Solriamfetol for ADHD in Adults: A Double-Blind Placebo Controlled Pilot Study

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I. BACKGROUND AND SIGNIFICANCE

There is need to improve options for management of Attention Deficit Hyperactivity Disorder

Attention-deficit hyperactivity disorder (ADHD) is a neurobiological disorder associated with high levels of impairment in adulthood[1-4], and is estimated to affect up to 5% of adults worldwide [5-7]. While currently approved pharmacotherapies for adults with ADHD are often effective, there are limits to their clinical utility. Stimulants are the mainstay of treatment for adults with ADHD due to larger effects than nonstimulants on ADHD[8-11]. Over two decades of study by our research team and others, including controlled studies of stimulant medications and open studies of tricyclic, monoamine oxidase inhibitor, and atypical antidepressants, reveal that 20-50% of adults with ADHD are considered pharmacologic nonresponders[12-14]. Moreover, adults who are considered responders clinically often show a 50% or less reduction in the core symptoms of ADHD[13]. In addition to residual ADHD symptom burden, pharmacologically treated patients also have residual burden in other cognitive capacities such as executive function challenges. For example, In a recent study of robust open label dosing with the amphetamine lisdexamfetamine, 40% of adults with ADHD were considered to have unresolved and clinically significant impairment in essential elements of behavioral executive control.[15] Therefore there is significant clinical need for interventions that support the self-regulatory challenges that are not managed by current pharmacotherapies.

Investigation into the neurobiological basis of ADHD has identified that a circuit involving prefrontal, subcortical and parietal regions is implicated in the pathological basis of ADHD.[16-20] Delay in cortical maturation of cortex might impair executive functions, resulting in the poor working memory, attention, and response inhibition in ADHD children.[21]

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor that the FDA has approved for treatment of excessive daytime sleepiness in patients with narcolepsy or obstructive sleep apnea[22]. It is a class IV controlled substance, and clinical trials suggest it is well tolerated. Conventional therapies for ADHD, including the stimulants methylphenidate and mixed amphetamine salts, and the nonstimulant atomoxetine, are thought to work in part through reuptake blockade and/or increased release of the catecholamines dopamine and norepinephrine. [13] Prior studies with modafinil and bupropion and mazindol also suggest ADHD benefit from these agents with dopamine and norepinephrine reuptake properties. Solriamfetol is thought to support dopamine and/or norepinephrine activity.

Prior clinical data to support efficacy in sleep disorder indications, and the product's well-elaborated safety profile, also suggest potential favorable application for ADHD care. Other agents approved by the FDA for ADHD are closely controlled substances (stimulant agents) or may take longer to work than first-line stimulants or have less effect than stimulants (e.g. atomoxetine and

guanfacine). If Solriamfetol had moderate effect size for ADHD symptoms, it may open up an option for a new method of treating ADHD.

Because Solriamfetol could have positive effects on ADHD symptoms, has not been evaluated in ADHD, and is expected to be and well tolerated, we propose to conduct a double-blind pilot study enrolling 60 adults with ADHD. Such a pilot study can determine whether Solriamfetol is likely to have a moderate effect size for this indication. Using a dose-optimization protocol, we will maximize ability to estimate clinical effects. To assess the safety and efficacy of Solriamfetol, we will use ratings of spontaneously reported adverse events and ADHD symptoms as primary outcome measures. Adults with moderate levels of ADHD will be enrolled. We choose to evaluate response over six weeks, as this has been a typical format sensitive to mild to moderate effects on ADHD, allows for dose titration, and sufficient exposure durations for participants to notice and evaluate a clinically useful effect.

Just as telemedicine has expanded the scope of clinical care, it is also expanding the scope of clinical trials[23]. The outpatient psychiatry clinics at Massachusetts General Hospital have used telemedicine for routine clinic appointments for qualifying patients after an in-person consultation. Telemedicine significantly lessens patient burden, as the patient does not have to come into the office for appointments, but still receives the same level of clinical care through the face-to-face video conference. Our research unit has conducted telemedicine research with positive experiences. As such, we propose to offer the option of telemedicine visits in this study.

II. SPECIFIC AIMS

Aim 1: Assess effect of solriamfetol on ADHD symptoms and associated ADHD features.

Hypothesis 1: Compared to pre-administration baseline, solriamfetol will be associated with a greater reduction than placebo of ADHD symptoms (1a). We also expect drug exposure to be correlated with a greater rate of individuals achieving an a priori definition of clinical improvement, with at least a 25% reduction in ADHD symptoms, and a CGI of much or very much improved (1b).

We secondarily will explore whether there are reduced symptoms of executive dysfunction (defined by a 0.5 standard deviation improvement on the Brief Rating Inventory of Executive Function-Adult Version (BRIEF-A) self-report total or subscale scores). We also will explore whether baseline ratings of sleepiness, or deficits on BRIEF predict improvements on the Adult ADHD Investigator Symptom Rating Scale (AISRS) or BRIEF measures.

