF-A.

5 - Study Design

5.1 General Design Description

Description of Study type

This will be a phase three, single-blind study, with a two-week, placebo lead-in and then a four-week forced titration treatment with Mydayis with starting dose of 12.5 mg/day with titration based on clinical response and potential adverse events.

Number and Description of Each Treatment Arm/Group

This will be a six-week trial after the screening period. After a two-week, subject single-blind, placebo lead-in, all patients will receive four weeks of Mydayis (12.5mg-37.5mg/day), with treatment order fixed. Study visits are hybrid; conducted remotely and in clinic.

Doses per Subject per Treatment

During the two-week, placebo lead-in, all subjects will receive 12.5mg Placebo at Visit 1 and Visit 2. During Visit 3, Mydayis treatment will be initiated at a dose of 12.5mg/day and will increase in increments of 12.5mg, based upon clinical response and tolerability, up to 25mg at Visit 4, up 37.5mg at Visit 5 and holding at the dose from visit 5 of up to 37.5mg at Visit 6. There will be no dispensation at Visit 7, which is the last in clinic/remote visit for this study. Patients will be seen weekly throughout the trial both in clinic and remote.

Our primary outcome is effects of Mydayis on overall adult ADHD symptoms via total AISRS Score. In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on the AISRS; TASS scores 1 hour, 4 hours and 14-15 hours post dose (total, inattentive and hyperactive-impulsive subsets) (for effects of Mydayis over time at different points of the day and within the day); expanded Adult ADHD Self Report Symptom Rating Scale (expanded-ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets); symptoms of executive function (BRIEF-A: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor); and neuropsychological tests (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA): Response Time Variability [RVP], Response Time, d', Errors of Omission, Errors of Commission, Post-Commission Response Times, Multiple Responses, Anticipatory Responses).

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the two-week, single-blind, placebo lead-in as the

independent variable. All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for placebo responders in the analyses. We have chosen a single-blind placebo lead-in to define placebo responders, which are defined as patients who experience ≥30% decrease in their total AISRS scores during placebo lead-in treatment. Placebo responders will be discontinued from the study. We anticipate that, based on the literature, 10% or fewer of patients will be placebo responders and that the overall discontinuation rate in the trial will be 20%. Changes within the day in TASS ratings 1 hour post dose vs. 4 hours post dose vs. 14-15 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

Statistical Power Analysis

Justification for sample size:

Up to 50 patients will be enrolled to be sure that 32 evaluable patients reach the end of treatment at week six. The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 32 evaluable patients, will give a power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size: it is half of the 1.2 effect size reported by *Spencer et al. (2008)* and thus is at the lower end of what we should expect to see in this study.

5.1.1 Study Date Range and Duration

The total expected length of the study from subject recruitment to follow-up is approximately 15-18 months. The individual recruitment from screening to the follow up GCP phone call will be approximately 7-8 weeks. Note: screenings/washouts can take a few weeks.

5.1.2 Number of Study Sites

This is an investigator-initiated protocol with funding from Shire. Shire will provide the investigational products Mydayis and placebo, in addition to some funding. This is a single site study, where all subjects are consented and all study activities are conducted in person and/or remotely at the address below.

NYU Langone Medical Center- Adult ADHD program

One Park Ave, 8th floor

New York NY 10016

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary objective of this proposal is to examine the efficacy of Mydayis on ADHD symptoms and executive function throughout the day into the early evening–(14-15 hours after first morning dosing). This study will extend the evidence basis for Mydayis in adult ADHD to include efficacy with a clinical ADHD symptom measure validated for DSM-5 adult ADHD. The *Spencer et al. (2008)* and *Weisler et al. (2017)* studies used the ADHD-RS scale; the former using DSM-IV adult ADHD criteria and training for adult ADHD prompts. The *Weisler et al. (2017)* study embedded adult ADHD prompts into the ADHD-RS. Although the ADHD-RS with prompts has been widely utilized in ADHD trials, it not yet been fully validated for DSM-5. The Adult ADHD Investigator Symptom Rating Scale (AISRS) is a similar scale to the ADHD-RS with adult prompts, but it employs adult stem questions (as compared to the ADHD-RS using childhood stem questions), rates the 18 DSM symptoms of ADHD and has been validated for the DSM-5 (*Silverstein MJ et al. 2018*). It has also been used in multiple adult ADHD clinical treatment trials evaluating atomoxetine, droxidopa, and OROS methylphenidate (see section on scales) and its use in a Mydayis trial will further the comparison of Mydayis results with these agents. Another purpose of this trial is to re-examine the clinical efficacy of Mydayis later in the day on ADHD symptoms; the data on ADHD symptoms via the TASS (*Spencer et al. 2008)* is a decade old and has not been examined in subsequent trials. This study will specifically examine TASS ratings 14-15 hours after morning dosing. We have chosen 14-15 hours to allow comparison to neuropsychological measures which could not be completed later in the day in the clinic. A third purpose is extend the data on the effects of Mydayis on executive function to include neuropsychological measures of executive function and specific clinical scales of executive function.

Background/Rationale

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by problems with sustaining attention, organization, planning, procrastination, daydreaming, restlessness, impulsivity and hyperactivity. Adult ADHD is a common and highly impairing disorder affecting 4.4% of the US population *(Kessler RC et al. 2006).* Recent factor analyses *(Adler et al. 2017)* have highlighted the importance of co-travelling symptoms of executive function deficits (organization, planning, time

management and working memory) in addition to the core symptoms of inattention and hyperactivity-impulsivity noted in the DSM (DSM-5) (*American Psychiatric Association 2013*). Furthermore, it has been posited that executive function deficits define the impairment in ADHD (*Barkley and Murphy 2010*). Psychostimulants are a mainstay of pharmacotherapy for adult ADHD and five sustained-release preparations have been FDA approved for adult ADHD. One of these preparations, Mydayis, is a triple-beaded preparation of mixed amphetamine salts, which, in early studies, (*Spencer et al. 2008)* has been shown to have a clinical duration of up to 16 hours via the TASS scale and a documented efficacy on adult ADHD DSM-IV symptoms via the ADHD-RS (where training on use of adult ADHD prompts was given but not utilized with scale administration). Data from this study also supported some efficacy of Mydayis on co-travelling symptoms on executive function as measured by subsets of the Brown ADD Scale. However, specific executive function clinical scales and neuropsychological tests of executive function were not utilized, and executive function was not assessed later in the day. This proposal specifically addresses these issues by using the AISRS, an ADHD symptoms scale validated for DSM-5, re-assessing ADHD clinical symptoms later in the day via the TASS, and utilizing clinical scales (BRIEF-A) and neuropsychological tests (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA)

5.2.2 Secondary and Exploratory Outcome Variables

Exploratory Objectives: We will explore correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day. We will also explore correlations of changes in neuropsychological assessments of executive function (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA) versus changes in BRIEF-A measures. Furthermore, we will examine potential differential effects of Mydayis in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A $\geq$ 65 at placebo-baseline). We will also examine correlations in self-report of ADHD symptoms on the ASRS versus clinician report of ADHD symptoms on the AISRS, and also changes in self report measures of executive function and emotional dyscontrol on the ASRS versus these measures on the BRIEF-A.

