Study Protocol:
A Pharmacokinetic/Pharmacodynamic Study of Methylphenidate Formulations in Pediatric Attention-Deficit/Hyperactivity Disorder (ADHD) Patients in a Laboratory Classroom

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1. Abstract

This is a randomized, double-blind, 4-treatment and 4-period crossover study conducted in a school laboratory environment to evaluate the hour by hour pharmacodynamic (PD) response and hour by hour pharmacokinetics (PK) of 3 different extended release methylphenidate (MPH) formulations as well as placebo in children with Attention Deficit/Hyperactivity Disorder (ADHD). The intra and inter subject outcomes will be used to test various PK/PD models to identify improved PK metrics that impact the therapeutic equivalence of methylphenidate extended release products. The school laboratory environment includes an analog classroom and lasts for a 14.5-hour school day. The complete study consists of three periods: Screening, Dose Titration and Double-Blind Crossover in a Laboratory Classroom.

2. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood onset, chronic neurobiological disorder [1] associated with significant levels of impairment in multiple aspects of functioning, including academic achievement, peer relationships, and impaired cognition estimated to afflict up to 10% of children worldwide. Stimulants remain the mainstay of treatment for ADHD across the lifecycle because of their well-documented safety and efficacy[2-5].

MPH is a short-acting stimulant with a duration of action of up to 4 hours and a pharmacokinetic half-life of 2 to 3 hours. Maximum drug concentration after oral administration occurs at about 2 hours. MPH is absorbed well from the gastrointestinal tract and easily crosses the blood-brain barrier. Due to its short half-life, MPH does not lead to a steady state plasma concentration. It is cleared from the body each night.

Swanson et al.[6] hypothesized that MPH may exhibit tachyphylaxis or acute tolerance based on the observation that MPH concentrations measured soon after an initial dose can cause a greater pharmacodynamic effect than concentrations occurring at a later time and manifests itself in a clockwise hysteresis in the plasma concentration-effect relationship. Initial long acting formulations were designed to overcome tachyphylaxis by using increasing plasma concentrations throughout the day, so called ascending PK profiles (e.g. Osmotic Release Oral System (OROS) MPH profile). However, a number of newer, long acting MPH formulations with more complicated PK profiles, including descending PK profiles during later periods of the day, have shown similar efficacy. Thus, the development of a useful model for predicting the therapeutic equivalence of extended release MPH products from PK profiles will need to accurately estimate the degree of tachyphylaxis across the day for each differing PK profile.

3. Credentials of Investigators

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Dr. Spencer's research activities have focused on studies of efficacy and safety of treatments for ADHD, and imaging studies of its pathophysiology. The Pediatric and Adult Psychopharmacology Unit has done adult and pediatric PK and Classroom analog studies for 15 years. Several pediatric studies examined the PK/PD relationship of long acting formulations of stimulants. A number of studies examined the relationship of pharmacokinetic profile and short- and long-acting formulations of methylphenidate on patterns of subjective responses and abuse potential. Dr. Spencer has established new pharmacoimaging paradigms using Positron Emission Tomography aimed at examining molecular mechanisms of disposition of stimulants in the brain while assessing their abuse liability. He was the Principal Investigator in a National Institute of Mental Health funded treatment study that examined the translation of improvement of ADHD symptoms into increased cognitive and functional capacities as well as quality of life in adults with ADHD. Dr. Spencer was also the PI in a large, NIMH funded PET study examining dopamine transporter binding and genetic markers in Adults with ADHD. He edited a book on adult ADHD, published 300 scientific articles and published 46 book chapters. Dr. Spencer's CV is included in a separate document.

Dr. Childress has extensive experience in ADHD research. She has been the principal investigator on more than 50 industry sponsored ADHD clinical trials. This includes 23 laboratory classroom trials and two single-site ADHD pharmacokinetic studies. The laboratory classroom studies are often small studies with two to five sites. Several of these trials have directly led to the FDA approval of currently marketed stimulants. Dr. Childress's CV is included in a separate document.

4. IRB Oversight

The submission will be reviewed by the following Institutional Review Boards:

Partners Human Research Committee (PHRC)
116 Huntington Avenue, Suite 1002
Boston, MA 02116
Phone: 617-424-4148

New England Independent Review Board
85 Wells Avenue, Suite 107
Newton, MA 02459
Phone: 617-243-3924

5. Objectives

Specific Aim 1: To develop a new population PK/PD model to better predict ***onset*** of action of a long acting MPH compound, as assessed in a laboratory classroom setting, accounting for placebo and tachyphylaxis effects. **Hypothesis 1a**: The new PK/PD model will better predict initial efficacy and tolerability within a defined confidence interval than the traditional PK model that relies solely on Area Under Curve (AUC) and maximum concentration observed (Cmax). **Hypothesis 1b:** Our new PK/PD model will reliably quantify the effects of traditional covariates such as dose, sex, age, illness presentation (hyperactive/impulsive and inattentive), severity of illness (as determined by impairment or number of symptoms) as potential factors affecting the inter-individual variability on the PK time-course and on the PD response.

Specific Aim 2: To develop a new population PK/PD model to better predict ***midday*** effects of a long acting MPH compound, as assessed in a laboratory classroom setting, accounting for placebo and tachyphylaxis effects. **Hypothesis 2a:** The new PK/PD model will better predict midday efficacy and tolerability within a defined confidence interval than the traditional PK model that relies solely on AUC and Cmax. **Hypothesis 2b**: Our new PK/PD model will reliably quantify the effects of traditional covariates such as dose, sex, age, illness presentation (hyperactive/impulsive and inattentive), severity of illness (as determined by impairment or number of symptoms) as potential factors affecting the inter-individual variability on the PK time-course and on the PD response.

Specific Aim 3: To develop a new population PK/PD model to better predict ***offset*** of action of a long acting MPH compound, as assessed in a laboratory classroom setting, accounting for placebo and tachyphylaxis effects. **Hypothesis 3a:** The new PK/PD model will better predict offset of action within a defined confidence interval than the traditional PK model that relies solely on AUC and Cmax. **Hypothesis 3b**: Our new PK/PD model will reliably quantify the effects of traditional covariates such as dose, sex, age, illness presentation (hyperactive/impulsive and inattentive), severity of illness (as determined by impairment or number of symptoms) as potential factors affecting the inter-individual variability on the PK time-course and on the PD response.

6. Regulatory Status

All of the medications used in this study are FDA-approved for the treatment of ADHD in children and adolescents. However, we will be using a 72 mg dose of Osmotic Release Oral System (OROS) MPH (Concerta) and methylphenidate hydrochloride extended-release by Mallinckrodt (will henceforth be referred to as Mallinckrodt MPH ER). Although this dose is approved for use in adults and adolescents, the 72 mg dose is not approved by the FDA for use in patients aged 6 to 12 years. The third methylphenidate formulation we are using in this study is Quillivant XR, for which the 60 mg dose has been approved by the FDA for use in patients aged 6 to 12 years. The 60 mg dose of Quillivant XR is considered to be equivalent to the 72 mg dose of Concerta and the 72 mg dose of Mallinckrodt MPH ER. Furthermore, in a study that compared mean plasma concentration-time profiles of MPH transdermal system (MTS) and Concerta in children aged 6-12, the d-MPH Cmax of 30 mg of MTS was 64% greater than the Cmax of 54 mg of Concerta[7]. In addition, the d-MPH interdose AUC of 30 mg of MTS was 41% greater than the AUC of 54 mg of Concerta[7]. The 30 mg MTS is approved in this age range and has shown to be well tolerated. Assuming a linear PK at higher doses, the estimated Cmax and AUC for the 72 mg dose of Concerta would still be less than that of the 30 mg of MTS product. The 72 mg doses of Concerta and Mallinckrodt MPH ER are also commonly used in clinical practice off label because they have been found to be beneficial and well tolerated for some children. Upon review of the IND (Investigational New Drug) application for our study, which included the 72 mg dose, the FDA determined that the study meets all requirements for an exemption from IND regulations, and thus an IND is not required for this study.

7. Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood onset, chronic neurobiological disorder [1] associated with significant levels of impairment in multiple aspects of functioning, including academic achievement, peer relationships, and impaired cognition estimated to afflict up to 10% of children worldwide. Stimulants remain the mainstay of treatment for ADHD across the lifecycle because of their well-documented safety and efficacy [2-5].

Methylphenidate (MPH) is a stimulant medication with a pharmacokinetic (PK) time of maximum concentration (Tmax) of about 2 hours, a half-life (T ½) of 2 to 3 hours and a pharmacodynamic (PD) duration of action of up to 4 hours. Initial extended release formulations proposed an ascending PK profile to overcome acute tolerance (tachyphylaxis) associated with this treatment. Tachyphylaxis would suggest that higher concentrations of MPH may be needed over time for sustained PD effects and is supported by a clockwise hysteresis in the plasma concentration-effect relationship [6]. However, a simple tachyphylaxis model has been challenged by the advent of a number of equally effective extended release MPH formulations with distinctly different PK profiles (shapes) [8-11]. This wide range of effective long acting MPH formulations with diverse PK/PD profiles calls for novel approaches to link PK profiles to the time-course of PD activity of extended release MPH products in order to identify improved PK/PD metrics. Such novel approaches with improved PK/PD metrics are critical for the determination of generic equivalency of MPH compounds.

Long acting MPH formulations traditionally considered equivalent by PK (i.e., the 90% confidence intervals for the Area Under Curve $(AUC)_{0\text{-infinity}}$ ratio are inside the 80%–125% range) were shown to be *significantly different* in PD for onset, early vs. late midday effectiveness as well as timing of offset [12-16]. To address these limitations, we propose to test the PK/PD relationship of three MPH formulations with distinct PK profiles: Concerta, Mallinckrodt MPH ER, and Quillivant XR. In each model, we will separately assess the initial (onset), midday, and terminal (offset) portions of the PK/PD relationship to determine the degree to which new PK metrics predict objective PD measures of efficacy in ADHD symptoms as assessed through an analog laboratory classroom methodology. A disease–drug–trial model paradigm will be applied to the data to integrate MPH PK findings, covariates, time course of clinical outcomes, placebo effects, drug's pharmacologic effects, and trial execution characteristics. This approach will provide guidance for the evaluation of the impact of different concentration-time profiles on the PD effect of MPH extended release products. A population PK/PD model will be developed using individual observations collected in the target pediatric population to explain the drug response, accounting for the placebo effect and for the time varying response of MPH (tachyphylaxis). The proposed PK/PD model will be initially based on a model previously developed for MPH[17]. This model was implemented using a meta-analytic approach using mean data extracted from published papers. This model was able to predict pediatric PD [both math tests Permanent Product Measure of Performance (PERMP) (Appendix VI) and behavioral ratings Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) (Appendix V)] from adult PK data of long acting MPH formulations. A clear limitation of this approach, however, is the reliance on adult group data. To improve upon these limitations, we propose to generalize the model by 1) using ***pediatric*** PK instead of adult PK; 2) most importantly, to use ***individual PK and PD measurements*** rather than relying on mean observations and 3) to separately address **onset, midday, and offset**. Our overarching objective is to provide a validated PK/PD model appropriate for predicting, with a known uncertainty level, the impact of a given PK profile on the therapeutic equivalence of MPH extended release products. The findings from this novel PK/PD study will help establish scientific and regulatory standards for assuring therapeutic equivalence of generic MPH extended release products.