Aim 2: Assess the safety of solriamfetol in the treatment of ADHD among adults

Hypothesis 2: Solriamfetol will be well tolerated by adults with ADHD.

III. SUBJECT SELECTION

We plan to enroll 60 subjects of any gender identity between the ages of 18-65 in the study. No pediatric subjects will be recruited for this study. We will recruit subjects through advertisement in the general community, using flyer and internet advertisements, via postings on Rally, Research Match, and from the referral pool of patients of the Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital. As noted elsewhere, however, the informed consent process with a subject must occur with a different clinician than one they have seen as a treating provider.

Individuals who express interest in the study will be screened for eligibility by the study coordinator or a research assistant via phone. A phone script will be used that is IRB-approved. If they meet criteria, the participant will be asked to complete study scales online via RedCap, a secure

online data capture system. These self-report scales will include the ADHD Rating Scale (ADHD-RS), Adult Self-Report Form (ASR), BRIEF-A, Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI). If a subject completed any of these scales for another study in our department or through the adult ADHD clinical program within the past year prior to screening they may not have to repeat the scale(s) for the current study unless asked to do so by a study staff member based upon clinician judgment. However, in the case where scales completed previously will be reviewed, verbal permission will be obtained from the participant that it is okay to review these previously completed scales to assess inclusion and exclusion criteria.

Subjects who have participated in research in our program may be eligible to participate in this study. Other medical records on a subject will not be used at any point, unless explicit written permission is provided by the subject.

Many subjects referred to this study will first participate in our general screening protocol entitled, “Screening Protocol for Adults with Attention Deficit Hyperactivity Disorder” (Protocol # 2002-P-001856). Under this protocol, advertisements from our research group include a link that allows individuals to contact us by email, phone, or via a URL link to a REDCap form. After participating in this screening protocol, subjects are referred to specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability).

Study Entry Criteria

Inclusion Criteria:

1. Adults ages 18-65 years of age.
2. A diagnosis of childhood-onset ADHD, meeting the DSM-V criteria for ADHD in adulthood, including at least 5 current symptoms of inattentive or impulsive-hyperactive traits, and childhood onset by age 12, defined as two symptoms of inattentive or of impulsive/hyperactive traits by the age of 12.
3. A score of 20 or more on the Adult ADHD Investigator Symptom Report Scale (AISRS)

Exclusions

1. Individuals with known renal insufficiency or renal impairment.

2. A history of intolerance to solriamfetol

3. Pregnant or nursing females, and individuals unwilling to use adequate contraceptive methods to avoid conception while they are receiving study agent and for 1 month after the last dose of study agent. For female subjects of childbearing potential adequate contraceptive methods will include: a medically acceptable form of birth control (such as male or female condoms with or without spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed IUD, hormonal contraceptives like birth control pills, or abstinence). For male subjects this will include use of male condom, being status post vasectomy at least 4 months prior to initiation of study drug exposure, or abstinence during the study.

4. A known unstable major medical illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including hypertension ≥ 140/90 mmHg), endocrinologic (e.g. thyroid), neurologic (e.g. seizure), immunologic, hematologic, or psychiatric (including an active substance use disorder, psychosis, bipolar disorder, major depression) disorder.

5. Any medical condition that the Principal Investigator (PI) believes will be exacerbated by study participation.

6. A history of cancer (except localized skin cancer without metastases or in situ cervical cancer) within 5 years prior to screening.

7. A known history of narrow-angle glaucoma.

8. Current (within 3 months) DSM-V criteria for abuse or dependence with any psychoactive substance other than nicotine.

9. Multiple adverse drug reactions, defined as previous moderate to severe adverse experiences while on two or more chemically unrelated compounds, where these reactions were unpredictable from the known pharmacology of the drug.

10. Any other concomitant medication with primarily central nervous system activity that are catecholaminergic such as stimulants or atomoxetine, or have strong noradrenergic mechanisms of action such as duloxetine or venlafaxine or buproprion. Subjects may be included who are taking stable doses of agents with primary serotonergic (such as selective serotonin reuptake inhibitors or buspirone), gabaergic (such as gabapentin, pregabalin), or other anticonvulsants. We will also allow participation by individuals with rare (predicted to be less than twice a week) use of prn benzodiazepines or sedative-hypnotics.

11. Current use of MAO Inhibitor or use within the past two weeks.

12. Concomitant medications with high potential for dopaminergic or sympathomimetic effects.

13. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.

14, Reasonable suspicion of inability, in the judgement of the investigator, to appropriately monitor experiences during the study and take steps to report these experiences or respond in a manner preserving personal health and safety.

15. If clinically appropriate, any subjects taking medication exclusionary to the study (including agents used for management of ADHD) must be tapered off this medication prior to baseline visit for the length of 5 half-lives of the medication, corresponding to 95% of the agent leaving the participant's system), plus several days or otherwise sufficient period of time to allow assessment of eligibility for participation off medication.

16. Any condition, including a moderate to severe untreated sleep disorder or other mental health disorder, that renders inability, in the investigator's judgement, to determine whether ADHD symptoms are primarily due to ADHD.