5.3 Study Population

The study population will consist of males and females between the ages of 18-55, inclusive. They will be referred from area clinicians, NYU clinicians via EPIC (slicer dicer) and advertisements such as flyers, online search engine searches and StudyKIK.

The population must have ADHD and no comorbid psychiatric issues requiring treatment; exception for major depression, dysthymia and anxiety disorders in remission, but stable on psychiatric medications for three weeks or more at the discretion of the principal investigator

They should also meet all inclusion and not meet any of the exclusion criteria. In the opinion of the investigator, subjects must be of good health and a good candidate for a clinical research trial.

Up to 50 patients will sign consent and be screened, 34 will be enrolled into the single-blind placebo lead-in, and 32 patients will be randomized into the four-week treatment phase to be sure that at least 30-32 evaluable patients reach the end of treatment at week six.

Good clinical practices will ensure we call subjects one week after their last dose of study medication to ensure they are not experiencing any adverse events and have connected to treatment as usual in the community.

5.3.1 Number of Participants

In this study, approximately 100 subjects will be phone prescreened, which will give us at least 50 participants coming in for screening and consenting for participation. Up to 50 patients will be enrolled to be sure that 30-32 evaluable patients reach the end of treatment at week six. We expect some of the subjects to screen fail either during the telephone phone screen or during the in clinic/remote visit. Clinic visit screen failures can occur during the MINI (psychiatric interview), ACDS (ADHD diagnosis interview) or upon notice of abnormal safety test results.

The remaining 34 subjects will be randomized/enrolled into the treatment. During the two-week, placebo lead-in, if the subject has a 30% decrease in the AISRS, they will not move into the 4-week treatment period of the study. We are aiming to have at least 30-32 subjects complete the study.

Subjects who are asked by the investigator to end participation due to the ≥30% decrease in their AISRS will be given a letter of their participation in the study and the ADHD Referral List, if requested by subject.

The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 32 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size it is half of the 1.2 effect size reported by (*Spencer et al. 2008)* and thus is at the lower end of what we should expect to see in this study.

5.3.2 Eligibility Criteria/Vulnerable Populations

The principal investigator, or his assigned co-investigator, will determine eligibility based on inclusion/exclusion criteria, and review of all medical and psychiatric screening assessments. We will not recruit any participants that are identified as vulnerable.

Inclusion

1) The study population will consist of male and female outpatients between 18 and 55 years of age, inclusive.

2) Primary diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the 16 criteria as determined by the Adult Clinician Diagnostic Scale version 1.(ACDS v1.2).

3) Current diagnosis of comorbid major depressive disorder, anxiety disorder or dysthymia comorbid diagnoses in remission and stable on medications for three weeks. Medication to treat these comorbid disorders will be held constant for the duration of the protocol.

Exclusion

1) Primary diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the 16 criteria as determined by the Adult Clinician Diagnostic Scale version 1.(ACDS v1.2).

2) Any other current psychiatric disorder, determined via the M.I.N.I, which requires pharmacotherapy treatment: exception for major depression, dysthymia and anxiety disorders in remission but stable on psychiatric medications for three weeks or more at the discretion of the principal investigator

3) Current suicidal ideation or history of suicide attempts, based on the Columbia- Suicide Severity Rating Scale (C-SSRS).

4) Lifetime history of bipolar disorder or any psychotic disorder as per the M.I.N.I requiring treatment: exception for major depression, dysthymia and anxiety disorders in remission, but stable on psychiatric medications for three weeks or more at the discretion of the principal investigator

5) Pregnant or breastfeeding women 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 would compromise the subject's safety.

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

MYDAYIS [my-DAY-is] extended-release capsules, is a mixed salts of a single-entity amphetamine product. CII.MYDAYIS is a federally controlled substance (CII) because it contains amphetamine that can be a target for people who abuse prescription medicines or street drugs. MYDAYIS is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in people 13 years of age and older. It is a medication taken orally daily once in the morning. It can be taken with or without food. Subjects will be cautioned about drinking alcohol during treatment with MYDAYIS. Subjects will be cautioned about taking any other medications or supplements during the study.

Shire will provide MYDAYIs and the placebo comparator. They will be identical as the subject is blinded.

6.1.2. Dosage, Admin, Schedule

During the two-week, single-blind, placebo lead-in, all subjects will receive 12.5mg placebo at Visit 1 (Baseline) and Visit 2 (Week 1 Placebo Lead in).

During four-week, treatment period, Mydayis will be initiated at a dose of 12.5mg/day at Visit 3 and can be titrated up (in the judgment of the investigator) in increments of 12.5mg, based upon clinical response and tolerability. Dose increases up to 25mg at Visit 4, up 37.5mg at Visit 5 and holds at the dose from Visit 5 of up to 37.5mg at Visit 6. Note there is no dispensing on Visit 7; last in clinic/remote visit.

Patients will be seen weekly throughout the trial. Participants are given dosing instructions and will return to the clinic weekly for review of compliance. Subjects must have over 80% compliance to continue in the study.

Compliance will be tracked by counting the remaining pills in the bottle at each visit. Subjects are reminded to bring back their pills and empty bottles at each visit. Subjects are instructed that noncompliance without the doctor's approval would be dangerous. It may warrant reevaluation of their continued participation.

Investigational pharmacy will accept and document returns from research team/subjects. The Investigational Pharmacy will also dispense study medication to the research team/subjects.

6.1.3 Method of Assignment/Randomization

There is no plan for an assignment/randomization method after screening is complete and principal investigator has evaluated subject to be eligible for the study. The pharmacy

will receive an electronic copy of the first and last page of the subject's signed inform consent with the subject's contact information sheet. The pharmacy will dispense to subjects on a weekly basis. The first two dispensations will be 12.5 mg placebo and the following four weeks will be Mydayis starting at 12.5 titrating up to 25mg then holding at 35.7 mg for two weeks.