8. Study Design and Methods

8.1 Inclusion and Exclusion Criteria

All potential subjects must satisfy the following inclusion/exclusion criteria:

8.1.1 Inclusion Criteria:

1) Male and female outpatients
2) Ages 6-12 years at time of screening
3) Judged by the investigator to be physically healthy and suitable for participation in the study
4) Diagnosis of DSM-5 ADHD combined, predominantly inattentive or hyperactive/impulsive presentation, per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
5) Clinical Global Impressions-Severity (CGI-S) ≥ 3
6) $\geq 90^{th}$ percentile normative value for gender and age on the ADHD RS-IV total score at screening or baseline
7) Subject has a parent/legal guardian who is willing and able to give written informed consent for the subject to participate in the study
8) Subject must be able to give assent to participate in the trial
9) Subject and parent/legal guardian must be able to speak and understand English
10) Able to tolerate screening skin prick
11) Willing to comply with all study procedures

8.1.2 Exclusion Criteria:

1) Current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Subjects with Autism Spectrum Disorder or Pervasive Developmental Delay diagnoses will be determined eligible or ineligible by clinician judgment on a case-by-case basis depending on the severity of the symptoms. Subjects with school phobia or separation anxiety will not be eligible
2) Cognitively impaired, in the investigator's opinion
3) Any clinically significant chronic medical condition that, in the judgment of the investigator, may interfere with the subject's ability to participate in the study
4) Seizure disorder excluding a history of febrile seizures
5) Thyroid disease
6) Tourette's disorder or chronic tic disorder (mild medication induced tics are allowed)
7) Serious cardiac condition including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension
8) Glaucoma
9) Current or recent (within the past year) DSM-5 drug dependence or substance abuse (excluding nicotine and caffeine)
10) Pregnant or nursing females. Females must have a negative urine pregnancy test at screening as well as four additional visits. All subjects must be abstinent or use adequate and reliable contraception throughout the study
11) Currently treated and satisfied with ADHD medication

12) Current psychotropic medications other than sedative hypnotics for sleep
13) Use of atomoxetine, clonidine, guanfacine or a monoamine oxidase inhibitor within 28 days of the baseline visit
14) Participation in another investigational medication study within 30 days prior to screening
15) Clinically significant abnormal laboratory result, electrocardiogram (ECG) result, physical examination, or vital signs at screening that the investigator considers to be inappropriate to allow participation in the study
16) Planned use of prohibited drugs from the baseline visit through the end of the trial
17) History of allergic reaction or a known or suspected sensitivity to any substance that is contained in the study drugs
18) Food allergies that are determined by the PI as too severe to be easily accommodated for during the study
19) Inability to swallow study medication

8.2 Enrollment

We plan to enroll 150 subjects in order to have approximately 75 subjects complete the study. We estimate a 20% screen fail rate, 15% withdrawal rate during the dose optimization phase, and a 25% withdrawal rate during the double-blind phase. Our conservative estimate for the drop-out rate in the double-blind phase will be at most 25%; our estimate is based on Dr. Childress' experience with double-blind PK studies, in which there were usually 10% drop-out rates. We are using a more conservative estimate of 25% to try to take into account the longer duration of our double-blind phase with the use of skin pricks as opposed to the use of catheters. Our sample's size of 75 subjects is considered appropriate for providing an estimate of the PK and the PK/PD model parameters with a sufficient precision. Approximately 50 subjects will be enrolled at Massachusetts General Hospital and approximately 100 subjects will be enrolled at the Center for Psychiatry and Behavioral Medicine (CPBM).

8.3 Study Design

This is a randomized, double-blind, 4-treatment and 4-period crossover study conducted in a laboratory school environment to evaluate the hour by hour PD response and hour by hour PK of 3 different extended release MPH formulations as well as placebo in children with ADHD. The intra- and inter- subject outcomes will be used to test various PK/PD models to identify improved PK metrics that impact the therapeutic equivalence of methylphenidate extended release products. The school laboratory environment includes an analog classroom and lasts for a 14.5-hour school day. The complete study consists of three periods: Screening, Dose Titration and Double-Blind Crossover in a Laboratory Classroom.

Subjects will be randomly assigned to one of 24 different treatment sequences for the Double-Blind Crossover portion of the study. The double-blind phase will consist of four periods: each week will consist of blinded treatment with one of the three treatments or placebo from Sunday through Saturday. On the last day of each period (Saturday), subjects will be evaluated in a

laboratory classroom setting. Subjects will receive blinded treatment each week based on the treatment sequence they were assigned. For example, if a subject is assigned the first treatment sequence (see Section 8.8), the first week the subject will receive blinded Quillivant XR treatment, the second week the subject will receive blinded Concerta treatment, the third week the subject will receive blinded Mallinckrodt MPH ER treatment, and the fourth week the subject will receive blinded placebo treatment. On Saturdays, the blinded doses of each study drug will be administered at the school site by study staff on the morning of the test laboratory classroom day. On the other days, the medication will be taken at home in the morning before 10:00 AM. The crossover design of the study will allow subjects to serve as their own controls.

While children, parents, investigators, and staff will know all of the study medications involved in this study, they will remain blind to the subject's treatment at any given time during the double-blind period. Randomization data will be kept confidential until the time of unblinding, and will only be accessible by bioanalytical personnel involved in analysis. The identity of the medications will be unknown to children, parents, and study staff as the medication will all be identical in packaging, labeling, appearance, and schedule of administration. The MGH research pharmacy technicians and a CPBM designated member of study staff will not be blinded, as they will need to dispense the appropriate medication for each subject to the appropriate study investigator. The unblinded personnel will not be responsible for any subject interactions or study assessments so as not to impact data integrity.

During the double-blind period, the subject will take a placebo in addition to the blinded Concerta, blinded Quillivant XR, blinded Mallinckrodt MPH ER, or blinded placebo. The subject will only receive one actual medication at a time, but will take both a tablet and a liquid to help maintain the blind. This is necessary because the different medications come in different forms. Each week the subject will receive a liquid medication (three of the four weeks the liquid will be a placebo). Only one week the subject will receive liquid Quillivant XR. Each week the subject will also receive a tablet. One week the subject will receive brand Concerta, one week Mallinckrodt MPH ER, and the other two weeks the tablet will be a placebo.

8.4 Study Assessments

The following assessments and instruments will be used:

Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID 7.0.0): The MINI-KID is a widely used structured diagnostic interview used to assess the presence of DSM-5 child and adolescent psychiatric disorders. The MINI-KID will be performed at the screening visit to confirm ADHD diagnosis and to assess any co-morbidities (Appendix I).

Clinical Global Impressions (CGI) scale for ADHD: The CGI is a measure of global illness severity (CGI-S; 1 = not ill to 7 = extremely ill) and improvement (CGI-I; 1 = very much improved to 7 = very much worse). A score of ≥ 3 (indicating at least mild severity) is required for inclusion. The CGI will be performed at screening, baseline, and all consecutive study visits and is based on the investigator's clinical assessment of the subject (Appendix II).

ADHD-Rating Scale-IV (ADHD-RS-IV): The ADHD-Rating Scale is a parent-rated scale used to assess which ADHD symptoms are present and the frequency of symptom interference with daily functioning. The ADHD-RS-IV will be completed by a rater based on parent interview for each visit. A score ≥ the 90th percentile normative on the home version values for gender and age on the total score, hyperactive-impulsive subscale or the inattentive subscale is required for inclusion. The ADHD-RS-IV will be performed at screening, baseline, and all consecutive study visits (Appendix III).

Demographic Questionnaire: A brief demographic interview will be conducted with the parent/guardian. This interview will be used to estimate socioeconomic status, as well as to collect information about any educational accommodations, past head injuries, and trauma. This interview will be performed at screening (Appendix IV).

Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale: The SKAMP scale is a validated 13-item rating of subjective impairment of classroom observed behaviors (0 = normal/no impairment; 1 = slight impairment; 2 = mild impairment; 3 = moderate impairment; 4 = severe impairment; 5 = very severe impairment; 6 = maximal impairment). The SKAMP consists of four subscales: SKAMP-Attention, SKAMP-Deportment, SKAMP-Quality of Work, and SKAMP-Compliance. Scores will be obtained during each classroom cycle during each full laboratory classroom day at pre-dose, and at 0.5, 1.5, 2.5, 4, 5, 6, 8, 10, and 12 hours post-dose. The scores will be based on the child's behavior during 20 minutes of each cycle. The SKAMP will be completed by the raters, who will undergo substantial training prior to the study. On the practice laboratory classroom day, the SKAMP will be administered at pre-dose, 0.5 and 1.5 hours post dose (Appendix V).

Permanent Product Measure of Performance (PERMP): The PERMP involves objective individualized mathematics tests of 400 items, with 80 items per page and subjects have 10 minutes to work on the problems. They are told to work on problems from left to right starting at the top of the page and not to skip any problems or rows. If a subject completes the first page, he or she will turn the page immediately and start working on the problems on the next page. There are four levels: Basic, Easy, Moderate and Difficult. PERMP attempted and correct scores will be obtained during each laboratory classroom day at pre-dose and at each post-dose time point. On the practice laboratory classroom day, each subject will be given the level of math test assigned at the baseline visit after taking the Placement Test. The Placement Test consists of one page of Basic problems, one page of Easy problems, one page of Moderate problems and one page of Difficult problems. Subjects have 2 minutes to work on each page of the placement test (totaling approximately 8 minutes). Subjects must be able to correctly complete at least 11 basic problems on the placement test to be included in the trial. The test level is assigned by adding the total number of problems completed correctly for each practice level divided by 2. The correct level should be greater than 5 and closest to 10. (For example, a score of 14 on Basic and 7 on Easy would result in an assignment of the Easy level). The test level may be changed during the practice day at the discretion of the study staff. The level cannot be changed after the practice visit (Appendix VI).

Columbia Suicide Severity Rating Scale (C-SSRS): The C-SSRS will be used to assess suicidal thoughts or behaviors at screening and all subsequent visits (Appendix VII). There are Children's Screening/Baseline and Since Last Visit versions. The Screening version will be administered at the screening and baseline visits, and the Since Last Visit version will be administered at all subsequent visits.

8.5 Study Procedures

8.5.1 Initial Evaluation Procedures and Screening Tests (Visit 1)

After obtaining IRB-approved informed consent/assent, participants will be screened for eligibility. Since this visit will take between 3 and 5 hours to complete, it may occur over two days. Only subjects who meet all of the criteria for enrollment after these assessments will continue with study procedures. In the event that subjects meet all eligibility criteria except for completing the placebo swallow test, subjects may be rescreened a maximum of 2 times while learning to swallow. All screening procedures are performed solely for the purpose of determining if individuals are eligible for participation in the study. The following procedures will be done at this visit:

- Obtain informed consent from one parent/guardian and assent from the subject.
- Check inclusion/exclusion criteria
- Parent/guardian will be queried about adverse events and concomitant medications
- Demographics, psychiatric, and medical history: Participants and their parents/guardians will be asked about family, education, home environment, occupation, and the child's medical and psychiatric history
- Parents/guardians/subjects will be asked about the child's mental health in the MINI-KID, a structured diagnostic interview used to assess the presence of DSM-5 child and adolescent psychiatric disorders. This interview may take up to 2 hours to complete.
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Clinical Global Impressions (CGI)
- ADHD-Rating Scale-IV (ADHD-RS-IV): parent questionnaire about participants symptoms of ADHD
- Electrocardiogram (ECG)
- Brief physical examination
- Vital signs: blood pressure, heart rate, temperature, and respiratory rate
- Height and body weight
- Urine drug test: screen for prescription drugs and illegal drugs including marijuana, cocaine, Phencyclidine (PCP), amphetamines and sedatives
- Urine pregnancy test for females
- Blood draw: Approximately 13 milliliters or 2.6 teaspoons of blood will be drawn for laboratory tests, including hematology, serum chemistry, and PK. A numbing cream will be offered
- Placebo swallow test
- Practice skin prick and PK sampling (see section 8.5.7 for PK sampling details). A numbing cream may be offered

8.5.2 Washout Period

Once all inclusion and exclusion criteria have been verified, instructions for washout for those subjects taking exclusionary medications will be given, and the baseline visit will be scheduled (Visit 2). The washout period will last three to seven days in duration (with the exception of atomoxetine, clonidine, guanfacine or a monoamine oxidase inhibitor, which require a 28 day washout), depending on the half-life of the medication currently being taken, and will take place after the screening visit and prior to the baseline visit. This will allow the regular medications to leave the participant's body before he/she begins taking the study medication and will allow the investigators to obtain an accurate baseline assessment of ADHD behaviors. The subject may resume his/her normal medication the day following the final classroom visit.