IV. SUBJECT ENROLLMENT

Informed consent will be obtained prior to the performance of any protocol procedures and prior to administration of study drug. The informed consent document will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by a board-certified physician who is either the primary investigator or a co-investigator. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel is necessary to consider his/her participation in the study as well as consult with family members or their physicians. Participation in this study is voluntary and the subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent.

V. STUDY PROCEDURES

We will conduct a 6-week double-blind pilot clinical trial exploring efficacy and tolerability of solriamfetol in adults with ADHD who fulfill the inclusion and exclusion criteria for participation. Enrollment will stop once 60 subjects have consented and been exposed to study agent or placebo.

Virtual or written informed consent will be obtained via Adobe esign or courier mail service after subjects are screened for potential participation, prior to the performance of other protocol procedures, and prior to administration of study drug. Screening of participants will involve use of a survey, which may be reviewed in person or via televisit or telephone. We also may post all or part of this form on REDCap, for participants to complete at their convenience if they prefer. During screening, we will collect minimum identifying information that allows communication or re-contacting, such as first name or telephone number. The information collected from this phone survey will be reviewed by study staff, and if they appear likely to meet criteria for safe inclusion in the study, the participant will be asked to schedule for an evaluation visit. As part of this evaluation, they will complete study scales online via RedCap, a secure online data capture system.

Informed consent will be obtained by a licensed study clinician or study staff. The study, risks and benefits will be explained in simple terms, and any questions from participants will be answered. Participants will be given as much time as they feel is necessary to make a decision regarding their consent. Subjects will be informed that participation is entirely voluntary, and they may withdraw consent at any time without penalty.

After providing study information and obtaining IRB approved informed consent, participants will undergo a comprehensive assessment including a psychiatric assessment with a clinician reviewing current and lifetime DSM-V Axis I conditions, medical history including history of any cardiac symptoms or abnormalities reported on routine clinical exams, and eligibility per inclusion and exclusion criteria. This assessment will also include staff-review of forms filled out online by study participants in REDCap. The information obtained at this visit will be reviewed to assure that all inclusion and exclusion criteria are met prior to receiving study agent at the baseline visit. Subjects who do not meet all the criteria for enrollment after these assessments will be discontinued.

We anticipate that a small minority of subjects may enter this trial following completion of withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects with redundant time commitments, we will use the following *diagnostic* data previously collected: If a subject has completed an equivalent evaluation with one of the study clinicians <u>within the previous year</u> prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures. With subjects' permission, we will use the diagnostic data that had been previously collected, and document this data and when it was collected in our substantiation of how the individual meets diagnostic criteria in the evaluation documentation for the current study. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history, to ensure that the subject meets all study entrance criteria.

Safety Assessments:

Vital signs (blood pressure, pulse) will be monitored at each visit during the study. If there is suspicion that the participant's eligibility to participate has changed (e.g., evidence they have taken an illicit drug), he/she will have a discussion with the doctor to determine if he/she can be in the study. It will be up to the principal investigator's judgement to determine if the subject continues to meet study inclusion and exclusion criteria. For example, subjects will be discontinued if there is suspicion of ongoing substance abuse by history or by confirmation of ongoing abuse by positive drug test, or evidence of inability to adhere to study procedures (e.g. missing two visits in a row, or otherwise insufficient participation to monitor safety in the judgement of the investigators). Drug testing will not

be done systematically but will be available to clinical investigators to determine participant eligibility and safety before and throughout study participation. Participants will be told at the time of consent that random drug screening may occur at the choice of study investigators.

Females who are able to have children will also have a urine pregnancy test at evaluation, and week 6 or study completion. If a participant has a positive pregnancy test she will not be able to take part in the study. As detailed in the exclusion criteria, all participants will be required to use contraception adequate to avoid conception, or to not participate. In the event that a subject becomes pregnant, we will ask the subject's permission to obtain information about the outcome of the pregnancy and the condition of the newborn. In the event that a subject reports contributing sperm to a pregnancy during the study period, we will also ask the subject's permission to obtain information about the outcome of the pregnancy and the condition of the newborn. Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

We will increase our chances of identifying exclusionary mental health conditions by supplementing the clinical interview for study eligibility with review of self-report on the Adult Self-Report (ASR), a self-report scale validated to identify major mental health conditions, prior to participation.

Subject Dosing and Visit schedule:

Visits will occur for evaluation, baseline, and weekly for weeks 1, 2, 3, 4, 5 and 6. Visits will be conducted at 7 day intervals, +/- 3 days. Doses will be assigned at each study visit for the period of time until the next visit, with forced-dose up-titration as tolerated from 75 mg at week one to 150 mg at week 2, and with intention that dosing remain stable for the last four weeks of study participation, such that investigators will ask a subject to go back down to 75 mg during any of the weeks following week 2 only if only if 150 mg is not tolerated. Thus, the most robust titration would be 75 mg until week 1, and 150 mg for the rest of study. The least robust titration where a subject maintains participation would be 75 mg for the duration of the study.