6.1.4 Blinding and Procedures for Unblinding

The study trial in regards to study drug is single blinded. The research staff, including study doctor, will know if the patient is receiving Mydayis or placebo. The subject will not know when they are on placebo or when they start the Mydayis treatment. The study pharmacist will know which study medication, either Mydayis or placebo, the patient is taking and can break the blind in case of an emergency.

6.1.5 Packaging/Labelling

Mydayis is an extended-release mixed amphetamine salts preparation formulated into a capsule. The doses that will be dispensed in this study are: 12.5mg, 25mg, and 37.5mg to be taken orally once a day in the mornings at approximately 5am.

Mydayis and placebo will be packaged in bulk stock bottles at the lowest dose of 12.5mg. They will be labeled according to the standard operating procedures of NYU Research Pharmacy. Investigator and research staff together with NYU Pharmacy will reach out to the sponsor for resupply. Expiry date will be included in the stock bottles. If expiry date changes at any time sponsor will send us documentation regarding product safety and change of the expiry date.

6.1.6 Storage Conditions

Mydayis is a controlled substance. It will be stored per NYU Investigational Pharmacy Standard Operating Procedures. It must be stored at room temperature between 68°F to 77°F (20°C to 25°C). Protect Mydayis from light. Pharmacy will dispose of remaining, unused, or expired Mydayis by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. Subjects will be instructed to keep Mydayis and all medicines out of the reach of children.

6.1.7 Concomitant therapy

Prior and Concomitant Therapy will be followed throughout the study. 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). Subjects will be encouraged to talk with the research team at each visit to document any new medicines, vitamins, and herbal supplements. Mydayis may affect the way other medicines work and other medicines may affect how Mydayis works. Taking Mydayis with other medicines or supplements can cause serious side effects.

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. This would be approximately 7-21 days per investigator's decision.

Disallowed medications

Use of any of the following medications is not permitted during the study; unless approved by investigator and documented in source.

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 using 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 or supplements that may interfere with the assessment of cognitive function are not permitted during the study.

6.1.8 Restrictions

Subjects will be screened for drug and alcohol abuse during the prescreen phase. Subjects are instructed on the dangers of drinking alcohol or engaging in drug use during treatment with Mydayis. They will be warned not to use Mydayis for any other condition except the condition for this study: ADHD. Subjects will be instructed and reminded at each study visit not to share this medication with other people, even if they have ADHD. They will be reminded that the Mydayis may harm those for who it is not prescribed for and it is against the law. Subjects will be reminded to report any adverse events or concomitant medications they are taking at each visit.

Subjects will be reminded to take their medication at 5am each morning, as the study assessments are dependent on the consumption of Mydayis at 5:00 am.

6.2. Assessments

The Adult ADHD Investigator Symptom Rating Scale (AISRS)

The AISRS is an 18-item, clinician-administered, semi-structured interview methodology developed to evaluate treatment responses (*Spencer et al. 2010).* The measure contains prompts and stem questions designed to capture the Diagnostic and Statistical Manual of Mental Disorders (DSM) symptoms of the disorder ADHD as they present in adulthood. Based on the responses from the patient, the administering clinician rates the symptom

severity as 0= none, 1= mild, 2= moderate, or 3= severe. The scale has been used and validated many times in a variety of clinical drug trials *(Adler & Gorny, 2015; Adler, Zimmerman, Starr, Silber, Palumbo, Orman & Spencer 2011 Goodman et al., 2017; Spencer et al., 2010)* .

The Adult ADHD Self-Report Scale (ASRS)

The Adult ADHD Self-Report Scale (ASRS) Symptom Checklist is a self-report that presents the 18 DSM ADHD symptoms in adult context and is rated on a frequency basis. It was developed by the World Health Organization (WHO) work group on adult ADHD, and comprises an 18-item Symptom Checklist that corresponds to the 18 symptoms found in the DSM and a six-item screener of which the items were extracted from the symptom checklist) to help identify adults at risk of ADHD*(Kessler et al., 2005;Ustun et al., 2017*). The Screener and the Symptom Checklist use a 5-point Likert-type scale to rate ADHD symptoms (0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4= very often). Depending on the question, "sometimes," "often," or "very often" suggest clinical impairment for that specific item. The ASRS v1.1 Symptom Checklist is designed to provide clinicians with an inventory of adult ADHD symptoms as the first part of a diagnostic evaluation or to be used in monitoring treatment response *(Adler, Shaw, & Alperin, 2015;Adler et al., 2006*). The ASRS has been expanded to include additional symptoms intended to assess executive function deficits (EFDs; nine items) and emotional dyscontrol (EC; four items). EFDs are deficiencies of high order cognitive processes, such as self-control, self-regulation, and ability to prioritize and to plan multiple tasks. EC includes symptoms of mood lability, irritability, and emotional overreactivity.

Time Sensitive Adult ADHD Symptom Scale (TASS)

The TASS scale is an 18-item scale matching the 18 DSM ADHD symptoms, with language changed to allow self-report ratings and assessment of ADHD symptoms throughout the day. It has been validated and used as a measure of change throughout the day in the in the Mydayis trial (*Spencer et al. 2008).*

The Clinical Global Impression Severity

The CGI-S scale is a validated, highly utilized measure of impairment in studies of adult ADHD and has been employed in prior Mydayis studies.

Behavior Rating Inventory of Executive Function®—Adult Version

The BRIEF-A is a 75 item self-report scale which is highly validated and normed It has three major scales: GEC, metacognition, and behavioral regulation scales and also has several subscales (see stats section). It is log transformed so scores ≥65 are considered significant as they are ≥ 1.5 SDs above the population mean. The scale has been used as a measure of executive function in several ADHD clinical trials *(Vyvanse and Mixed Amphetamine Salts: Adler, L.A. et al. 2014; atomoxetine: Adler, L.A. et al. 2014).*

WebNeuro Assessments

WebNeuro is a cognitive test battery used to identify markers of thinking, emotion, feeling and self-regulation. WebNeuro is a comprehensive neurocognitive assessment battery that can be completed over the internet. The electronically scored test has been proven to be reliable and valid when compared to scores done via paper and pencil. The WebNeuro platform is HIPPA compliant and can use the combination of personal and neurocognitive data making it an efficient battery for use in this research study.(Silverstien et al 2007) For the purpose of this study we will only be using three out of the available eleven cognitive assessments: Verbal Interference (or the Stroop Test), Continuous Performance Test -CPT(equivalent to the TOVA), and the Go/No-Go.