Subjects must complete a washout from all ADHD medications and other prohibited medications prior to study drug administration. Medication washout will be done with careful consideration of the adverse effects associated with the treatment and the effects of stopping that medication/treatment. Washout will be discussed with the participant, their parent/guardian, and current providers when applicable. Medications for underlying conditions including lithium, anti-depressants, anticonvulsants, and anti-psychotics, and other medications that are necessary for the safety and well-being of the child, will not be stopped for the purpose of this trial.

8.5.3 Prohibited Medications

Use of the following medications is not permitted during the study:

- Any medications for the treatment of ADHD
    - Alpha-2 adrenergic receptor agonists, modafinil, armodafinil, atomoxetine, or any stimulant class (methylphenidate- or amphetamine-based) agent
- Pseudoephedrine-containing treatments of allergies or colds

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during the study if the dose and regimen have been stable for at least 30 days prior to screening. Additionally, use of nonprescription pain medications is allowed during the study as long as these medications do not have psychotropic effects. Melatonin for sleep is also permitted. Short courses of prescription medications such as antibiotics for infections will be allowed. Non-sedating antihistamines will be allowed. If a child is given a prohibited medication at any point in the study, the investigators will decide the proper course of action on a case-by-case basis.

If a new diagnosis requiring a prohibited medication is made during the course of the study, the participant may be withdrawn.

Parents will be told that their child should not have more than one caffeinated drink (up to 8oz) per day during this study.

8.5.4 Baseline Visit (Visit 2)

This visit will occur within 56 days of the screening visit and will last approximately 1 hour.

The following procedures will be done at the baseline visit:

- Confirm inclusion/exclusion criteria
- Parent/guardian will be queried about adverse events and concomitant medications
- Urine drug test
- Urine pregnancy test for females
- Vital signs: blood pressure, heart rate, temperature, and respiratory rate
- Height and body weight
- ADHD-RS-IV and Clinical Global Impressions (CGI) scale for ADHD to determine symptoms
- C-SSRS
- PERMP: Subjects complete a placement math test, which lasts about 8 minutes
- Start subjects on 18 mg of brand Concerta. If subjects were previously on a stimulant prior to the washout period they may start the study medication on an equivalent dose of Concerta so that they can start at a dose they have already responded to and tolerated.
- Dispense a one week supply of study medication and distribute and explain dosing diaries, which contain instructions about administering the study drug, who to contact with questions, and other important information (Appendix VIII). Parents will be instructed not to give their child the study drug after 10:00AM, with the recommendation that they give it to them at least 1 hour prior to leaving for school. The parents will also be instructed to call the study researcher if they are confused about how much study drug their child should be taking, or when they should be taking it. They will be instructed to have their child take the medication intact with food; they will be told that the capsules should be swallowed whole and not crushed, chewed, or tampered with in any way. They will be told to call the study researcher right away if their child misses a dose for any reason, or if the medication is lost or damaged. They will also be reminded that it is very important that they bring any unused study drug and any empty packaging with them when they come to each study visit.

8.5.5 Optimization Visits (Visits 3, 4, 5, 6, 7, and 8)

During this period, subjects will make weekly visits (±3 calendar days) during which the dose of Concerta will be titrated at weekly intervals of 18 mg increments until an optimal dose is achieved or a maximum of 72 mg per day is reached. Although the 72 mg dosage is not FDA-approved for patients aged 12 years and under, the dose has been used off label in clinical practice and has been found to be beneficial for some children. The 72mg dose is FDA-approved for patients aged 13 years and older. Subjects will only be given the 72 mg dose if they have tolerated all previous doses well and could achieve further optimization at the higher dose. Since 72 mg tablets are not manufactured, subjects that titrate to this dose will be given two 36 mg tablets for each day. Criteria for optimal dose will be at least a 30% improvement on the ADHD-RS-IV score, a CGI-I of much or very much improved and tolerable adverse events. Each week, subjects who could benefit from further increase of methylphenidate may increase to the next dose level up to the maximum dosage (72 mg per day). Subjects who have intolerable adverse events may step down one dose level per week. Subjects on 36 mg may step down to 27 mg, subjects on 54 mg may step down to 36 mg, and subjects on 72 mg may step down to 54 mg of Concerta. Subjects who cannot tolerate at least 27 mg of Concerta will be discontinued from the trial. A subject may take 18mg through the duration of the optimization visits, but those

stabilized at 18 mg will not move forward to the classroom visits because there is no 18mg dose of the Mallinckrodt MPH ER. Also, if the subject is unable to tolerate a dose of Concerta that will provide at least a 30% decrease in ADHD-RS-IV score, the subject will be discontinued from the trial. At the end of this part of the study, no further dose changes will be made.

The following procedures will be done at the optimization visits:

- Parent/guardian will be queried about adverse events, concomitant medications and study medication compliance
- Collect any unused study drug, any empty study drug packaging, and dosing diaries
- Vital signs: blood pressure, heart rate, temperature, and respiratory rate
- Height and body weight (Visit 8 only)
- ADHD-RS-IV and CGI scale for ADHD to determine symptoms
- C-SSRS
- Increase dose if necessary and dispense a one week supply of Concerta, and distribute dosing diaries
- Urine drug test (Visit 6 only)
- Urine pregnancy test for females (Visit 6 only)
- Give parents instructions about the practice classroom day (Visit 7 only)

Randomization will occur between Visit 7 and Visit 8. Once Visit 7 is completed the subjects' optimal dose will have been established and they can be randomized following that visit. Randomization must occur prior to Visit 8 because the blinded drugs are dispensed at the end of the visit.

In order to provide more flexibility for the optimization phase, a variety of scenarios will be allowed at the discretion of a study clinician. These scenarios may include:

- Optimization phone visits:
    - If a subject optimizes early (e.g. titrates down from the 36mg to the 27mg dose and optimizes at 27mg by Visit 5), the subject will be given the option to complete the subsequent optimization visits over the phone; this will reduce travel time and subject burden. Also, if at any point a subject is unable to make an optimization visit in person, the subject may schedule a phone visit if the subject is on a stable dose (based on clinician judgment) of Concerta. If an optimization phone visit takes place:
        - Additional supply of study drug will be provided at the last in-person visit. Otherwise, the subject must come in at a separate time to pick up the study drug.
        - Drug accountability may be completed at the next in-person visit
        - Vital signs will not be collected for phone visits
        - If Visit 6 is a phone visit, the urine drug screen and pregnancy test may be completed at the previous in-person visit or at the next in-person visit.

- Extending the optimization period:
    - Subjects may remain on their optimal doses of Concerta until the practice classroom can take place. A sufficient number of subjects must be enrolled to

simulate the classroom environment, so Visit 8 may be delayed up to a maximum of 6 months to enroll or optimize more subjects. If this scenario occurs:

- Weekly phone calls will be made to the parents/guardians to collect any new information on adverse events, concomitant medications and study medication compliance.
- Subjects must complete an in-person visit with a study clinician 1 month after the previous in-person visit or if a refill prescription is needed. Vital signs may be collected at these visits if the clinician determines that it could be useful.

8.5.6 Practice Classroom Day (Visit 8)

For the last dose optimization visit (Visit 8), all subjects will attend a half-day practice laboratory classroom on a Saturday. Parents and children will arrive at 6:00 AM and will be introduced to the classroom staff and speak with the investigators. Parents will then be asked to depart, so that data is not compromised by their presence, as parental presence may influence the child's behavior (both positively and negatively). All parents will sign their child in upon arrival and will be asked to provide emergency contact information for that day. All study staff will be made aware of any allergies or any special accommodations that need to be made for each child. Before the parent leaves, the child must verbally assent to participate in the classroom day, and this will be documented by study staff. Children will be picked up at 11:00 AM. Only the parent that brought their child to the classroom will be allowed to pick up the child, unless previous arrangements have been made. Breakfast and snacks will be served.

At the end of Visit 8, the subject will receive blinded Concerta treatment, blinded Quillivant XR treatment, blinded Mallinckrodt MPH ER, or blinded placebo treatment determined by their randomization to take for the next week, beginning the following morning.

Subjects will begin taking their given treatment the following morning before 10:00 AM. The dose taken will be approximately equivalent to the optimized dose of Concerta.

The following will be included at the practice classroom visit:

- Arrival and Check-In
- ADHD-RS-IV, CGI Scale for ADHD, and C-SSRS scales, as well as queries about adverse events, concomitant medications and study medication compliance: may be completed with parent/legal guardian/subject up to 3 days before (by phone or in person) or on the morning of Visit 8
- Collect any unused study drug, any empty study drug packing, and dosing diaries
- Breakfast and snacks
- Study staff will administer last optimization dose of Concerta
- Vital Signs
- Height and body weight
- PERMP: Subjects complete math tests, which last 10 minutes each, three times during the day
- SKAMP: observers rate children's behavior in the classroom during the PERMP and a structured game for a total of 20 minutes each cycle. SKAMP will be administered three times during the day at pre-dose, 0.5 and 1.5 hours post dose

- Activities including classroom games, movies, arts and crafts, and athletic activities
- Dispense blinded study drug and distribute dosing diaries
- Give parents instructions for the next visit
- Pick-up and check-out

In the event that the Practice Classroom cannot happen on the Saturday as planned (example: a snow-related weather emergency), the study staff will first attempt to hold the classroom the following day (the Sunday of the weekend). If the Practice Classroom still cannot be held, it will be re-scheduled for the following week, pushing back Classroom Visits (Visits 9, 10, 11, and 12) accordingly.

Study coordinators will ensure subjects have adequate medication to dose through to the new Practice Classroom date.

8.5.7 Classroom Visits (Visits 9, 10, 11, and 12)

Visit 9 will take place one week after Visit 8 and will be the first full classroom school day consisting of approximately 14 hours of activities, including arts and crafts, movies, and athletic activities. Throughout the day, specific assessments will be employed to measure onset, duration and offset of the effect of each medication. The assessments will include subjective measures such as attention and behavior (SKAMP Rating Scale), as well as objective, individualized mathematics tests (PERMP). On classroom days, the blinded doses of each study drug will be administered at the school site by study staff in the morning.

Parents and subjects will arrive at 6:00 A.M. Parents will be offered coffee and snacks upon arrival, speak with the investigators and then will be asked to depart, so that data is not compromised by their presence, as parental presence may influence the child's behavior (both positively and negatively). All parents will sign their child in each morning and will be asked to provide emergency contact information for that day. All study staff will be made aware of any allergies or any special accommodations that need to be made for each child. Before the parent leaves, the child must verbally assent to participate in the classroom day, and this will be documented by study staff. Parents will return at 8:30 P.M. to pick up their child. Only the parent that brought their child to the classroom will be allowed to pick up the child, unless previous arrangements have been made. Breakfast, lunch, dinner, and snacks will be provided to the subjects. All meals will be provided at the same time every day, with the same meal options provided at each classroom visit. The two sites will coordinate to create standardized meals within and between sites based on similar nutritional values.

During this phase of the study, the child will be on each medication and the placebo for one week, as determined by the randomization sequence. The last day of each weeklong medication period is the classroom day. Parents do not dose their children on classroom days. Instead, study staff will give the subject the study drug the day of the classroom session at 8:00 AM. The precise time will be recorded and is crucial for maintaining the tight schedule for outcome measures.