This study will preferentially utilize synchronous visit telemedicine assessments in all visits to minimize subject burden. Efforts to maximize subject safety and convenience will include the option to have in-person meetings if public health conditions allow or are preferred by either a subject or study clinicians. Throughout the study, efforts will be made to maximize comfort of subjets primarily and, secondarily, meaningful research participation.

Subjects will be offered treatment follow-up for two visits with staff at the MGH Clinical and Research Program in Pediatric Psychopharmacology at the end of the study to facilitate transition to ongoing care. Subjects who complete the study will have the option of receiving two clinical care visits (one approximately monthly appointment over up to three months' time) at the completion of the study in which they will be seen by study staff. The three months of follow-up care are a courtesy that is offered to help find long-term care if needed. Subjects will receive referrals to clinicians in their communities. No research data will be collected at these follow-up visits.

Phone calls will be conducted by a study research assistant before and during visits to assess medication compliance and change in medication treatments. Pill counts will be done by study staff at every other study visit by visualization in person or by remote televisit. At any time, contact can occur by phone or in person as needed with a clinician or research assistant, based on the judgement of the study staff, or by needs of the subjects as they arise. Study clinicians are also available to subjects 24 hours each day by pager.

Randomization and Maintenance of double-blind

Randomization to active or placebo will occur once a subject is scheduled for a baseline visit, when the clinical trials pharmacy will be given a subject name that the pharmacy will associate with a number identifier. We have extensive experience maintaining blinding, wherein we have our central Mass General Hospital Clinical Trials Pharmacy pharmacy serve as the only part of the greater trial team that is aware of the assignment to active or placebo during study participation. The trials pharmacy will receive products identified by the sponsor as active or placebo fill, over-encapsulate these products to look identical, bottle these products with unique identifiers, maintains the placebo-active ratio, and maintain blinding until study completion. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data collection has been declared complete. In the extreme event where subject safety will be compromised by maintaining the blind, eg. an adverse event where treatment is dependent on knowing if they were on active or placebo medication, we will unblind the status of the subject's study agent, following emergency protocols in place in our department and institution.

Assessments and Instruments:

Our primary endpoint will be change in the Adult ADHD Investigator Symptom Rating Scale (AISRS), the instrument we will use to evaluate ADHD symptom burden. We also will evaluate spontaneously reported adverse events as our main outcome of tolerability. At screening evaluation, AISRS ratings and concurrent medication treatments will be recorded. In addition, at screening or baseline, a brief demographic interview will be conducted to obtain information used to calculate socioeconomic status.

Demographic information, including socioeconomic status data, will collected for each participant.[24]

During the study, the following assessments and instruments will be used:

Clinician rated assessments (rated at each in-office study visit, unless otherwise noted):

- Global Assessment of Functioning (GAF) scale. The GAF will assess global functioning using a scale from 1 (worst) to 100 (best). This will be collected at all study visits, excluding the screening visit.
- Clinical Global Impressions (CGI) scale for ADHD. The CGI is a measure of illness severity, improvement, and efficacy of treatment.
- Adult ADHD Investigator Symptom Rating Scale (AISRS). Each of the individual symptoms of ADHD is rated 0 to 3 on a scale of severity.
- Adverse Experiences (collected at all visits excluding the screening and baseline visits) and Concomitant Medications.

Subject rated scales (all scales rated at baseline and week 6 or drop visit:

- The 18-item ADHD Rating Scale to evaluate frequency of ADHD symptoms on a scale of 0 to 4 (ADHD-RS).
- The 86-item Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A) to assess levels of executive function deficits. [25]
- Pittsburgh Sleep Quality Index. This Index is a widely used measure which consists of 19 items which assess sleep quality over one month time period.
- Epworth Sleepiness Scale

Subject rated scale at baseline only

- In addition, at baseline the The Adult Self-Report Form (ASR) to measure a wide range of psychiatric syndromes (i.e., depressive problems, anxiety problems, antisocial personality problems) in adults. The ASR provides dimensional scale scores for each syndrome that are age- and gender-normed. [26]

Adverse Event Assessment and Reporting

All solriamfetol treatment-emergent serious adverse events (initial and follow-up) that require collection per protocol will be reported to Axsome Therapeutics via email within 1 business day of awareness of the serious adverse event.

As noted above, adverse events will be recorded at all visits other than screening and baseline. Investigators will characterize adverse event by description, note the severity (mild, moderate, or severe), whether it is expected (yes or no), relatedness (unrelated, definite, probable, or possible).

We will operate the study in compliance with our Human Research Committee's guidelines titled "Reporting Unanticipated Problems including Adverse Events" revised May 2020 – the full document is accessible at https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf . In general, we are required to and will follow all guidelines and practices elaborated by our Human Research Protection Program as outlined in https://www.massgeneralbrigham.org/researcher-support-and-resources/resources-collaborators-and-sponsors/human-research-protection-program-policy-guidance. In the "Unanticipated Problems" guideline, p*ossibly related to the research* means there is a *reasonable possibility* that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)). *Reasonable possibility* means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.