Go/No-Go

The Go-No is a cognitive test of the balance between automatic responding and response suppression. This tests impulsivity and inhibition by presenting a stimulus to respond to and a stimulus to suppress response to, or the go- and no-go stimuli, respectively.

Stroop Color Word Test (Verbal Interference)

The Stroop Test is a test of executive function where there is presentation of a list of colors, then words and then a list of colors and words where there is interference. It has been used as a measure of executive function in ADHD trials *(atmoxetine: Faraone et al. 2005).*

Test of Variables of Attention (TOVA) (Continuous Performance Test (CPT))

The TOVA is a continuous performance test, which also gives a measurement of executive function. The key measures of executive function are noted in the statistics section; specifically response time variability has been examined as a measure in both children and adults as measure sensitive to treatment effects (*metadoxine: Manor et al. 2012*; OROS methylphenidate: *Bron et al. 2014).* The TOVA test is FDA approved for ADHD.

6.2.1 Efficacy

To evaluate the efficacy of Mydayis, we will explore correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day. We will also explore correlations of changes in neuropsychological assessments of executive function (WebNeuro: Verbal Interference/Stroop, Go/No-Go, CPT/TOVA) versus changes in BRIEF-A measures. Furthermore, will examine potential differential effects of Mydayis in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A ≥65 at placebo-baseline). We will also examine correlations in self- report of ADHD symptoms on the ASRS versus clinician report of ADHD symptoms on the AISRS, and also changes in self-report measures of executive function and emotional dyscontrol on the ASRS versus these measures on the BRIEF-A.

6.2.2 Safety/Pregnancy-related policy

Throughout the study, we will monitor subjects for safety and possible pregnancy. During the screening and eligibility period, we will conduct and report, if applicable clinical laboratory results, to include pregnancy testing, ECG readings and the C-SSRS (conducted as needed per clinician discretion) if there are significant clinical findings. We will monitor subjects weekly for abnormal vital signs, adverse events, and concomitant medications. All adverse events results will be tabulated in manuscripts along with significance testing using the appropriate general linear model.

Subjects will be given a pregnancy contact sheet in the event there is a pregnancy. The pregnant woman will be given a pregnancy inform consent to read and sign to allow us to follow-up with the pregnancy until terminated or full term delivery.

6.2.2.1 Adverse Events Definition and Reporting

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of a study. Inter-current 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 significant

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event (SAE)** 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

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.

Reporting 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 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.

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
- 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

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) must be completed by the investigator and faxed to the study sponsor, Shire, within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site. Notify:

Sharon Hochman

Sr. Project Manager, US Medical Clinical Research

On Contractor assignment with Takeda Pharmaceuticals USA, Inc.

Mobile | +1 917 576 0040

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the 48 hours following the 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 IRB reporting 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.

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 7 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 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.

6.2.3 Pharmacokinetics

Pharmacokinetics will not be conducted for this study.

6.2.4 Biomarkers (if applicable)

Biomarker testing will not be done.

6.3 Study Procedures

Study Flow for Hybrid Study Visits.

During Screening/Baseline Visit (Week -3-0)

The screening visit will be conducted and completed in two parts: remote and in-clinic. During the remote portion, informed consent will be obtained at the screening visit before any study procedures are conducted. Study staff will review the inclusion and exclusion criteria, collect demographics, medical and psychiatric history, prior and concomitant medications, and confirm the ADHD diagnosis via the ACDS v 1.2 and AISRS. Subjects will then be placed on a hold in the screening phase, which can last 28 days up to 90 days. Subjects will be re-consented every 30 days and/or at baseline. Subjects will be called every other week during the holding phase to check willingness to continue to participate. During the dual remote/in-clinic portion, study staff will conduct a physical examination, medical review of systems, vital signs (pulse and blood pressure) and electrocardiogram (ECG/EKG). A blood sample will be collected for routine laboratory testing (hematology and blood chemistry) and a urine sample will be collected for urinalysis, urine pregnancy test (for females of child bearing potential), and urine drug screen. All or some of these clinical examinations can be waived from the screening process if subject can provide record from their primary care doctor and the principal investigator approves them. Trained Study staff will conduct the WebNeuro neuropsychological testing. Participant will complete self-report forms.

During Baseline:

Principal investigator or co-investigator will review all eligibility criteria, inclusive of inclusion and exclusion criteria. Study staff will review any new concomitant medications or adverse events and clinician will conduct a C-SSRS. Eligible participant will be given medication information sheet and bottle of blinded placebo.

1st Dosing information; At the end of Visit -1, eligible participants will begin the single-blind placebo lead-in. Participants will be instructed to take the single-blind placebo the next morning and continue to take IP once daily in the morning and to return all unused capsules at the next study visit. The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one-hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Placebo Lead-in Phase

Single-Blind Placebo Baseline Lead-in (Week 1, Visit 2)

Eligible participants will return to the study site for the placebo baseline visit within 21-90 days of Visit -1. If unable to come in within the 21 day range, subject will reconsent monthly and have some screening measures redone as per principal investigator discretion. Study staff will review inclusion and exclusion criteria and the results from the ECG, laboratory testing, and urinalysis. The following procedures and assessments will be performed during Visit 1: vital signs, AISRS, Expanded ASRS, CGI-S, and TASS. Concomitant medications and adverse events (AE), if any, will be noted.

At the end of Visit 1, eligible participants will begin the single-blind placebo lead-in. Subjects will be instructed to take the single-blind placebo the next morning, to continue to take IP once daily in the morning and to return all unused capsules at the next study visit. The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS will be done at half hour to one-hour post dose (5:30 to 6 am +/- 1 hour), the second TASS will be done 4 hours post dose (9am +/- 1 hour) and the third TASS will be done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Single-Blind Placebo Baseline Lead-in (Week 2, Visit 3)

Participants will return to the study site for the second week of Placebo baseline visit within 7 days of Visit 1. The following procedures and assessments will be performed at Visit 2: vital signs, AISRS, CGI-S, WebNeuro battery assessments, TASS, Expanded ASRS, C-SSRS and BRIEF-A. Concomitant medications and AEs, if any, will be noted. Drug accountability and compliance will be performed.

Participants with ≥30% decrease in total AISRS scores from Visit 1 to Visit 2 will be considered placebo responders and discontinued from the study.

All other participants will be prescribed 12.5mg of Mydayis. They are instructed to take the study medication once daily at 5 am in the morning and to return all unused medication at the next study visit.