On each classroom day, the subjects will have eight PK samples taken using Dried Blood Spot Analysis (DBS). Less than 2 milliliters (0.4 teaspoons) of blood will be taken for PK samples

using skin pricks. A total of about 15 milliliters or 1 tablespoon of blood will be collected in this study. Immediately prior to blood collection, the subject will be instructed to rub the selected area of skin to warm the area and stimulate blood flow. Only noninvasive areas of the skin will be selected to minimize pain. The selected area will then be cleaned with an alcohol pad and "milked" to increase blood flow prior to puncture of the skin with a lancet. The phlebotomist will continue milking the area until a large drop of blood forms. The open end of a glass capillary tube will be placed against the blood drop until blood fills the capillary to the volumetric mark. The DBS card will be spotted by placing the open end of the blood filled capillary in contact with the surface of the card. Following sampling, the puncture site will be cleaned and a bandage will be applied. Following blood application, the DBS cards will be allowed to dry for at least 60 minutes or until samples are dry and the blood spots turn dark red or brown. After the samples are dry, the individual DBS cards will be placed in sealed plastic bags with a desiccant pouch.

In our PK/PD simulation modeling we have determined that eight blood draws each classroom day is the optimal amount of blood draws to determine PK profiles to achieve the goals of this project. In addition we do not believe a reduction in the amount of blood draws to be necessary. Dr. Childress has completed four PK studies (12, 14, or 24 hours) with catheters in the same age group. Out of four studies with at least as many draws per day only two out of 41 subjects were lost for difficulties with phlebotomy that included difficulties placing the catheter that are not pertinent to this study. We will be using skin pricks for the blood draws as opposed to IV catheters for this study. The methods to obtain capillary blood samples by skin prick have evolved to be only minimally painful. A numbing cream option may be offered before the skin pricks to minimize discomfort. In the treatment of diabetes, many children do such skin pricks frequently (4 times per day every day of their lives).

Each classroom day will be precisely scheduled and will include cycles of varying length consisting of phlebotomy, classroom sessions, and recess time. Each classroom session will include an academic game (Appendix IX) and the PERMP. These sessions will last approximately 25 minutes; therefore, the time window for phlebotomy and recess is 30 minutes to allow ample time to collect all necessary samples from all subjects. SKAMP ratings will be determined by the participant's behavior during the classroom session. No more than 18 children will participate in each classroom session.

The following will be included at the classroom visits:

- Arrival and check in
- Parent/guardian will be queried about adverse events, concomitant medications and study medication compliance
- Collect any unused study drug, any empty study drug packing, and dosing diaries
- ADHD-RS-IV, CGI Scale for ADHD, and C-SSRS scales, as well as queries about adverse events, concomitant medications and study medication compliance may be completed up to 3 days before (by phone or in person) or the morning of the classroom visit
- Urine drug test (Visit 11 only)
- Urine pregnancy test for females (Visit 11 only)
- Study Staff will administer dose of study drug
- Vital signs

- Height and body weight (Visit 12 only)
- PERMP: Subjects will complete 10 minute math tests during each classroom session
- SKAMP: Observers will rate the subject's behavior throughout the day. Scores will be obtained ten times during each classroom session at pre-dose, and at approximately 0.5, 1.5, 2.5, 4, 5, 6, 8, 10, and 12 hours post-dose
- PK samples: phlebotomy (DBS) taken eight times at approximately 0.5, 1.5, 2.5, 4, 5, 6, 8, and 12 hours post-dose
- Breakfast, lunch, and dinner; subjects will be given snacks and drinks throughout the day to help them stay well hydrated and comfortable
- Activities including classroom games, movies, arts and crafts, and athletic activities
- Dispense week's supply of study medication and dosing diaries (Visits 9, 10, and 11 only)
- Pick-up and check-out

Time	**Time After Dose**	**Group Activity/ Classroom Game**	**Recess Activity**
0600	N/A (Arrival)	Vital Signs, Breakfast	Videos, Crafts
0730	-0.5 hours	Predose Classroom, SKAMP (Sound Baskets)	
0800-0805	Dosing		Videos, Crafts
0830	0.5 hours	Classroom, SKAMP (Math Bingo)	
0900	1.0 hours	Phlebotomy	Videos, Crafts
0930	1.5 hours	Classroom, SKAMP (Hangman)	
1000	2.0 hours	Phlebotomy	Videos, Crafts
1030	2.5 hours	Classroom, SKAMP (Concentration)	
1100	3.0 hours	Phlebotomy	Videos, Crafts, Lunch
1200	4.0 hours	Classroom, SKAMP (Pictionary)	
1230	4.5 hours	Phlebotomy	Videos, Crafts
1300	5.0 hours	Classroom, SKAMP (Phonics Jeopardy)	
1330	5.5 hours	Phlebotomy	Videos, Crafts
1400	6.0 hours	Classroom, SKAMP (Scramble Words)	
1430	6.5 hours	Phlebotomy	Videos, Crafts, Physical activity
1600	8.0 hours	Classroom, SKAMP (Zoom In)	
1630	8.5 hours	Phlebotomy	Videos, Crafts, Dinner
1800	10.0 hours	Classroom, SKAMP (Wheel of Fortune)	

1930	11.5 hours	Phlebotomy	Videos, Crafts
2000	12.0 hours	Classroom, SKAMP (Phonics Bingo)	
2030	12.5 hours	Dismissal	Goody Bags

The descriptions of the activities are described in Appendix IX.

In the event that any Classroom Visit cannot happen on the Saturday as planned (example: a snow-related weather emergency), the study staff will first attempt to hold the classroom the following day (the Sunday of the weekend). If the Classroom Visit still cannot be held, it will be re-scheduled for the following week. In the interim week, subjects will remain on the double-blind medication for an extra week. Study staff will work with subjects and the pharmacy to ensure participants will be able to receive this additional blinded medication. The study clinician will also repeat the weekly pre-classroom phone visit. Below please find an example of what this proposed change would look like:

Practice Classroom (Visit 8) – January 1st: occurs as planned
Beginning of Double Blind Phase
Classroom 1 (Visit 9) – January 8th: occurs as planned
Classroom 2 (Visit 10) – January 15th: cannot occur due to weather emergency.

- *Step 1:* Try to re-schedule for January 16th
- If January 16th cannot occur due to weather emergency:
- *Step 2:* Classroom Visit 2 will take place January 22nd
- *Step 3:* Ensure subjects have blinded medication sufficient to dose for January 15th – January 22nd and repeat Clinician pre-classroom call
- *Step 4:* Resume Classroom Visit 2 on January 22nd, resume usual medication double blind pace

Classroom 3 (Visit 11): Now scheduled for January 29th
Classroom 4 (Visit 12): Now scheduled for February 5th

While the subject's personal doctor may continue to resume medications the day following the last classroom visit, the subject may also request a medication prescription from the study doctor. The study doctor may choose to provide subjects with prescriptions immediately after the end of the last classroom visit if the study doctor deems it appropriate for those subjects to maintain functioning and/or reduce symptoms of ADHD through the last follow-up visit. Upon the last follow-up visit, the subject will either transition to outside care or continue to receive care through our clinic.

8.5.8 Follow-Up Safety Visits (Visits 13 and 14)

Subjects will return for two mandatory follow-up visits one week and two weeks (±3 days) after the last classroom visit. The following procedures will be done:

- Vital signs
- Height and body weight (Visit 14 only)
- C-SSRS
- Record adverse events and concomitant medications
- Urine pregnancy test for females (Visit 14 only)

- These visits will also be used to transition the subject to outside care or to continue treatment in our clinic. Subjects may restart their regular medications or be put on new medications by their personal doctor the day following the last classroom visit, unless the study doctor is prescribing them medications

8.5.9 Table of Assessments

	Screening	Washout	Enrollment and Dose Optimization						Laboratory Classroom					Follow-Up	
Visit	1	Between 1 and 2	2	3	4	5	6	7	8	9	10	11	12	13	14
Study Week	Up to -4	-4 – 0	0	1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent/ Assent	X														
MINI-KID Structured	X														
ADHD-RS-IV Rating Scale	X		X	X	X	X	X	X	X	X	X	X	X		
Demographics	X														
Psychiatric History	X														
Medical/Medication History	X														
Physical exam	X														
Inclusion/Exclusion Criteria	X		X												
Body Weight	X		X						X				X		X
Height	X		X						X				X		X
Sitting Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Test	X		X				X					X			
Urine Pregnancy Test	X		X				X					X			X
12-Lead ECG	X														
Hematology	X														
Serum Chemistry	X														
Urinalysis	X														
CGI (Clinical Global)	X		X	X	X	X	X	X	X	X	X	X	X		
C-SSRS (Suicide Rating)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization								X							
Dispense Study Drug			X	X	X	X	X	X	X	X	X	X			
SKAMP (Behavior)									X	X[a]	X[a]	X[a]	X[a]		
PERMP (Math Test)			X						X	X[a]	X[a]	X[a]	X[a]		
Skin Pricks	X									X[b]	X[b]	X[b]	X[b]		
Swallow Test	X														
Study Drug Compliance				X	X	X	X	X	X	X	X	X	X		

a: 7:30 AM, 8:30 AM, 9:30 AM, 10:30 AM, 12:00 PM, 1:00 PM, 2:00 PM, 4:00 PM, 6:00 PM, 8:00 PM
b: 9:00 AM, 10:00 AM, 11:00 AM, 12:30 PM, 1:30 PM, 2:30 PM, 4:30 PM, 7:30 PM

8.6 Standard vs. Experimental Treatment

All procedures in this protocol are being done solely for research. Parents of children with ADHD can speak with their primary care doctor to obtain a prescription for medication to treat their symptoms or a referral to a specialist if they do not wish to participate in this research. Stimulants are first line treatments for ADHD, but the current study procedures differ from standard of care.

8.7 Randomization

We will enroll approximately 50 subjects at the Massachusetts General Hospital (MGH) site in order to have at least 25 subjects complete the study. We will enroll approximately 100 subjects at the Center for Psychiatry and Behavioral Medicine (CPBM) site in order to have at least 50 subjects complete. We will randomize subjects within sites so as not to confound the distribution of sequences between sites. The order of assignment will be generated by a statistician who is not involved in any of the study procedures and will provide the randomization list to the MGH Research Pharmacy and the unblinded staff member at CPBM to dispense the medication in the order of the treatment sequence that will be associated with the randomization code from the list. The list can be generated either through websites or software programs like Excel. Each site's randomization list will include a subject ID and an associated treatment sequence. Subject IDs will be 5-digit ID numbers assigned at each site to subjects upon enrollment using different number ranges to distinguish between the two sites (ie. MGH: 37000-37100, CPBM: 39000-39100). At the MGH site, the research pharmacy will dispense the medication to the investigators. At the CPBM site, the unblinded staff member will dispense the medication to the other investigators. No one else at the site will know which treatment sequence subjects are assigned to and the unblinded staff member will not be involved in any other study procedures. Subjects will be randomly assigned after Visit 7 to one of 24 different treatment sequences for the 4-week double-blind period. While it is possible to use a 4 X 4 Williams design in which each treatment is immediately preceded equally often by all the remaining treatments, the Williams design is balanced for first order carryover effects only; we will be using all sequences to avoid higher order carryover effects. The following are the possible treatment sequences:

ORDER	Week 1	Week 2	Week 3	Week 4
1	Quillivant XR	Concerta	Mallinckrodt ER	Placebo
2	Quillivant XR	Concerta	Placebo	Mallinckrodt ER
3	Quillivant XR	Mallinckrodt ER	Concerta	Placebo
4	Quillivant XR	Mallinckrodt ER	Placebo	Concerta
5	Quillivant XR	Placebo	Concerta	Mallinckrodt ER
6	Quillivant XR	Placebo	Mallinckrodt ER	Concerta
7	Concerta	Quillivant XR	Mallinckrodt ER	Placebo
8	Concerta	Quillivant XR	Placebo	Mallinckrodt ER
9	Concerta	Mallinckrodt ER	Quillivant XR	Placebo
10	Concerta	Mallinckrodt ER	Placebo	Quillivant XR
11	Concerta	Placebo	Quillivant XR	Mallinckrodt ER
12	Concerta	Placebo	Mallinckrodt ER	Quillivant XR
13	Mallinckrodt ER	Concerta	Quillivant XR	Placebo

14	Mallinckrodt ER	Concerta	Placebo	Quillivant XR
15	Mallinckrodt ER	Quillivant XR	Concerta	Placebo
16	Mallinckrodt ER	Quillivant XR	Placebo	Concerta
17	Mallinckrodt ER	Placebo	Concerta	Quillivant XR
18	Mallinckrodt ER	Placebo	Quillivant XR	Concerta
19	Placebo	Concerta	Mallinckrodt ER	Quillivant XR
20	Placebo	Concerta	Quillivant XR	Mallinckrodt ER
21	Placebo	Mallinckrodt ER	Concerta	Quillivant XR
22	Placebo	Mallinckrodt ER	Quillivant XR	Concerta
23	Placebo	Quillivant XR	Concerta	Mallinckrodt ER
24	Placebo	Quillivant XR	Mallinckrodt ER	Concerta

9. Product Information

The following medications will be used in this study:

9.1 Quillivant XR

Quillivant XR (methylphenidate hydrochloride) extended-release (oral suspension) is a central nervous system (CNS) stimulant indicated for the treatment of Attention-Deficit/Hyperactivity Disorder. The medication is a powder that, after reconstitution with water, forms an extended-release oral suspension formulation of methylphenidate intended for once daily oral administration. The medication contains about 20% immediate-release and 80% extended-release methylphenidate.

The medication is supplied as a powder for oral suspension, which will be reconstituted with water prior to dispensing by the MGH research pharmacy or by CPBM. The specified amount of water will be added to the bottle (see below). The bottle adapter will be inserted into the neck of the bottle, the bottle cap replaced, and the bottle shaken for at least 10 seconds to prepare suspension. Quillivant XR is stable for up to 4 months after reconstitution. The medication will be stored by the MGH pharmacy and by CPBM at 25° (75°F). Excursions will be permitted from 15° to 30°C (59° to 86°F).

Amount of drug in bottle	**Amount of water to add**	**Final reconstitution volume**
300 mg	53 mL	60 mL
600 mg	105 mL	120 mL
750 mg	131 mL	150 mL
900 mg	158 mL	180 mL

Quillivant XR is manufactured by Tris Pharma, Inc. and distributed by Pfizer, Inc.

9.2 Concerta

Concerta (methylphenidate hydrochloride) extended-release (tablets) is a CNS stimulant for the treatment of Attention-Deficit/Hyperactivity Disorder. 18mg, 27mg, 36mg, and 54mg tablets will be used in this study.

The medication will be stored by the MGH pharmacy and by CPBM at room temperature, 15° to 30°C (59° to 86°F).

Concerta is manufactured and distributed by Janssen Pharmaceuticals, Inc.

9.3 Mallinckrodt MPH ER

Mallinckrodt methylphenidate hydrochloride extended-release (tablets) is a CNS stimulant for the treatment of Attention-Deficit/Hyperactivity Disorder. 27mg, 36mg, and 54mg tablets will be used in this study.

The medication will be stored by the MGH pharmacy and CPBM at room temperature, 15° to 30°C (59° to 86°F).

Mallinckrodt MPH ER is manufactured and distributed by Mallinckrodt Inc. Recent U.S. Food and Drug Administration (FDA) regulatory action issued that Mallinckrodt methylphenidate ER can no longer be considered a generic form of Concerta, due to findings that the two drugs are not bioequivalent. The FDA has not identified any serious safety concerns with the product.

9.4 Blinding and Unblinding of Medication

In case of an emergency, the MGH investigators will be able to contact the research pharmacy for emergency unblinding 24 hours a day by page. CPBM investigators will be able to contact a designated unblinded study staff member for emergency unblinding 24 hours a day. This staff member will be a nurse with extensive experience with these types of studies and will be trained by the Principal Investigator.

9.4.1 Blinding of Concerta and Mallinckrodt MPH ER

Concerta and Mallinckrodt MPH ER will be blinded by Retain Pharmacy Solutions using over-encapsulation. The following procedures will be used by the facility:

- Record manufacturing and lot number on compounding document
- Review procedure for using the hand fill capsules machine
- Weigh out lactose powder (NF) and fill into a Swedish Orange Opaque hard gelatin capsule (manufactured by Capsugel)
- Check the weight of completed capsules minus the weight of empty capsules. The average weight must be in range +/- 5%
- Record the weight and document on appropriate compounding document
- Polish capsules using muslin or cheese cloth with a small amount of light mineral oil
- Place capsules into an appropriate size bottle, and place a cap on the bottle
- Label with the expiration date
- Store at room temperature

9.4.2 Blinding of Quillivant XR

Tris Pharma has agreed to provide the placebo and active Quillivant XR to an external blinding facility. Tris Pharma will provide unreconstituted (powder) Quillivant XR, as well as bottles to transfer the Quillivant XR into once it has been reconstituted by the external facility. The external facility will ensure the packaging for the placebo and active are identical. The external facility will reconstitute the Quillivant XR in batches and ship the reconstituted Quillivant XR to each study site for each cohort of the study. The external facility will store the unreconstituted (powder) Quillivant XR until the sites ask for the next shipment.

9.5 Study Drug Storage and Dispensing

At the MGH and the CPBM sites, all study medication will be stored at the appropriate temperature and dispensed by the Massachusetts General Hospital Research Pharmacy or the CPBM unblinded staff member. The Research Pharmacy and the unblinded staff member are responsible for reviewing the prescription for completeness, selecting the appropriate medication for the patient according to randomization, documenting drug accountability, and labeling the final product in compliance with federal and state law. A back-up unblinded staff member will be available at the CBPM site if needed.

Prior to initiation of the study, the research pharmacist will meet (and/or teleconference) with the MGH and CPBM research teams to ensure all requirements are defined. Additional meetings (and/or teleconferences) will occur throughout the study to ensure compliance with the protocol.

9.6 Study Drug Accountability

The investigators will maintain adequate records of the study drug including the dates, quantity, and use by subjects. Use of Concerta and Mallinckrodt MPH ER will be assessed by counting the pills returned. Use of Quillivant XR will be assessed by weighing the bottles of the medication. Unused study drug will be collected from study subjects at each visit and will be documented. All unused study drug at MGH will be returned to the Research Pharmacy and accountability will be documented.

All unused medication will be documented in the drug accountability log and disposed of by the Research Pharmacy and CPBM according to federal regulations.

10. Duration of Study

Each participant will take up to 44 weeks to complete the study:

- Screening Period: 8 weeks
- Optimization Period: 3-30 weeks
- Double-blind Cross-over Period: 4 weeks
- Follow-up: 2 weeks

11. Location of Study and Personnel

11.1 Massachusetts General Hospital Site

The screening visit, baseline visit, and optimization visits will take place at:
Massachusetts General Hospital – Warren Building
55 Fruit Street
Boston, MA 02115

The Classroom visits will take place at a rented space from a school in the Boston area. All study activities will take place in a designated room in order to avoid interactions with anyone at the school who is not involved in the study and to protect the privacy of the study participants. The school that will be used is:
Michael Driscoll School
64 Westbourne Terrace
Brookline, MA 02446

11.2 Center for Psychiatry and Behavioral Medicine

The screening visit, baseline visit, and optimization visits will take place at:
Center for Psychiatry and Behavioral Medicine
7351 Prairie Falcon Road, Suites 150 & 160
Las Vegas, NV 89128

The Classroom visit will take place in suites 150 and 160. Suite 150 includes classroom space.

11.3 Classroom Personnel

Each classroom day will have present at least one coordinator, two teachers, two raters, one counselor for every three children, and at least one licensed physician investigator. Appropriate phlebotomy staff will be present to collect PK Samples.

The coordinators will be responsible for implementing study procedures and removing disruptive children from the classroom until they are ready to return. They will also be responsible for obtaining the EKG's and vital signs.

The teachers will be responsible for conducting the classroom sessions, including leading the games and transitioning the children to the next activities.

The raters will complete the SKAMP throughout the day. Every attempt will be made to have the same raters will complete the SKAMP for the same children throughout the double-blind portion of study to ensure consistency.

The counselors will help the children with the recess activities and will keep the children entertained throughout each of the classroom days. They will also help administer meals and snacks to the children.

The physician(s) will be present to dose the children at the start of the day, to monitor adverse events, and to oversee and assist with PK samples and vital signs.

12. Analysis

The objective of the study is to develop a new population PK/PD model in ADHD patients to better predict onset of action, the midday effects, and the offset of action of a long acting MPH compound, as assessed in a laboratory classroom setting, accounting for placebo and tachyphylaxis effects. Our six hypotheses are tested within the framework of the PK/PD model that effectively describes the relationship between MPH concentrations and clinical outcomes that may impact the therapeutic equivalence of methylphenidate extended release products. We do not expect to adjust for multiplicity as independent evaluations will be conducted on the initial action period, midday efficacy periods, as well as on the offset of action period.

12.1 Sample Size Justification

The sample size of 75 subjects is considered as appropriate for providing an estimate of the PK and the PK/PD model parameters with a sufficient precision. In order to do standard power calculations there needs to be prior knowledge of the correct PK/PD model and variability. To determine the correct PK/PD model and variability is the main objective of the study. At this point we can only use examples from the literature.

The rationale for PK sample size was derived from the paper:

- Andre Jackson. Impact of Release Mechanism on the Pharmacokinetic Performance of PAUC Metrics for Three Methylphenidate Products with Complex Absorption. Pharm Res (2014) 31:173–181.
    - In this study 3 Methylphenidate modified-release formulations were evaluated: 34 subjects were treated with Concerta, 19 subjects were treated with Ritalin LA and 31 subjects were treated with Focalin XR. Using these data a population PK model was developed and successfully used for comparing the different formulations.

The rationale for PD sample size was derived from the papers:

- Wigal SB, Greenhill LL, Nordbrock E, Connor DF, Kollins SH, Adjei A, Childress A, Stehli A, Kupper RJ. A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2014 Dec;24(10):562-9.
    - In this study the primary efficacy endpoint was the SKAMP-Total scores over time points collected 1.0-12.0 hours after dosing. These end-points were

evaluated using a mixed-effects analysis of covariance. The evaluable population included 20 participants. MPH-MLR showed a significant decrease in SKAMP scores compared with placebo in children with ADHD 6-12 years of age, indicating a decrease in ADHD symptoms.

- Brams M1, Muniz R, Childress A, Giblin J, Mao A, Turnbow J, Borrello M, McCague K, Lopez FA, Silva R. A randomized, double-blind, crossover study of once-daily dexmethylphenidate in children with attention-deficit hyperactivity disorder: rapid onset of effect. CNS Drugs. 2008;22(8):693-704.
    - Eighty-six children (6-12 years) with ADHD diagnosed using the DSM-IV criteria were randomized to receive dexmethylphenidate ER 20 mg/day or placebo, sequentially, for 7 days, with the final dose administered in a laboratory classroom setting on day 7 of each treatment period. The primary efficacy comparison was change in the SKAMP-Combined score from pre-dose to 0.5 hours post-dose, with additional secondary assessments at 1, 2, 4, 6 and 8 hours post-dose.
- Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared with d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol. 2008 Jun;18(3):248-56.
    - This was a multicenter, double-blind, crossover study included children (N = 84) 6-12 years of age, stabilized on total daily doses of 40 mg to 60 mg d,l-MPH or 20 mg/day or 30 mg/day d-MPH who were randomized to different treatment sequences. Primary efficacy was measured by the change from pre-dose in SKAMP Rating Scale-Combined scores at 2 hours post-dose (d-MPH-ER 20 mg/day versus d,l-MPH- ER 36 mg/day).