Other key elements of this guideline are summarized here:

Unanticipated problems must be reported promptly to the Human Research Committee so that the Committee can consider whether (1) the risks to subjects are still minimized and reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result; and (2) any changes to the research or other corrective actions are warranted in order to protect the safety, welfare, or rights of subjects or others.

Per Mass General Brigham Human Research Committee standards, any adverse event that is an unanticipatedd untoward or unfavorable medical occurrence, including abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, that indicates that the research places subjects at increased risk of physical or psychological harm than previously known or recognized will be submitted through a electronic reporting system (called Insight) to the Human Research Committee as an Other Event, Adverse Event. The following information will be included in the report:

(1) a detailed description of the adverse event;
(2) the basis for determining that the event is unexpected in nature, severity, or frequency;
(3) the basis for determining that the event is related or possibly related to the research procedures;
(4) the basis for determining that the research places subjects at an increased risk of harm (i.e., a serious adverse event); and
(5) whether any changes to the research or other corrective actions are warranted

Such unanticipated problems involving risks to subjects or others will be submitted to the Human Research Committee within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem.

Serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:
• results in death;
• is life threatening (places the subject at immediate risk of death from the event as it occurred);
• requires inpatient hospitalization or prolongation of existing hospitalization;
• results in a persistent or significant disability/incapacity;
• results in a congenital anomaly/birth defect; or
• any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Data Collection:

All data will be collected and entered into electronic data capture systems using a combination of Study Trax and/or REDCap, or an equivalent privacy-rule compliant electronic data capture system that streamlines data collection and data integrity. As a convention, we will refer to REDCap in the rest of this protocol. These software programs allows researchers to design and implement study surveys electronically for collecting, storing, retrieving, and manipulating data. Study subjects will enter survey responses and research staff will enter gathered data from study visit evalutions into electronic assessment forms using computers remotely or at the research site. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture of self-report and clinician data entry eliminates the need for subsequent data entry by staff, thus minimizing human error. However, in the event that an electronic data capture system is unavailable or malfunctioning, study staff will print all study instruments and study data will be collected in paper form.These surveys are completed securely via the Internet by using any device with standard web access and browsers. For this study, participants and staff will complete the electronic assessments on computer terminals remotely or at the research site under the supervision of study staff.

Concomitant Medications / Treatments:

A detailed past and present treatment history will be taken as part of initial evaluation. Concomitant medications with primarily central nervous system activity, other than ADHD pharmacotherapy as noted above, are not allowed in this study. Non-pharmacological treatments thought to be effective for ADHD such as individual, family or group therapy will be allowed if they were in place before the patient joined the study. Any such therapy regimen must remain the same throughout the study.

If clinically appropriate, any subjects taking medication exclusionary to the study must be tapered off this medication prior to baseline visit for the length of 5 half-lives of the medication, corresponding to 95% of the agent leaving the participant's system), plus several days to assess the participant off medication. Individuals may participate if they prefer not to take a previously optimized treatment for documentable reasons such as side effects, perceived risks, personal preference, or lack of sufficient benefit. However, subjects will not enter the study if it would require tapering or otherwise stopping a medication that is optimally and comfortably managing a clinical concern likely to cause unaccommodated suffering of the participant. For example, a participant may prefer to participate in the trial after stopping a stimulant treatment that causes side effects but helps them in school, during a summer vacation period where the consequences of stopping and participating will be accommodated by lack of school participation and more time to complete daily tasks. Medication tapers will be monitored by the study clinician in agreement with the research subject and in consultation with the prescribing physician. No subject will be removed from a stable and effective treatment regimen for the purposes of participating in the study.

Subjects will be instructed not to take any medications or supplements that are contraindicated by exclusion criteria for the study. All new medications and supplements started during the study will be reviewed by the PI, and subjects may be dropped from study participation, but their data will be retained in the safety and intent-to-treat analyses with PI discretion.

In addition, any subject found to be taking medication listed as exclusionary during the course of the study or the seven days prior to randomization will be evaluated by the PI for ongoing eligibility.

Study Discontinuation Criteria

Examples of individuals who will discontinue study participation include those who: 1) develop intolerable adverse events (AEs) despite dose adjustments; 2) have (a) clinically relevant serious AE(s) as determined by the investigator; 3) have worsening ADHD symptoms (much worse or very much worse as rated on CGI-Improvement at two consecutive visits); or 4) have emergent adverse mental health state including psychosis, suicidality, substance use, or worsening mood and/or anxiety; 5) are non-adherent to study procedures or withdraw from the study; 6) intend to be or become pregnant.

If study participation is discontinued due to safety reasons, participants will receive two follow-up visits, giving adequate time for appropriate psychiatric referrals to treaters in their communities. Subjects found to be taking substances listed as exclusionary during the course of the study may be discontinued based on PI evaluation of their eligibility.