The TASS will be done three times on days of administration: V1, V3, V4, V5, V6, and V7. The recommended dosing is at 5 am +/- 1 hour. The first TASS will be done at half hour to one-hour post dose (5:30 to 6 am +/- 1 hour), the second TASS will be done 4 hours post dose (9am +/- 1 hour) and the third TASS will be done 14-15 hours post dose(7pm+/- 1 hour). All TASS administrations will be via telephone.

Treatment Phase

MYDAYIS Treatment Phase (Week 1-4, Visit 4-7)

Participants will return to the study site every 7 days during the MYDAYIS treatment phase. The following procedures and assessments may be performed at Visits 4-7: vital signs, AISRS, CGI-S,TASS, Expanded ASRS, C-SSRS, Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Note: WebNeuro battery and BRIEF-A assessments are done only at Visit 7.

Participants must take 80% of the prescribed doses of study medication in order to be considered compliant The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one-hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Subjects will receive a re-supply of study medication at the end of every visit during the Mydayis treatment phase. The dose of Mydayis can be clinically adjusted (in the judgement of the investigator) starting at Visit 4 in 12.5mg increments based upon clinical response and side effects, up to a maximal dose of 37.5 mg/day. Participants will be instructed to return all unused medication at each study visit.

Withdrawal/End of Treatment (Visit 7)

Participants will return to the study site for Visit 7 within 7 days of Visit 6. The following procedures and assessments will be performed at Visit 7: vital signs, AISRS, CGI-S, WebNeuro battery assessments, TASS, Expanded ASRS, C-SSRS and BRIEF-A.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants should report taking at least 80% of the prescribed study medication in order to be considered compliant.

The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour).

Participants will be given the Adult ADHD Referral list to help with the transitioning into treatment as usual. Those that complete the study, at the principal investigator's

discretion, as a courtesy can receive a letter stating their diagnosis and participation in the study.

GCP FOLLOWUP: Telephone call

Study staff will make a phone call to the participant within 7 days of Visit 7. Patient will be asked about how they are feeling. Did they transition into treatment as usual? Concomitant medications and AEs, if any, will be noted.

*Unscheduled Visits approved by the principal investigator will be documented in source documents. These visits would be for safety labs/EKGs, early withdrawal or missed visits.

6.3.1 Study Schedule

Description	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	**Telephone call**
	Week -3-0 Screening	**Week -3-0 Screening/ Baseline**	**Week 1 Placebo Lead in**	**Week 2 Placebo Lead in**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**1**

6.3.2 Informed Consent

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 for a copy of the Subject Informed Consent Form.

This consent form will be submitted with the protocol for review and approval to 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

Participants will indicate consent by providing a written or electronic (REDCAP) signature on the Informed Consent Form (ICF) and Health Release Form. REDCAP consent forms are identical to hard copy consents.

Participants will provide a written or electronic signature on the informed consent document prior to any procedures being done specifically for the study. Participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

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.

6.3.3 Screening

Prescreen

Subjects will be telephone prescreened with an IRB-approved script and prescreen form. The subjects will give verbal consent. The telephone prescreen will take about 10 minutes to conduct and decreases the burden of having subjects come into the clinic to easily screen fail for age, weight or prior medications. The prescreen form of the prescreen failures are destroyed. Those who pass prescreen are given an appointment for the hybrid Screening/Baseline in-remote/clinic visit.

During Screening/Baseline Visit (Week -3-0)

Informed consent will be obtained at the screening visit before any study procedures are conducted. Study staff will review the inclusion and exclusion criteria, collect demographics, medical and psychiatric history via the MINI, prior and concomitant medications, vital signs (pulse and blood pressure) and confirm the ADHD diagnosis via the ACDS v 1.2 and AISRS. Study staff will conduct a physical examination, medical review of systems, and electrocardiogram (ECG). A blood sample will be collected for routine laboratory testing (hematology and blood chemistry) and a urine sample will be collected for urinalysis, urine pregnancy test (for females of child bearing potential), and urine drug screen. Subjects can opt out of these test if they can produce medical records from Primary Care Physician documenting safety tests completed within one year and the Principal Investigator can determine eligibility based on these tests and study screening procedures. Trained Study staff will help with setup and administration of webneuro. Participant will complete self-report forms.

During Baseline:

Principal investigator or co- investigator will review all eligibility criteria, inclusive of inclusion and exclusion criteria. Study staff will review any new concomitant medications or adverse events and a clinician will conduct a C-SSRS. Eligible participant will be given medication information sheet and bottle of blinded placebo.

6.3.4 Recruitment, Enrollment and Retention

This study 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. We use slicer dicer through EPIC to help identify subjects. There are radio and print advertisements created and approved to help with recruitment. We will get subjects that will find us via online search and call the ADHD clinic. We will give them information about the study and then if interested we will conduct the IRB approved prescreen. Trained and qualified research staff will conduct prescreen. Research staff will review prescreen and schedule the potential subject for screening visit.

Subject, if eligible, will be scheduled for a screening visit. If subject request a watermarked copy of the ICF, they can either pick one up or we can email the ICF in a secure e-mail. We will add “safe” in brackets to the subject line. Subject is reminded not to sign that one. The same ICF without the watermark will be provided at the Screening visit for the subject to sign.

Included as appendices or attachment to this protocol are any documents that will be used (letters, telephone scripts, in person introduction scripts, advertisements, emails, letters to the patient's physician or other healthcare provider known to the patient, etc.)

6.3.5 Study Visits

Study Flow for Hybrid; remote and in clinic visits

During Screening/Baseline Visit (Week -3-0): The screening visit takes about four hours

Informed consent will be obtained at the screening visit before any study procedures are conducted. Study staff will review the inclusion and exclusion criteria, collect demographics, medical and psychiatric history, prior and concomitant medications, vital signs (pulse and blood pressure) and confirm the ADHD diagnosis via the ACDS v 1.2 and AISRS. Study staff will conduct a physical examination, medical review of systems, and electrocardiogram (ECG). A blood sample will be collected for routine laboratory testing (hematology and blood chemistry) and a urine sample will be collected for urinalysis, urine pregnancy test (for females of child bearing potential), and urine drug screen. If available, Principal Investigator will review medical records from Primary Care Physician

documenting safety tests completed within one year to determine continued eligibility based on these tests and study screening procedures. Trained study staff will help set up and administer the webneuro. Participant will complete self-report forms.