The population PK analysis will be performed in the following sequence of steps:

1) Exploratory data analysis
2) PK model development
3) PK/PD model development
4) Covariate analysis
5) Model evaluation

12.2 Exploratory Data Analysis

Exploratory data analysis will be performed to graphically evaluate the structure of the data and to inform the process for implementing the formal data analysis, to provide a rationale for model selection, to search for extreme values and/or potential outliers, to examine the correlation between covariates, and to assess possible trends in the data. A variety of graphs and tables will be generated, including linear and semi log scatter plots of MPH concentrations & PD measurements vs. time and PD measurements vs. MPH concentrations using individual data.

12.3 Model Development

A population PK and a population PK/PD model will be developed to describe the time course of the MPH PK concentrations and the relationship between PK and PD endpoints. These endpoints

will include (but will not be limited to) the SKAMP scores and PERMP scores. The modeling process will be conducted using a non-linear mixed-effect modeling approach.

The inter-individual variability (IIV = Random effect) model describes the unexplained random variability in individual values of structural model parameters (Fixed effect). It will be assumed that the IIV of the PK and PD parameters will be log-normally distributed. The relationship between a PK parameter (P) and its variance will be therefore expressed as:

$$P_j = P_{TV} e^{\eta p}$$

Where P_j is the value of the PK and PD parameter for the j_{th} individual, P_{TV} is the typical value of P for the population, and ηP denotes the difference between P_j and P_{TV}, normally distributed with a mean zero and variance ωp^2.

The residual variability, which comprises, but is not limited to, intra-individual variability, experimental errors, process noise and/or model misspecifications, will be modeled using additive, proportional and combined error structures as described below:

- Additive error: $y_{ij} = yt_{ij} + \varepsilon 1_{ij}$
- Proportional error: $y_{ij} = yt_{ij}(1 + \varepsilon 1_{ij})$
- Combined additive and proportional error: $y_{ij} = yt_{ij}(1 + \varepsilon 1_{ij}) + \varepsilon 2_{ij}$

Where y_{ij} is the j_{th} observation in the i_{th} individual, yt_{ij} is the corresponding model prediction, and $\varepsilon 1_{ij}$ (or $\varepsilon 2_{ij}$) is a normally distributed random error with a mean of zero and a variance of σ^2.

12.4 PK Model

Two modeling approaches will be applied for evaluating the multiphasic PK profile of MPH following conventional or modified release formulations: a) a model independent approach and b) a model based approach. Modified release formulations are characterized by two phases of drug release: a first phase determined by the immediate release dose fraction to provide a therapeutic drug level shortly after administration, and a second extended release phase to provide the dose fraction required to maintain an effective therapeutic level for a prolonged period.

The objectives of the two approaches will be to estimate PK metrics appropriate for characterizing rate and extent of absorption in each phase of the drug release and the evaluate the disposition and eliminating processes. The metrics will include (but they will not be limited to) partial AUC, Tmax and Cmax associated with each absorption phase.

The model independent approach is expected to provide a basic description of the MPH PK while the model based approach is expected to provide a more comprehensive description of the PK time course.

This approach will be based on the evaluation of alternative models; the initial one will be based on a two compartment model with sequential or parallel zero- and first-order absorption processes. The benefit of using a model based approach is to apply trail simulation to final model retained

jointly with the PK/PD model (see below) for predicting the PD outcomes given a particular shape in the absorption of a new formulation.

The PK model will have the same disposition and elimination components but an absorption component specific to the different products evaluated.

12.5 PK/PD Model

The objective of the PK/PD model development will be to assess the onset of the response, the level of efficacy, and the duration of the response given a specific PK time course.
The rate of change of the response (R) over time following placebo will be described by the indirect-response model:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R \qquad (1)$$

where k_{in} represents the zero-order constant for production of the response and k_{out} defines the first-order rate constant for loss of the response.

As stationarity is assumed, the response variable (R) begins at an average baseline (RoPlac), changes with time, and returns to (RoPlac). Thus:

$$K_{in} = k_{out}\ RoPlac$$

which reduces the number of parameters in the model.

Inspection of the score changes over time after placebo administration (Figure 1) indicates an increase of the SKAMP score from baseline can be accounted by a time dependent stimulation of k_{in} or by a time dependent inhibition of k_{out}.

According to the Kimko's model, the second option will be applied and the following model will be used:

$$\frac{dR}{dt} = k_{in} - f(t) \cdot k_{out} \cdot R \qquad (2)$$

Where f(t) is a function that can be derived using individual data rather than working on mean observations as done in the Kimko's model.

At variance to what has been done by Kimko, we can now proceed in the analysis using a two-stage approach. This modeling approach can be implemented because in our trial we dispose of data on placebo and on active drug in each subject.

Step 1: The placebo data will be fitted to the model and the individual parameter values will be estimated for each subject (k_{in}, k_{out} and f(t)).

Step 2: The drug action will be included in the model as a function counteracting the placebo response. This will be modeled as:

$$\frac{dR}{dt} = k_{in} \cdot g(cp) - f(t) \cdot k_{out} \cdot R \quad (3)$$

Where g(Cp) is a MPH concentration (Cp) dependent inhibitory function of the k_{in} model component that was estimated in Step 2. The model will be defined as:

$$g(Cp) = 1 - \frac{Emax * Cp}{IC50 + Cp} \quad (4)$$

Where Emax is the maximum drug effect; IC50 is the MPH concentration that corresponds to half of the maximum effect and Cp is the MPH concentration.

A time dependency of IC50 will be considered to account for tachyphylaxis. This time dependent function will be defined as:

$$IC50 = IC50_0 \left[1 + \frac{t^{\gamma}}{t_{50}^{\gamma} + t^{\gamma}}\right] \quad (5)$$

Where t is time, t_{50} is the time at which half of the tachyphylaxis occurs and γ is the shape of the tachyphylaxis effect.

Model (4 and 5) assumes that the PD response varies with MPH concentration and with time: the same MPH concentration at different times has a different impact on PD.
Model (5) can be extended to evaluate the impact of MPH PK metrics (such as Tmax, Cmax, AUC, formulation, individual covariates,…) on tachyphylaxis:

$$h(t, c) = t^{\gamma} + \alpha_i \cdot c_i$$

$$IC50 = IC50_0 \left[1 + TEmax \cdot \frac{h(t,c)}{h50(t,c) + h(t,c)}\right] \quad (6)$$

Where TEmax is the maximal tachyphylaxis effect and ci and αi are the i^{th} covariate and the i^{th} coefficient associated with this covariate respectively.

Model Comparison:
The comparison of alternative models for the selection of the base model will be performed using the log-likelihood ratio test for nested models or the Akaike information criterion (AIC) for non-nested models. For nested models, an alternative model will be considered as a significantly better descriptor of data when the reduction in the objective function value (OFV) associated with this model will be ≥3.84, $\chi 2 < 0.05$ for 1 degree of freedom (df). For non-nested models, the model with the lower AIC value will be considered as the preferred one.

12.6 Covariate Analysis

Graphical and statistical approaches along with consideration of the underlying scientific rationale will be used to identify which covariates will be examined on the appropriate PK/PD parameters and to assess the mathematical form of their relationships.

For PK analysis, the following covariates will be considered: dose, sex, age, illness presentation (hyperactive/impulsive and inattentive), and severity of illness (as determined by impairment or number of symptoms).

For the PK/PD analysis, the following covariates will be initially considered: dose, sex, age, illness presentation (hyperactive/impulsive and inattentive), and severity of illness (as determined by impairment or number of symptoms). In addition, PK metrics (such as Tmax, Cmax, AUC, partial AUC, and formulation) will be explored as factors potentially affecting the shape of PD response.

Covariate model building will be implemented as a step-wise process consisting of a forward and a backward selection procedure. The likelihood ratio test will be used to evaluate the significance of incorporating or removing fixed effects into the population model based on alpha levels that are set a priori. For forward selections, a significance level of 0.01 will be used and for backward elimination a significance level of 0.001 will be used.

12.7 Step-wise Forward Addition Procedure

Initially, each covariate individually will be included in the model to identify significant covariates where significance was defined a-priori as a reduction in the objective function value (OFV) of ≥ 6.64, $\chi 2 < 0.01$ for 1 degree of freedom (df). Next, the significant covariates and/or those considered clinically important will be added to the base model one covariate into one parameter at a time. The most significant covariate will be included into the model first. This new model will serve as a new starting model for the next iteration. The test of significance and adding-on steps will be repeated until all significant covariates were included.

12.8 Backward Elimination Procedure

After the full model is defined, a backward elimination process will be followed. First, the effect of the covariate is assumed to significantly contribute to the full model if the OFV increases by more than10.83 points ($\chi 2 < 0.001$ for 1 df), a priori) upon removal of that covariate. After the impacts of all variables in the full model are evaluated, the covariate with the smallest non-significant effect on the OFV will be removed from the model. This process will be repeated until all remaining variables significantly contributed to the model's ability to describe the data when the variable is removed. The model resulting from the backward process will be the "final model".

A covariate will be retained in the final model, despite not meeting the criteria above, only if there is a strong pharmacological, clinical, or physiological rationale for its inclusion.

Model performance/validation and stability will be assessed using visual predictive checks and bootstrapping.

12.9 Visual Predictive Check

A visual predictive check method will be utilized to evaluate the adequacy of the final model, including the effects of statistically significant covariates. This assumes that parameter uncertainty is negligible, relative to inter-individual and residual variance [18]. The basic premise is that a model and parameters derived from an observed data set should produce simulated data that are similar to the original observed data.

At least two hundred replicates of the original dataset will be simulated, based on the final model, and a 90% prediction interval will be computed based on the simulated datasets. The observed concentration versus time data will be plotted on the prediction interval to visually assess the concordance between the simulated and observed data. Statistics of interest including the mean will be calculated from the simulated and observed data for comparison. The distributions of quantiles (5th, mean, and 95th) of simulated data will be compared graphically to the observed data quantiles.

12.10 Bootstrapping

Bootstrap analysis will be conducted using Perl-speaks-NONMEM (PsN) (version 3.4.2) software. Bootstrap is a tool for calculating bias, standard errors and confidence intervals of parameter estimates. It does so by generating a set of new datasets by sampling individuals with replacement from the original dataset, and fitting the model to each new dataset [19]. At least 100 resampled datasets will be analyzed and statistics around the PK/PD parameters estimates will be reported.

12.11 Missing Data

The missing data will not be imputed and the incomplete individual observations will be included in the analyses as the non-linear mixed effect modeling approach used to conduct the PK and the PK/PD analyses does not require complete data sets. However, the dropout mechanism will be explored using a model-based approach. The following dropout mechanisms will be evaluated: Missing Completely At Random (MCAR), Missing At Random (MAR), and Missing Not At Random (MNAR). A parametric time-to-event model approach will be used to explore the different dropout mechanisms using alternative hazard distributions such as exponential, log-normal, and Weibull.

12.12 Statistical Evaluation of the Results

In the current FDA Draft Guidance on Methylphenidate Hydrochloride for products referencing Concerta Extended-Release Tablets (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf) it is recommended to consider the Cmax, AUC0-4, AUC4-8, AUC8-12, and AUC0-∞ to characterize the MPH PK. Quillivant XR FDA bioequivalence guidance uses the same metrics: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM427808.pdf. The rationale for the use of partial AUC (PAUC_PK) is based on the multi-phasic PK properties of the extended-release formulations of MPH: MPH is initially release as bolus followed by a slower drug delivery during the day. This particular MPH release has been

proposed to control the morning symptoms of ADHD while the later release phase is required to control afternoon symptoms of ADHD during the school day.