VI. BIOSTATISTICAL ANALYSIS

Data processing and management followed procedures developed by the investigators and used in ongoing studies. Up to 30 subjects will receive Solriamfetol, and up to 30 subjects will receive placebo. Changes in outcome ratings within and between study groups will be tested.

Hypothesis 1 will be our main testable hypothesis, tested by evaluating whether the group receiving stimulant treatment has a significantly greater improvement in ADHD symptom rating. We will also explore exploratory hypotheses. This will include comparing the active and placebo arms on: the rate of individuals achieving an a priori definition of clinical improvement, with at least a 25% reduction in ADHD symptoms, and a CGI of much or very much improved (1b), and the rate of reduced symptoms of executive dysfunction (defined by a 0.5 standard deviation improvement on BRIEF-A self-report total or subscale scores) (1c).

All other analyses will be exploratory and p-values will be reported as nominal, and not used to infer significance. We will also explore descriptively whether baseline sleep problems, sleepiness, or deficits in domains of the BRIEF predict improvement on AISRS or BRIEF ratings.

Our primary test of Hypothesis 2 will be review of the occurrence of moderate or severe adverse events, and description of reasons for study dropout. We will also report rates of the same adverse event in active and placebo arms occurring two or more times for a particular subject.

We will also report whether there is a difference in change in baseline to endpoint sleepiness and changes in sleep quality during the study.

Data processing and management will follow procedures developed by the investigators and used in ongoing studies.

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VII. RISKS AND DISCOMFORTS

All efforts are made to minimize risks to subjects. Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of co-investigator study clinicians. Adverse events will be recorded and reported according to institutional policies. Risks of the study agent have been considered in developing the exclusionary criteria for this proposal.

Study clinician evaluation and subject questionnaires:

Some questions may make subjects feel uncomfortable. Subjects may refuse to answer any question they wish. In the event that a participant reports risk of harm to himself or herself, or to another person, study clinicians will assess the level of risk, and take appropriate actions, including disposition of an immediate referral to a local Psychiatric Emergency Room.

Risks of Study Agent – Solriamfetol:

Solriamfetol is approved by the US Food and Drug Administration to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

FDA indications for Solriamfetol include recommendation for starting at 75 mg in patients with daytime fatigue in narcolepsy, and titration from 75 mg to 150 mg after three days. Our protocol titrates more conservatively, following the weekly pattern of dose increase that is more typical of clinical trials in ADHD. While this interval for increase was chosen primarily to give subjects longer to evaluate ADHD symptom experiences, and to mimic pattern of study assessments in other ADHD trials, it will also give greater time for subjects to evaluate adverse effects before increasing them with a dose increase.

We chose not to exceed 150 mg in this study in keeping with FDA approved dosing for individuals with excessive daytime sleepiness. The package label notes that heart rate and blood pressure changes appear to be dose-dependent in populations studied, such that doses above 150 mg could be expected to add more risk. The label advises to avoid patients with known cardiovascular and cerebrovascular disease, preexisting hypertension, and patients with advanced age, advice we follow in this protocol.

Most common adverse reactions (≥5% and greater than placebo) were headache, nausea, decreased appetite, insomnia, and anxiety. The product label carries suggestions to dose medication at least 9 hours before bedtime, advice we will give patients. It also suggests to “measure heart rate and blood pressure prior to initiating and periodically throughout treatment. Control hypertension before and during therapy. Avoid use in patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems” and “Use caution in treating patients with a history of

psychosis or bipolar disorders. Consider dose reduction or discontinuation of SUNOSI (solriamfetol) if psychiatric symptoms develop". Our protocol is sensitive to identifying these risk categories.

We do not have reason to believe that individuals taking solriamfetol would be risking greater negative outcomes than those observed in sympathomimetic agents already used for ADHD. Commonly observed side effects associated with the use of these FDA-approved stimulants include insomnia, decreased appetite, dry mouth, headache, or increased pulse. Other less common side effects include irritability, stomach pain, onset of tics, or mood changes. Stimulants have also been associated with more rare, but serious, adverse effects such as sudden death, stroke, and heart attack in adults with a history of heart disease. Side effects of atomoxetine are similar to those of stimulants, but notably include fatigue, nausea, increase in heart rate, increase in blood pressure, sexual side effects, agitation or changes in mood. The label for atomoxetine carries warnings about rare reports of liver failure and of suicidal ideation. If solriamfetol produced side effects similar to these other catecholamine agents, our assessment schedule and clinical expertise give high likelihood of both identifying and supporting any clients who experience such negative experiences.

Confidentiality:

All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Results of urine or drug pregnancy testing will not become part of the subject's medical record.