During Baseline (Week -3-0): Takes about two to four hours

Principal investigator or co-investigator will review all eligibility criteria, inclusive of inclusion and exclusion criteria. Study staff will review any new concomitant medications or adverse events and clinician will conduct a C-SSRS. Eligible participant will be given medication information sheet and bottle of blinded placebo.

1st Dosing information: At the end of Visit1, eligible participants will begin the single-blind placebo lead-in. Participants will be instructed to take the single-blind placebo the next morning and continue to take IP once daily in the morning and to return all unused capsules at the next study visit. The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one-hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour).

Single-Blind Placebo Baseline Lead-in (Week 1, Visit 2): takes approximately two hours.

Eligible participants will return to the study site for the placebo-baseline visit within 21 days of Visit1. In some cases subjects can be on hold for 90 days with bimonthly check ins. Study staff will review inclusion and exclusion criteria and the results from the ECG, laboratory testing, and urinalysis. The following procedures and assessments will be performed during Visit 1: vital signs, AISRS, Expanded ASRS, CGI-S, and TASS. Concomitant medications and adverse events (AE), if any, will be noted.

Eligible participants will begin the second week of the single-blind placebo lead-in. Participants will be instructed to take the single-blind placebo the next morning and continue to take IP once daily in the morning and to return all unused caps capsules at the next study visit. The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Single-Blind Placebo Baseline Lead-in (Week 2, Visit 3): takes approximately two and a half hours.

Participants will return to the study site to finish the second week of placebo lead-in within 7 days of Visit 2. The following procedures and assessments will be performed at

Visit 2: vital signs, AISRS, CGI-S, WebNeuro battery assessments (Verbal Interference/Stroop, Go/No-Go, CPT/TOVA), TASS, Expanded ASRS, C-SSRS and BRIEF-A. Concomitant medications and AEs, if any, will be noted. Drug accountability and compliance will be performed.

Participants with ≥30% decrease in total AISRS scores during the placebo lead-in will be considered placebo responders and discontinued from the study.

All other participants will be prescribed 12.5mg of Mydayis. They are instructed to take the study medication once daily at 5 am in the morning and to return all unused medication at the next study visit.

The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Treatment Phase- Hybrid Visits

MYDAYIS Treatment Phase (Weeks 1-4, Visits 4-7): takes approximately two hours.

Participants will return to the study site every 7 days during the MYDAYIS treatment phase. The following procedures and assessments may be performed at Visits 4-7: vital signs, AISRS, CGI-S, WebNeuro battery assessments (Verbal Interference/Stroop, Go/No-Go, CPT/TOVA), TASS, Expanded ASRS, C-SSRS and BRIEF-A. Note; Webneuro and Brief-A only done on visit 7.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants must take 80% of the prescribed doses of study medication in order to be considered compliant.

The TASS will be done three times on days of administration. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour). All TASS administrations will be via telephone.

Participants will receive a re-supply of study medication at the end of every visit during the Mydayis treatment phase. The dose of Mydayis can be clinically adjusted (in the judgment of the investigator) starting at Visit 4 in 12.5 mg/day increments based upon clinical response and side effects, up to a maximal dose of 37.5 mg/day. Participants will be instructed to return all unused medication at each study visit.

Withdrawal/End of Treatment (Visit 7): takes approximately two and a half hours.

Participants will return to the study site for Visit 7 within 7 days of Visit 6. The following procedures and assessments will be performed at Visit 7: vital signs, AISRS, CGI-S,

WebNeuro battery assessments (Verbal Interference/Stroop, Go/No-Go, CPT/TOVA), TASS, Expanded ASRS, C-SSRS and BRIEF-A.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants should report taking at least 80% of the prescribed study medication in order to be considered compliant.

The TASS will be done three times on days of administration. The recommended dosing is at 5am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour).

Participants will be given the Adult ADHD Referral list to help with the transitioning into treatment as usual. Those that complete the study, and at the principal investigator's discretion, as a courtesy, can request and receive a letter stating their diagnosis and participation in the study.

GCP FOLLOWUP: Telephone will take about 10-15 minutes

Study staff will make a phone call to the participant within 7 days of Visit 7. Patient will be asked about how they are feeling. Did they transition into treatment as usual? Concomitant medications and AEs, if any, will be noted.

6.3.6 End of Study and Follow-up

Withdrawal/End of Treatment (Visit 7)

This hybrid visit will be conducted for subjects who have completed their treatment at Visit 7, subjects who wish early withdrawal or subjects whom the investigator deems participation is no longer effective or safe.

Participants will return to the study site for Visit 7 within 7 days of Visit 6. The following procedures and assessments will be performed at Visit 7: vital signs, AISRS, CGI-S, WebNeuro battery assessments (Verbal Interference/Stroop,Go/No-Go,CPT/TOVA), TASS, Expanded ASRS, C-SSRS and BRIEF-A.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants should report taking at least 80% of the prescribed study medication in order to be considered compliant.

The TASS will be done three times this day. The recommended dosing is at 5 am +/- 1 hour. The first TASS is done at half hour to one hour post dose (5:30 to 6 am +/- 1 hour), the second TASS is done 4 hours post dose (9am +/- 1 hour) and the third TASS is done 14-15 hours post dose (7pm+/- 1 hour).

Once all assessments and procedures for this visit are completed, participants will be given the Adult ADHD Referral list to help with the transitioning into treatment as usual.

Those that complete the study, and at the principal investigator's discretion, as a curtesy, can request and receive a letter stating their diagnosis and participation in the study.

6.3.7 Removal of subjects

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. In order to withdraw their permission from the study, patients must send 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, it is no longer safe for the patient to participate in the study. We can get verbal permission to follow-up with the patient in the event they suffer adverse events. We will document three attempts to contact the patient via phone. If unable to contact, we will send the patient a certified letter. (Attachment)

6.4 Statistical Method

6.4.1 Statistical Design

Statistical Analysis Plan: Our primary outcomes are the correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day into early evening. In secondary analyses, we will also analyze the following variables: Evaluation of ADHD symptoms on AISRS; the TASS 1 hour, 4 hours and 14-15 hours post dose: (total, inattentive and hyperactive-impulsive subsets); expanded ASRS (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets); symptoms of executive function (BRIEF-A: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor); and neuropsychological tests (Verbal Interference/Stroop: Color, Word and Interference Score;Go/No-Go: Accuracy, False Negative errors, False Positive errors, and Response Time; CPT/TOVA: Response Time Variability [RVP], Response Time, d', Errors of Omission, Errors of Commission, Post-Commission Response Times, Multiple Responses, Anticipatory Responses).