On this basis the proposed PAUC_PKs values are expected to characterize the different components of the clinical response:

- AUC_PK$_{0\text{-}4}$ systemic exposure responsible for onset of action of MPH
- AUC_PK$_{4\text{-}8}$ systemic exposure responsible for midday effects of MPH
- AUC_PK$_{8\text{-}12}$ systemic exposure responsible for the offset of action of MPH
- AUC_PK$_{0\text{-}\infty}$ systemic exposure responsible for overall response of MPH

The PAUC values will be computed for each subject using the trapezoidal rule on the MPH PK curve.

The clinical response will be characterized by the partial PAUC_SKs under the SKAMP clinical score curve. In particular the following PAUC_SK will be considered:

- AUC_SK$_{0\text{-}4}$ clinical response characterizing the onset of action of MPH
- AUC_SK$_{4\text{-}8}$ clinical response characterizing the midday effects of MPH
- AUC_SK$_{8\text{-}12}$ clinical response characterizing the offset of action of MPH
- AUC_SK$_{0\text{-}\infty}$ overall response of MPH

The PAUC_SK values will be computed for each subject using the trapezoidal rule on the change from baseline of the SKAMP score.

The proposed analysis will be based on the evaluation of the predictive performance of the PAUC_PK values with respect to the predictive performance of PK metrics derived from the PK/PD model. The PK model will use a dual process (double Weibull in-vivo release model) to describe the absorption rate (PA) of the modified release formulations of MPH.

$$aw_1(t) = f \cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)}$$

$$aw_2(t) = (1-f) \cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)}$$

$$PA = aw_1(t) + aw_2(t)$$

The PK metrics derived from the model-based approach will be:

- MAUC_PK$_{0\text{-}4}$ model predicted systemic exposure responsible for onset of action of MPH
- MAUC_PK$_{4\text{-}8}$ model predicted systemic exposure responsible for midday effects of MPH
- MAUC_PK$_{8\text{-}12}$ model predicted systemic exposure responsible for the offset of action of MPH
- MAUC_PK$_{0\text{-}\infty}$ model predicted systemic exposure responsible for overall response of MPH
- MAUC_PK$_{0\text{-}x}$ model predicted systemic exposure responsible for onset/midday/offset of action of MPH; where x will be selected as the most informative time

- Model predicted fraction of the dose released in the 1st process (f)
- Model predicted fraction of the dose released in the 2nd process (1-f)
- Model predicted time to absorb 63.2% (a typical parameter of the Weibull model) of the dose released in the 1st process (td)
- Model predicted time to absorb 63.2% (a typical parameter of the Weibull model) of the dose released in the 2nd process (td1)
- Model predicted time sigmoidicity factor for the 1st process (ss)
- Model predicted time sigmoidicity factor for the 2nd process (ss1)

The relation between the PAUC_PKs and the model-predicted parameters with the PAUC_SKs values will be initially described by an Emax model:

PAUC_SK= EMAX*PAUC_PK/(PAUC_PK50+PAUC_PK)

The choice of this model was motivated by the preliminary evaluation of the exposure/response relationship of MPH with the longitudinal change in the SKAMP scores. This evaluation indicated that the change in the SKAMP score does not linearly increase with the MPH exposure but follow a sigmoidal shape. In the Emax model PAUC_PK50 represents the value of the PAUC_PK necessary for delivering 50% of the maximal response (Emax). Other models will be eventually considered according to the characteristics of the data generated in the study.

The analysis will be conducted according to a multi-stage process:

Stage 1: The PAUC metrics and the model predicted PK metrics will be used to fit the Emax model. The normalized prediction distribution error (NPDE) will be used to assess the predictive performance of each model (Comets et al., Computer Methods and Programs in Biometrics 2008; 90:154-166). A Wilcoxon signed rank test will be used to test whether the mean of NPDE is significantly different from 0, a Fisher test will be performed to test whether the variance is significantly different from 1, a Shapiro-Wilks test was performed to test whether the NPDE follows a normal distribution, finally, a global p-value through Bonferroni correction will also be obtained.

Stage 2: The relative performance of the Emax model associated with the PAUC and the model-based metrics will be compared only for the models providing successful results in stage 1 (model validation step). The preferred model will be the one with lowest bias and higher precision. The bias will be estimated using the normalized estimation errors (NEE) and precision with the relative root mean squared error (RMSE):

$$NEE = \frac{1}{n}\sum \frac{Pred - Obs}{sd(Pred)}$$

$$RMSE = \sqrt{\frac{1}{n}\sum(Pred - Obs)^2}$$

Where Pred is the model predicted value (PAUC_SK), Obs is the observed PAUC_SK value, and sd is the standard deviation of the predictions.

12.13 Software

All data preparation, summary statistics and graphical display presentation will be done using SAS (version 9.3) and R (3.0.2 version). The population PK and PK/PD analysis will be conducted using the NONMEM software, Version 7.3 (ICON Development Solutions). NONMEM will be executed in a Windows Vista operating system using the Fortran compiler gfortran version 4.6.0. The R-based package Xpose (version 4.3) will be used as a model building aid for population analysis using NONMEM. The Perl based software PsNwill be used to perform bootstrapping and visual predictive checks.

13. Subject Selection and Recruitment

13.1 Equitable Selection of Subjects

No children will be categorically excluded from the research provided they meet all inclusion/exclusion criteria. We do not exclude subjects based upon review of gender, ethnicity, or race.

13.2 Recruitment

Subjects will be recruited from clinic patients who are dissatisfied with their current treatment and self-referrals who have been made aware of the study via advertisements in the local media and flyers posted around the hospital and community. We may also advertise at schools in the area, but only in the event that the school principal provides written authorization to do so beforehand. We will provide the school principal with information about the study and a document for him/her to sign if he/she wishes to provide the written authorization. Parents will be given information about the study and if interested, a consultation will be scheduled to discuss available ADHD treatment and potential study participation. If the parent/guardian and subject continue to be interested in participation, they may be provided with a copy of the informed consent and assent forms to review. Participants will have as much time as they feel is necessary to make a decision regarding study participation. All subjects who enter the study will undergo standard screening procedures.

In the event that a clinic patient is not satisfied with their current treatment plan, their treating doctor may provide the patient with the study recruitment letter, which includes contact

information for a research coordinator. Interested patients can choose whether or not to contact the research coordinator for more information and if they wish to proceed with standard screening procedures. The patient may be given the consent and assent forms to review with their primary care physician and family members and then proceed to discuss the study with a study staff member. The patients will be told that participation is voluntary and that their decision whether or not to participate will not affect the medical care they receive at any time.

Subjects at the Massachusetts General Hospital site may be pre-screened through a separate Screening Protocol, through which all subjects will be screened for general inclusion and exclusion criteria by phone. After satisfying initial inclusion and exclusion criteria, appropriately qualified subjects will be referred to the current study. The Screening Protocol is HIPAA-compliant and is approved by the PHRC.

13.3 Justification for Excluding Certain Populations

Pregnant women will not be included due to the unknown effects of medications on fetuses. Subjects who do not understand English cannot participate because the study requires that subjects and their parent/guardian be able to verbally communicate with study staff during the classroom visits and assessments. The assessment instruments are not available and have not been adequately standardized in languages other than English. Adding the complexity of a translator has the potential to make the subject experience exhausting.

Children will be included in this study because we are approximating a normal classroom, which requires children to be about the same age. All of the classroom studies that have examined the time course of stimulants have used a 6-12 age range, and it is unknown how the laboratory classroom would perform with other ages. Past studies have included children and adolescents in the same classroom, and the younger children were less likely to participate, skewing the data.

14. Risk/Benefit Ratio

All efforts are made to minimize risks to subjects. Risks are minimized by careful subject selection, including only subjects that are appropriate. This protocol is designed to ensure that safety measurements are completed prior to initiation of medications and that the subject's response is closely monitored. All procedures used are consistent with sound research design and do not unnecessarily expose subjects to risk.

There are few serious risks involved with this study, while the benefits (in terms of understanding the importance of different formulations of stimulants) may have enormous impact on patients, families, and society. Therefore, the study is reasonable to conduct.

14.1 Risks

14.1.1 Risks of Study Medication

Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of study investigators. Adverse events will be recorded and reported according to institutional policies.

The medications used in this study are all FDA-approved for the treatment of ADHD in children and adolescents. Subjects will be given three formulations of MPH throughout the study: Concerta, Quillivant XR, and Mallinckrodt MPH ER.

Commonly observed side effects (≥5% and twice the rate of placebo) associated with the use of these medications include:

- Loss of appetite
- Insomnia
- Stomachache
- Weight loss
- Emotional changes
- Agitation
- Anxiety
- Tachycardia
- Nausea
- Vomiting
- Dizziness

Less common side effects (≥1% of subjects in clinical trials and greater than placebo) associated with the use of these medications include:

- Excoriation
- Insomnia
- Tic
- Eye pain
- Rash
- Dry mouth
- Palpitations
- Depression
- Shortness of breath

These side effects tend to be mild.

Rare, but serious side effects of these medications (≤1%) include stroke, serious heart rhythm disturbances, and sudden death; these risks are increased in those with pre-existing structural heart abnormalities, myocardial infarction, cardiomyopathy, or coronary artery disease. Other rare, but serious side effects include seizures, eyesight changes, and blockage of the esophagus, stomach or intestine. There are also reports of changes in behavior or cognition, including psychotic symptoms, and aggression/hostility. Children with a history of tics may experience return

symptoms. Cases of priapism and circulation problems in fingers or toes have also been reported with the use of stimulant medications.

The medications used in this study are federally controlled substances that can be abused or lead to dependence. With the exception of the 72mg dose of Concerta and Mallinckrodt MPH ER, dosing for this protocol is within the FDA approved dosing range for this age group and is consistent with our group's clinical experience with these medications. As previously stated, the 72 mg will only be given to children who optimize to that dose level and could benefit from a higher dose. The use of these medications at a higher dose is commonly done off-label in clinical practice.

Subjects will be given the contact information to reach the study investigator 24 hours a day, 7 days a week. The PI will review any and all reports of adverse events. Subjects are repeatedly advised that they can discontinue participation in the study at any time.

Subjects will be monitored for adverse events at each visit and all events will be recorded. A subject may be dropped from the study at any time due to adverse experiences.

If the subject has worsening ADHD symptoms that in the opinion of the investigator warrants an early termination, the subject will be withdrawn. If the subject is unable to achieve at least a 30% improvement of ADHD symptoms as rated on the ADHD-RS-IV during the dose-optimization period, he/she will be withdrawn from the study.

14.1.2 Risks of Allergic Reactions

Children could have allergic reactions to drugs. An allergic reaction may include such symptoms as skin rash, itching, redness, shortness of breath, swelling of the face or throat, and even heart failure. Parents/guardians and subjects will be instructed to call 911 should the subjects have trouble breathing.

14.1.3 Risks of Drug Interactions

Use of the study drug with other medications or supplements may change how the medications work. We will ask the parent/guardian to report all prescriptions and over-the-counter medications or supplements the subject is taking during the study.

14.1.4 Risks of the Washout Period

The study investigator may ask that the subject stop taking his/her usual medication before taking the study drug. During this washout period, if the subject stops taking his/her medication for ADHD, mood or anxiety, his/her symptoms might get worse. Medication washout will be monitored by the investigators in agreement with the parents and in consultation with the prescribing physician when applicable. Medications for underlying conditions including lithium, anti-depressants, anticonvulsants, and anti-psychotics, and other medications that are necessary for the safety and well being of the child, will not be stopped for the purpose of this trial.