Data obtained from this study will not identify the subjects individually. Subjects will be assigned code-names and ID numbers. Data obtained from our studies may be published, but no subjects will be identified individually in these publications. Original research-related records may be reviewed by the Partners Human Research Committee, and regulatory authorities, for the purpose of verifying clinical trial procedures and/or data. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

Email communication:

Any email communication will be done using Send Secure encryption per Partners polcy, unless a subject has authorized non-secure email communication. Before sending or responding to an unencrypted email message to an individual, the individual must acknowledge understanding of, and agreement to, accept the risks as communicated to them via the following language "The Partners standard is to send email securely. This requires you to initially set up and activate an account with a password. You can then use the password to access secure emails sent to you from Partners HealthCare. If you prefer, we can send you "unencrypted" email that is not secure and could result in the unauthorized use or disclosure of your information. If you want to receive communications by unencrypted email despite these risks, Partners HealthCare will not be held responsible. Your preference to receive unencrypted email will apply to emails sent from this research group/study only." This language will be copied into an email response to an individual, or may be read over the phone to the individual, or an individual could agree by reading this in person and signing this statement, or simply by agreeing verbally.

VIII. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ADHD, a trial of a supplement that could be continued after the

study, and the opportunity to contribute to medical science and thus help others with similar difficulties.

VIII. Visual Timeline of Key Study Elements

	Eval.	Baseline (Visit 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6/drop
Consent	X							
Eligibility	X							
Vital Signs (BP, pulse)		X*	X	X	X	X	X	X
Clinician Evaluation	X							
AISRS	X	X	X	X	X	X	X	X
ADHD-RS	X*							X
CGI ratings		X	X	X	X	X	X	X
GAF		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X
BRIEF-A		X*						X
ASR	X*							
ESS		X*						X
PSQI		X*						X
Pill counting				X		X		X
Pregnancy test	X							X

* Can be completed at either evaluation or baseline visit as long as those visits are within 10 days

**If a subject terminates participation early, all assessments at week 6 will be made at study completion.

IX. Monitoring and Quality Assurance

The Principal Investigator will meet regularly with study staff to address procedural issues and the study coordinator will audit each subject's data within 48 hours of each study visit. Furthermore, all data will be audited by the study statistician with the assistance of the database manager on a regular basis to ensure the progress of the study and confirm that all necessary data is being collected and can be transitioned to the statistical package smoothly. Co-investigators are actively involved in the monitoring and quality assurance of these trials. Periodic quality assurance audits will ensure accuracy and completeness of all subject documents, IRB files and correspondence, and the informed consent documentation.

XI. Telehealth Remote study procedures

Subjects will be offered the option to participate via remote telehealth. Individuals may choose a mixture of in-person and telehealth visits, or just one or the other, as suits scheduling convenience or prudent safety practice. For example, during a public health infectious disease crisis such as the COVID-19 pandemic, risks to participants may be reduced by remote televisits. We will not conduct in-person visits unless approved by Partners healthcare and Massachusetts General Hospital.

Recent Virtual Visit Clinical Growth for COVID-19

Virtual visits are real-time visits between patients and providers using the audio and video capabilities of electronic devices. These visits enable patients to continue their routine and follow-up care with Massachusetts General Hospital providers remotely without having to physically visit a hospital or outpatient facility. Since March 2020, virtual visit capabilities at Mass General have significantly expanded to allow more providers to offer this resource to patients in light of COVID-19. On average prior to March 2020, just over 1,000 clinical virtual visits were completed each month (October 2019 – February 2020) via audio and video. In May 2020, more than 85,000 telehealth visits were completed (includes both via video and audio as well as audio only). Between March and August 2020, Mass General Brigham (the parent company of Massachusetts General Hospital) reported over one million telehealth visits occurred within the greater system.

Technology Platform

The videoconferencing technology which will be used by Dr. Surman's research group in this protocol is currently being used in clinical practice across Massachusetts General Hospital. It has been approved for use by Partners Information Systems and MGH Health Information Services.

This study leverages a videoconferencing platform where clinicians and patients/participants can use personal computers, tablets, and smartphones to communicate easily and securely using real-time video and audio. Visits will be conducted remotely over the Partners-approved video platform, which is HIPAA-compliant. The technology leverages a waiting room functionality so that the provider must admit the patient from the virtual waiting room into the meeting, thus preventing unauthorized entry.

Set Up (Patient)

We will send a letter to patients/study participants with instructions to set up the program on their personal devices. We will also send emails with a videoconference link and any required login information prior to any visit. When the patient/study participant logs into the meeting, clear and concise instructions will appear that instruct the patient to wait in the waiting room until the provider/researcher joins the room and admits them.

Training/ Resources

The MGH Center for TeleHealth will provide training session(s) to educate the lead investigators on utilizing telemedicine for virtual visits and the Research Assistants on training patients and clinicians to use the technology. The Center will also provide tip sheets and instructions for the team on how to use the technology.

The following elements describe methods we will use to ensure clinical and research standards are maintained when telehealth is utilized in the study.