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the single-blind placebo lead-in as the independent variable.

All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for placebo responders in the analyses. We have chosen a single-blind placebo lead-in to define placebo responders, which are defined as patients who experience ≥30% decrease in their total AISRS scores during placebo lead-in treatment and will be discontinued from the protocol. We anticipate that based on the literature that 10% or fewer of patients will be placebo responders and that the overall discontinuation rate in the trial will be 20% (*Manor et al. 2012*). Changes within the day in TASS ratings 1 hour post dose vs. 4 hours post dose vs. 14-15 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

Statistical Power Analysis

Justification for sample size: Up to 50 patients will be enrolled to be sure that 32 evaluable patients reach the end of treatment at week six. The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 32 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size; it is half of the 1.2 effect size reported by *Spencer et al.* (2008) REF and thus is at the lower end of what we should expect to see in this study.

6.4.2 Sample Size Considerations

Justification for sample size: Up to 50 patients will be enrolled to be sure that 32-30 evaluable patients reach the end of treatment at week six. The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. Our primary analysis, which uses a two-sided test with a type I error of 0.05, shows that 32 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size; it is half of the 1.2 effect size reported by *Spencer et al*. (2008) and thus is at the lower end of what we should expect to see in this study.

6.4.3 Planned Analyses

6.4.3.1 Primary Analyses

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the single-blind placebo lead-in as the independent variable. All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for placebo responders in the analyses. We have chosen a single-blind placebo lead-in to define placebo responders, which are defined as patients who experience ≥30% decrease in their total AISRS scores during placebo lead-in treatment and will be discontinued from the protocol. We anticipate that, based on the literature, 10% or fewer of patients will be placebo responders and that the overall discontinuation rate in the trial will be 20% (*Manor et al. 2012*). The changes within the day in TASS ratings, 1-hour post dose vs. 4 hours post dose vs. 14-15 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

6.4.3.2 Secondary Objectives Analyses

In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on AISRS, TASS 1 hour, 4 hours and 14-15 hours post dose: (total, inattentive and hyperactive-impulsive subsets) (for effects of Mydayis over time at different points of the day and within the day); expanded Adult ADHD Self Report Scale (ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets); symptoms of executive function (BRIEF-A: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor); and neuropsychological tests (Stroop: Color, Word and Interference Score; and TOVA: Response Time Variability [RVP], Response Time, d', Errors of Omission, Errors of Commission, Post-Commission Response Times , Multiple Responses, Anticipatory Responses).

6.4.3.3 Safety/Pregnancy-related policy

Throughout this study, we will monitor safety and possible pregnancy by conducting safety clinical tests during screening and eligibility period. We will collect blood tests and urine test to ensure safe participation in the study. In addition, we will conduct the Columbia Suicide Severity Rating Scale (C-SSRS) to evaluate continued mental health and suicidality. We will monitor weekly vital signs (temperature, pulse, respiration, and blood pressure). Adverse events and concomitant medications will also be monitored. All

adverse events will be tabulated in manuscripts with significant testing using the appropriate general linear regression model.

We will report to Shire and our IRB within the necessary times. See section on adverse events. In addition, we will provide pregnant women with a pregnant woman contact sheet and pregnant woman ICF requesting permission to follow pregnant women to pregnancy outcome.

6.4.3.4 Analysis of Subject Characteristics

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

6.4.3.5 Interim Analysis

Interim analysis will not be done.

6.4.3.6 Health economic evaluation

Analysis to evaluate heath economic impact, which may include net health benefits, cost-effectiveness, cost-utility, and cost benefits of the intervention will not be done.

6.4.3.7 Other

No additional analysis other than what was already discussed will be done.

6.4.4 Subsets and Covariates

Statistical Analysis Plan: Our primary outcome is effects on overall adult ADHD symptoms via total AISRS Score. In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on AISRS, TASS 1 hour, 4 hours and 14-15 hours post dose: (total, inattentive and hyperactive-impulsive subsets) (for effects of Mydayis over time at different points of the day and within the day); expanded Adult ADHD Self Report Scale (ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets); symptoms of executive function (BRIEF-A: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), and neuropsychological tests (Verbal Interference/Stroop: Color, Word and Interference Score; Go/No-Go: Accuracy, False Negative errors, False Positive errors and Response Time and CPT/TOVA: Response Time

Variability [RVP], Response Time, d', Errors of Omission, Errors of Commission, Post-Commission Response Times, Multiple Responses, Anticipatory Responses).

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the single-blind placebo lead-in as the independent variable. All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for placebo responders in the analyses. We have chosen a single-blind placebo lead-in to define placebo responders, which are defined as patients who experience ≥30% decrease in their total AISRS scores during placebo lead-in treatment and will be discontinued from the protocol. We anticipate that, based on the literature, 10% or fewer of patients will be placebo responders and that the overall discontinuation rate in the trial will be 20%. Changes within the day in TASS ratings 1 hour post dose vs. 4 hour post dose vs. 14-15 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

Exploratory Objectives: We will explore correlations of TASS ratings with AISRS ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day. We will also explore correlations of changes in neuropsychological assessments of executive function (WEBNEURO; STROOP, GO/NO-GO, CONTINUOUS PERFORMANCE TEST) versus changes in BRIEF-A measures. Furthermore, we will examine potential differential effects of Mydayis in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF- A >= 65 at placebo-baseline). We will also examine correlations in self-report of ADHD symptoms on the ASRS) versus clinician report of ADHD symptoms on the AISRS, and also changes in self-report measures of executive function and emotional dyscontrol on the ASRS versus these measures on the BRIEF-A.

6.4.5 Handling of Missing Data

Missing outcome data will be handled in regards to analysis in the following way: last observation will be carried forward.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Ethical Considerations

This study is to be conducted in 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.

7.2 Institutional Review Board (IRB) Review

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. 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.

7.3 Subject Confidentiality

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.

7.4 Deviations/Unanticipated Problems

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

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (e.g., 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 or designee at the earliest possible time by telephone. The investigator, medical monitor 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 with the Data Safety Monitor.

7.5 Data Collection

The documentation into the source documents for research visits should occur in real time and no later than 3 business days from the date of the visit. If the documentation is later than three business days, this should be considered a late entry with an explanation. Documentation of the data should occur within 7 business days of the visit. If not entered within that time period, we will document in the source documents the reason for the delay.

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.

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.

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.