14.1.5 Risks of Placebo

Due to the design of the experiment, each child will have one week where they are randomized to placebo. During this week, the participant may experience some discomfort and a re-occurrence of ADHD symptoms. Use of placebo is important to assess which effects are caused by the ADHD medication and which are not. Many controlled studies involve children being on placebo for four weeks or more, and we do not expect one week of placebo to impact subject safety. If a child's symptoms deteriorate and the subject's safety is jeopardized, the child will be removed from the study. As previously stated, subjects will be given the contact information to reach the study investigator 24 hours a day, 7 days a week. The PI will review any and all reports of adverse events. Subjects are repeatedly advised that they can discontinue participation in the study at any time. Appropriate follow-up and actions will be taken if the investigator has any safety concerns.

If the subject experiences worsening of ADHD symptoms that in the investigator's opinion warrants early termination, the subject will be discontinued. Worsening symptoms will not lead to emergency unblinding unless the investigator determines it is needed for safety reasons.

14.1.6 Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effects of the study drugs on an embryo or fetus, or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, the subject cannot take part in the study if she is pregnant. If the subject becomes pregnant during the study, she will be withdrawn from the study. If a participant becomes pregnant during the study, she will be instructed to stop taking study medications and we will ask permission to obtain information about the outcome of the pregnancy and the condition of the newborn.

14.1.7 Risks of Blood Draws:

The subject may experience some discomfort during the blood draws. The subject may have a bruise or pain where we take the blood samples. There is also a small risk of feeling lightheaded, fainting, or possible infection. Subjects may be offered numbing cream before each blood draw.

14.1.8 Risks of Electrocardiogram:

The sticky pads used for the ECG may sometimes cause discomfort such as skin redness or itching. If the skin under the patches needs to be shaved, irritation from shaving also could occur.

14.1.9 Psychosocial Risks:

Answering questions and filling out questionnaires about mental health may cause subjects some discomfort because the questions can be very personal. Though we hope subjects will fully complete all protocol assessments, subjects may skip any questions that they do not wish to answer.

The classroom days last from approximately 6:00 am until 8:30pm, and the children may become bored or frustrated while completing tasks. When the participants are not performing the study tasks, they will be able to participate in fun activities including arts and crafts, movies, and athletics. Activities will be carefully planned and there will be one counselor present for every three children to accommodate the needs of the participants. Because the subjects will be ages 6-12, they will be familiar with the school environment and should not have difficulty spending the day away from their parents. Children diagnosed with school phobia or separation anxiety will not be eligible to participate.

14.2 Potential Benefits

Because methylphenidate is an FDA approved agent for the treatment of ADHD, this study may provide beneficial information to study participants about their response and toleration of MPH.

The parents or guardians of the subjects will be given the results of an extensive neurobehavioral baseline assessment including the clinical and structured interview, providing them with substantial information at no cost. The study will also include baseline medical assessments including vital signs, routine labs, and ECGs. Furthermore, the opportunity for the children to have the same frequency of visits outside of the trial is unlikely. Usual clinical practice is to see patients monthly. We will see subjects weekly. The subjects will titrate to an optimal dose of a first line medication (OROS methylphenidate) within a few weeks as opposed to a few months. OROS methylphenidate can be given after the study by the child's personal clinician or the study doctor. Another potential benefit to the children is that we will be able to assess by direct observation how the children behave and respond to treatment in a classroom setting and provide parents and clinicians with a detailed narrative description. In addition, the subjects often find the classroom days to be fun because learning is made into games, they are with other children who have ADHD, and they are not disciplined because of their ADHD symptoms.

The study will further the understanding of the relationship of blood levels of MPH to the efficacy of MPH in different formulations. The study may provide important new information to best match effective and tolerable MPH formulations to individual patients. Therefore, the study may have enormous benefits to society.

14.3 Alternative Treatments and Procedures

Parents of children with ADHD can speak with their primary care doctor to obtain a prescription for medication to treat their symptoms or a referral to a specialist if they do not wish to participate in this research.

14.4 Early Termination

Subjects will be withdrawn from the study if they:

- Develop an adverse event despite dose adjustments that is determined to be intolerable based on clinician judgment. An intolerable event is any side effect or worsening of mood or ADHD symptoms that are determined by the investigator to be excessive in severity or in duration
- Have a serious adverse event (SAE). 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
  - 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
- Have worsening ADHD symptoms (as determined by clinician judgment indicated through a score of 6 or 7 on the CGI Global Improvement scale) that warrants an early termination
- Are unable to achieve at least a 30% improvement of ADHD symptoms as rated on the ADHD-RS-IV during the dose optimization period
- Are unable to tolerate 27mg or greater of Concerta during the dose optimization period
- Have emergent psychosis, suicidality, or severe worsening mood and/or anxiety (as determined by clinician judgment and/or any positive answer given on the C-SSRS scale)
- Are non-compliant or voluntarily withdraw
- Become pregnant or are found to be abusing substances during the study

Subjects must be willing to comply with all study procedures to participate (see inclusion criterion #11). If subjects do not agree to comply with all study procedures at screening or baseline, they will be withdrawn from the study. However, if at any other point during the study, a subject is not willing to comply with a study procedure, but wishes to remain in the study, the investigator will determine if the subject will or will not be withdrawn from the study with consideration to subject safety and data integrity. For example, if a subject states that they will comply with all skin pricks at screening but later refuses one or more on a classroom day, the investigator will decide if it is appropriate for the subject to remain in the study.

In the event that a subject is unable to attend a classroom visit (ie. due to illness) the investigator will determine if the subject will or will not be withdrawn from the study.

All participants who stop the study early will be asked to return for the two follow-up safety visits, giving adequate time for appropriate psychiatric referrals to providers in the community. If the subject has a separate psychiatrist, the subject will be referred back to his/her care. If the subject agrees, the investigator will notify the subject's treating psychiatrist of early withdrawal.

15. Payment for Participation

The parent/guardian will be given $595 for completing the study. They will be paid $15 for the baseline visit and each of the optimization visits, $15 for each of the follow-up visits, $75 for the practice classroom day, and $100 for each of the classroom visits. Payments will be made in the form of a check. Children will also receive a toy after the screening blood draw and will receive prizes at the end of each full classroom day. The toys and prizes include stuffed animals, coloring books, plastic jewelry, and crafts supplies. Children will also receive a themed T-shirt on the practice classroom day to wear at each classroom visit. The T-shirts will not include any study-related information and will be character-themed (such as Frozen, Despicable Me, or Finding Nemo). The children will not be required to wear the T-shirt during the day if they do not wish to. However, T-shirts are an added safety measure by allowing all staff to easily identify

subjects. If a subject does not complete the study, the parent/guardian will be paid for the visits that were completed.

16. Adverse Event Reporting

Consistent with good clinical practice, safety will be monitored at each study visit. The investigators will be available 24 hours a day by page. Subjects will be monitored for adverse events at each visit. All adverse events are recorded and will be reported to the IRB according to IRB guidelines.

All adverse events will be collected and recorded in the study record, and will be followed up until resolution. All adverse events will be evaluated for duration, severity, frequency, seriousness, action taken, outcome, and causal relationship to the study.

In case of an emergency, the site investigator will be able to contact the research pharmacy or the designated CPBM staff member for emergency unblinding 24 hours a day. The blinded information is to be broken only when knowledge of such treatment may have an impact on future treatment decisions or aid in the emergency treatment of the subject. This decision can only be made by Dr. Spencer or Dr. Childress. Any subject for whom the blind is broken will be discontinued from the study. If an SAE occurs at the CPBM site, the coordinating site investigator, Dr. Spencer, should be informed of the event within 24 hours so appropriate actions may be taken.

17. Data Management and Confidentiality

17.1 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will monitor the conduct of the study and safety issues. The head of the DSMB for this trial will be a psychiatrist with extensive clinical and research experience related to the pharmacology of neuropsychiatric disorders and will not be an investigator for this study. The DSMB will review all adverse events, review issues related to subject eligibility, assess the benefits and risks of the protocol on an ongoing basis, and identify safety signals and trends. The DSMB will promptly report discrepancies or problems to the FDA. The DSMB will have the authority to stop the study or remove individuals from the study and take whatever steps are necessary to protect the safety and well being of participants. The DSMB will meet every 6 months and a report will be submitted to RIHSC and each institution's IRB following each meeting.

17.2 Data Management

Ongoing quality control will include regular data verification and protocol compliance checks to be performed by the Principal Investigator, sub-investigators, research coordinators, and data analyst. Each staff member will undergo focused training on each task for which they are

responsible and will perform quality control for others similarly engaged. Each site will be responsible for their own data management, but all data will be assessed by the Principal Investigator on a bimonthly basis and at the DSMB meetings every six months. All data will either be collected using paper case report forms and entered into StudyTRAX, an electronic data capture system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11, or will be collected directly through StudyTRAX.

17.3 Privacy and Confidentiality

Subject information collected during the study will be kept confidential by the study investigator and staff and will not be made publicly available unless disclosure is required by law. Subjects will be assigned ID numbers that will appear on all subject data for the study. Only study staff and co-investigators will have access to the information linking subjects to their ID numbers. Information will be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff.

At the onset of an initial clinical encounter, subjects will be informed of federal privacy guidelines that pertain to them under the Healthcare Insurance Portability and Accountability Act (HIPAA). All research-related records created as a result of subject participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Results of the clinical laboratory blood testing will become part of a subject's Massachusetts General Hospital or Center for Psychiatry and Behavioral Medicine medical record, and subjects will be informed of this. Results of urine drug or pregnancy testing will not become part of the subject's medical record. Subjects at Massachusetts General Hospital will be contacted regarding future studies only if they indicate that they are interested in being contacted by initialing in the specific section of the Massachusetts General Hospital consent form.

Data obtained from this study will not identify those subjects individually. Subjects will be assigned ID numbers. Data obtained from our studies may be published. Original medical records may be reviewed by the IRB 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 recorders will be password-protected and restricted to study staff. Study records will be destroyed in accordance with the established institutional policy. Biological samples will not be stored for future use and will be anonymized and disposed of following the study in accordance with the established institutional policy.

When voice recordings are used, they will be labeled with the subject's ID number, and only the study coordinators and investigators will have access to the recordings. These recordings will be used to monitor the completeness of study evaluations and the similarities and differences between different raters. These recordings will be saved securely using a password-protected database and maintained for 1 year after completion of the study for the purpose of verifying data and maintaining study reliability and will then be deleted after this time. Voice recordings will only be used at the Massachusetts General Hospital site. Video recordings may also be used during this study at the Center for Psychiatry and Behavioral Medicine site on classroom days for reliability, but will only be used if all subjects participating in the cohort agree. Only the study coordinators and investigators will have access to the recordings. These recordings will be

saved securely using a password-protected database and maintained for 1 year after completion of the study for the purpose of verifying data and maintaining study reliability and will then be deleted after this time.

Parents will receive information about the results of their study testing in the form of a letter summarizing the results of the diagnostic assessments.

17.4 Quality Assurance/Quality Control

Ongoing quality control will include regular data verification and protocol compliance checks to be performed by the Principal Investigator, sub-investigators, research coordinators, and data analyst. Each staff member will undergo focused training on each task for which they are responsible and will perform quality control for others similarly engaged.

For quality control purposes, audio of clinician-administered measures may be recorded, with subjects' permission, obtained during the informed consent process. These recordings will be used to monitor quality control and inter-rater reliability.

17.5 Monitoring

The study investigators, research coordinator, and Principal Investigator will monitor study progress including enrollment, adherence to inclusion/exclusion criteria and the protocol, as well as any adverse events. The Principal Investigator will be responsible for ensuring that adverse events are reported to the local Institutional Review Board and the FDA Research Involving Human Subject Committee (RIHSC) in compliance with local and federal requirements.

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