A. Remote Informed Consent Procedures

Prior to the completion of any study procedures, the study clinician will remotely conduct informed consent procedures with the participant. The study clinician will be a licensed physician and either the Principal Investigator or a coinvestigator. Study staff will provide the participant with an IRB-approved consent form via courier mail service or an encrypted email, unless the subject has formally allowed non-encrypted email, as described elsewhere in this document. In the event that email encryption is waived via verbal consent from the participant, the study coordinator will communicate with them via unencrypted email moving forward. This correspondence will include information about why they are receiving the consent form and directions to inform study staff when the consent form has been received. Study staff will then schedule a time for the study clinician to conduct informed consent procedures with the participant via telephone call. The study clinician will call the participant at the scheduled time and conduct informed consent procedures, per the following existing guidelines: review the informed consent form, explain the risks and benefits of study participation, discuss alternatives to participation, and answer any questions the participant may have. If the participant decides to participate in this study, they will sign the consent form. All written signed form(s) will then be sent via courier mail serivce to the study clinician who performed the informed consent procedures for signature. The study clinician will then send the signed form(s) to the study coordinator via courier mail service. The study coordinator will perform a completeness check prior to the start of any study procedures and provide the participant with a copy of the signed form(s) via courier mail service or (un)encrypted email. Copies of all virtually signed form(s) will automatically be sent to the study clinician, the study coordinator, and the participant.

B. Study Visits via Telemedicine

1. Study Visit Timeline

To accommodate scheduling and communication logistics, elements of the initial evaluation (pre-baseline) study visit may occur over more than one day, and other study visits may occur at various points within the same day.

2. Telemedicine

This study will be preferentially conducted by remote telemedicine methods, with option for in-person assessments if needed. Audio and visual communication will be required for evaluation and baseline visits for a subject to participate. If a participant plans to participate by telehealth only, participants with predictable lack of access to audio and visual means of communication will not be enrolled in the study.

All telehealth study visits and study procedures (excluding informed consent procedures) will be conducted via the MGH telemedicine platform, TeleHealth, which is maintained by Partners HealthCare. In the event that TeleHealth malfunctions or the participant does not have access to a device compatible with the TeleHealth platform, the study visit will be completed via secure Zoom web interface, or if not possible, by telephone call. If at any point during a telemedicine study visit, the participant endorses any safety concerns or any acute clinical issues emerge, the study clinician will take the necessary steps to ensure the participant receives the appropriate follow-up clinical care.

3. Clinician Assessments and Rating Scales

As demonstrated by the prior incorporation of telemedicine study visits in studies conducted by our research unit, clinician assessments and rating scales can safely and effectively be completed remotely. The study clinician will enter data into REDCap for televisits, a secure, HIPAA compliant web-based application hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure and Services (ERIS).

4. Informant Assessments and Rating Scales

Informant assessments and rating scales can safely and effectively be completed remotely via REDCap as well. The study coordinator will provide the participant with an online link and access code to these REDCap questionnaires via (un)encrypted email.

5. Safety Measures

Urine Pregnancy Screen

Women of child-bearing potential will complete a urine pregnancy test as part of the evaluation study visit and Week 6/drop study visits. Study staff will order a urine pregnancy test online and ship it directly to the participant's home address. The test will be ordered and shipped in advance to ensure delivery prior to the applicable study visit. On the day of the visit, the participant will complete the test after the study coordinator or a study clinician has reviewed the proper procedure for completing the test. In addition, the participant will provide the study coordinator with visual confirmation of the result via TeleHealth video system or image sent by (un)encrypted email.

Vital Signs

The study coordinator will ship a blood pressure and heart rate monitor to each participant, and ask the participant to self-report the vital signs on the same day as the study visit via telephone call or image sent by (un)encrypted email. The study coordinator will note that these data points were provided by study subject report, rather than study staff measurement.

III. Remote Study Medication Dispensation

Study medication will be stored at, ordered from, and dispensed by the MGH Clinical Trials Pharmacy (CTP). Study staff will pick the study medication that is assigned to each participant from the MGH CTP, remaining blinded to whether it is active or placebo product, and send it via courier mail service directly to the participant's home address. Staff will be trained to follow all guidelines elaborated by the MGH CTP and Drug Enforcement Agency in this process. The study medication will be ordered and shipped in advance to ensure delivery prior to the baseline study visit, with sufficient supply to cover partipation throughout the study. Participants will be given 75 mg strength size active/placebo pills, such that they can take one or two to make up 75 mg or 150 mg per daily dose. Individuals will be given clear instructions to adhere to the agreed-upon dosing schedule between study visits, must keep the study agent in a safe place where other's would not take it in error, must not divert any study agent, and must return study agent to the investigators at the end of the study. Returns will be done either in person at end of study visit or by same-day courier pickup. Where possible, study medication orders for participants from this and other studies within this department will be coordinated so that they can be picked up and mailed in bulk. The study coordinator retrieving study medication orders will be listed as a member of study staff on all applicable studies. Per standard research procedure, the study clinician will record reported medication compliance in the applicable Chart Note. After the completion of study participation, the participant will send the leftover study medication and bottles to the study coordinator via mail courier service. The study coordinator will complete a thorough capsule count at that time and maintain the study medication until it can be returned to MGH and discarded in a biohazard container.

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