7.6 Data Quality Assurance

The principal investigator 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. The investigator will ensure all research staff working on this protocol meet the acceptance of the IRB. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this clinical trial. The training will be documented on training logs.

Either institution or senior research staff may conduct quality assurance audits. Audits will include, but are not limited to: IMP supply, presence of required documents, the informed consent process, and comparison of the data in REDCap against the paper source documents. The senior research staff, investigator or co-investigator will also spot check charts, REDCap, and sign off on completed subjects.

During each subject's visit to the clinic, research staff will record progress notes to document all significant observations. The investigator or co-investigator will sign these notes at each visit.

At a minimum, these notes will contain: documentation of the informed consent process, any revised consents, eligibility (inclusion/exclusion criteria prior to study medication administration), date of the visit and the corresponding visit in the trial schedule. The note will also include the presence or absence of adverse events (severity, frequency, duration, action taken, outcome and relationship to study medication as assessed by the investigator/co-investigator). Notes will also include changes in concomitant medications or dosages. Included in the progress note will be all telephone numbers or other means of contact that provide any significant clinical information. Source documents and source

data will meet the same fundamental elements of data quality (e.g. attributable, legible, and accurate)

This study will use NYU Tisch Laboratory. We will rely on their list of normal and abnormal values and will maintain all laboratory information in regulatory binder. We will use an NYU cardiologist to read all EKGs and respond with clinical judgement to the investigator regarding inclusion or exclusion of subjects in accordance with Good Clinical Practices.

We will retain all standard operating procedures in the essential documents folder and will also circulate among the staff at start of the project and at each amended change.

7.7 Study Records

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.

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

7.8 Access to Source

The source documents will be all the clinical findings and observations collected either on the actual scale or on the specific source documents for each study visit. This will include all the laboratory and EKG results. The results of the documents will be entered into REDCap and rechecked for accuracy. The REDCap form will have a check off at the bottom of the page indicating completion of entry into REDCap

REDCap is a secure web application used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments). REDCap supports online or offline data capture for research studies and operations. De Identified Data in REDCap can be exported into excel sheets for analysis.

Subjects are called three times a day from an NYU mobile device. TASS information will be entered directly into redcap via network desktop

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

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7.9 Data or Specimen Storage/Security

In this study, data will be collected, stored (digital, hard copy, etc.) and maintained in a secure manner (encryption, password protection, etc.).Only minimal information will be collected from the prescreens. Prescreens will be shredded after all necessary information is collected. The prescreens of those who have passed to screening will be added to a source chart and stored in a locked cabinet in a locked room until eligibility is determined. Once eligible, the subject is baselined and all source documents are stored in the same manner in a locked room in a locked cabinet. Data will be entered into the secure data capture system REDCap. Unidentified data will also be stored in our shared drive for writing purposes.

7.10 Retention of Records

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.

7.11 Study Monitoring

This study will be monitored according to the **monitoring plan.** 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.

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
- 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 source charts will be reviewed for accuracy and completeness on a weekly basis by research staff. Subject REDCap data will be spot-checked by research staff once a month for any discrepancies and for completion.

Dr. Adler 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, Study Monitor and manufacturers who will donate the study drug (Shire Pharmaceuticals Group plc.)

7.12 Data Safety Monitoring Plan

Medical Monitoring

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. 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. Donald C. Goff, MD is Director at Nathan Kline Institute, Marvin Stern Professor and Vice Chair for Research Department of Psychiatry

NYU Langone Medical Center. Dr. Goff. Dr. Goff is board certified in psychiatry and licensed to practice medicine in the state of New York.

Medical Monitor:
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7.13 Study Modification

Study modifications and specific recommendations for these protocol modifications, should they be necessary, will be elaborated, with accompanying rationale for each. This will be reported to sponsor, IRB, Medical Monitor and manufacturers who will donate the study drug (Shire Pharmaceuticals Group plc.).

After IRB approval the protocol, change will be communicated to the team at our weekly meeting. The protocol training for the change will be documented in the Protocol Training Logs. The change will be implemented as soon as possible.

7.14 Study Discontinuation

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, experiences from adverse events, or patient becomes pregnant), the subject will be discontinued from the study. These are the possible reasons for termination from the study:

- Adverse events
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Withdrawal by subject
- Noncompliance
- Protocol violation
- Other

Documentation of study discontinuation will be added to subject source records. Withdrawal assessments will be conducted if investigator deems it is necessary. This will also be documented in the subject's source document folder..

7.15 Study Completion

18 months after start of recruitment

7.16 Conflict of Interest Policy

All study members will complete the NYU financial disclosure forms. 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.

7.17 Funding Source

Shire will provide the study with the Investigational product and resources to conduct the study-

Sharon Hochman

Sr. Project Manager, US Medical Clinical Research

On Contractor assignment with Takeda Pharmaceuticals USA, Inc.

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7.18 Publication Plan

The investigator at NYU will have the primary responsibility for publishing the study results. The data will be analyzed and discussed prior to submission of the study results for publication.

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 investigator of this study.

Appendices

Appendix #	Title	Section	Topic
1		Synopsis	Visit Schedule Table (Optional)
2		Synopsis	Study Flow Chart (optional)
3		2 Background	2.1.1 Preclinical Experience
4	FDA 2017 Reference ID: 4114154 Medication guide	2 Background	2.1.1 Preclinical Experience
5		6 Methods	6.1.1 Identity of Investigational Product/New Drug
6		6 Methods	6.1.1 Identity of Investigational Product/New Drug
7		6 Methods	6.1.6 Storage Conditions
8	ICF Progress Note Template	6 Methods	6.3.2 Informed Consent

9	Informed Consent Process and Documentation	6 Methods	6.3.2 Informed Consent
10	ICF	6 Methods	6.3.2 Informed Consent
11	Pregnant Partner Contact Sheet (Version: 09/08/2014)	6 Methods	6.3.2 Informed Consent
12	Pregnant Partner Information Release Form	6 Methods	6.3.2 Informed Consent
13	schedule of events and providers	6 Methods	6.3.3 Screening
14	Phone_Screen	6 Methods	6.3.4 Recruitment, Enrollment and Retention
15	Phone _Script_Verbal_Consent	6 Methods	6.3.4 Recruitment, Enrollment and Retention
16	follow up letter	6 Methods	6.3.7 Removal of subjects
17	Statistical-Analysis-Plan	6 Methods	6.4.1 Statistical Design

18	medical monitoring plan	7 Trial Administration	7.12 Data Safety Monitoring Plan

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