CLINICAL STUDY PROTOCOL

Title:	An open-label, multicenter, multiple-dose, safety and tolerability study of Adhansia XR® extended-release capsules in children 4 to 12 years of age
Protocol number:	ADA4004
Study phase:	Phase 4
Test product:	Adhansia XR® (methylphenidate hydrochloride extended-release capsules)
Regulatory agency identifier number(s):	NDA 212038
Sponsor:	Purdue Pharma LP One Stamford Forum Stamford, CT 06901-3431 USA
Contract research organization:	[redacted]
Protocol version and date:	Version 2, 26 Apr 2021

This study will be performed in compliance with the principles of Good Clinical Practice.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
[Amendment 1]	*26 Apr 2021*
ADA4004 Version 1.1	*04-Dec-2020*

Amendment 1 (26-April-2021)

Overall Rationale for the Amendment:

1. Incorporating FDA recommended revisions to the protocol.
   a. Development of a 12.5-mg strength of Adhansia XR.

      Adding statements to the protocol indicating that dosing in children 4 to < 6 years of age as well as the PK substudy will not start until the availability of the 12.5-mg dose strength of Adhansia XR.

   b. Addition of the 12.5-mg strength as the starting dose for children 4 to less than 6 years of age and 25-mg strength as the starting dose for children 6-12 years of age.

   c. Removal of the 85 mg dose: Implementation of a maximum dose of 70 mg/day for children 4 to 12 years of age.

   d. Clarified the washout period for prohibited concomitant medications is at least 5 half-lives or 3 days, whichever is longer.

   e. Clarified height to be measured at each visit using a stadiometer.

   f. Additional testing if greater than trace proteinuria is detected in the urine during study treatment: Quantification of urine protein and urine creatinine from a first morning void urine specimen.

2. Clarification to clinical supply product complaint (CSPC).
3. Addition of suspected diversion monitoring section.
4. Clarifications throughout protocol for consistency with changes.

Section # and Name	Description of Change	Brief Rationale
Synopsis: Study Design Synopsis: PK Substudy [redacted]	Added a statement indicating that dosing in children 4 to < 6 years of age and PK substudy will not start until the 12.5 mg dose strength is available	FDA recommendation
Synopsis: Inclusion Criteria #4 [redacted]	Deleted developmental and deleted reference to DSM-IV	Clarification

Section # and Name	Description of Change	Brief Rationale
Synopsis: Study Design Washout Period Synopsis: Inclusion Criteria #5 [redacted]	Clarified that current ADHD medication(s) and prohibited concomitant medications must be discontinued for a minimum of 3 days or 5 half-lives, whichever is longer.	FDA recommendation
Synopsis: Study Design Baseline Visit [redacted]	Starting dose level of Adhansia XR is 12.5 mg in children 4 to < 6 years of age or 25 mg in children 6 to 12 years of age	FDA recommendation
[redacted]	[redacted]	[redacted]
Synopsis: Test Product [redacted]	Removed 85 mg dose strength Addition of the 12.5 mg dose strength	FDA recommendation
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Throughout protocol	Clarifications and corrections in line with other major changes	Clarification, consistency

PROTOCOL SUMMARY

Protocol number: ADA4004

Protocol title: An open-label, multicenter, multiple-dose, safety and tolerability study of Adhansia XR extended-release capsules in children 4 to 12 years of age diagnosed with attention deficit/hyperactivity disorder

Sponsor: Purdue Pharma LP

Study phase: Phase 4

Study sites: Multicenter study in USA

Objectives and Endpoints:

Objectives	Endpoints
Open-label, 12-month safety and tolerability	
Primary: • To assess the long-term safety and tolerability of Adhansia XR (methylphenidate hydrochloride extended-release capsules) in children 4 to ≤12 years of age who have been diagnosed with attention deficit/hyperactivity disorder (ADHD)	• Adverse events (AEs), vital signs, body mass index (BMI), physical examinations, electrocardiograms (ECGs), clinical laboratory tests, and the Columbia-Suicide Severity Rating Scale (C-SSRS)
[redacted]	[redacted]
Pharmacokinetic Substudy (children 4 to <6 years of age)	
Primary: • To characterize the pharmacokinetics (PK) of methylphenidate hydrochloride from multiple doses of Adhansia XR in children 4 to <6 years of age who have been diagnosed with ADHD	• Plasma methylphenidate concentrations • PK data for a Bayesian analysis of methylphenidate
Secondary: • To assess the safety and tolerability of multiple doses of Adhansia XR in children 4 to <6 years of age who have been diagnosed with ADHD	• AEs, vital signs, BMI, physical examinations, ECGs, clinical laboratory tests, and C-SSRS

Study design:

This is a multicenter, open-label, dose-optimized, multiple-dose study of Adhansia XR in male and female pediatric subjects ≥4 years of age and ≤12 years of age who have been diagnosed with ADHD. The study will consist of a 12-month, open-label, safety and tolerability study and a nested PK study. **Recruitment and dosing in children 4 to <6 years of age (including nested PK substudy), will begin when the 12.5 mg strength of methylphenidate hydrochloride extended-release capsules (Adhansia XR) is available**.

The 12-month long-term safety study will have the following periods/visits:

1. Screening Period: (Day -28 to Day -4). Screening assessments will only proceed once informed consent/assent has been obtained. The screening period may take up to 24 days; however, there is no minimum number of days for screening, and subjects may start washout as soon as eligibility has been confirmed.
2. Washout Period: (minimum Day -3 to Day -1). Current ADHD medication(s) must be discontinued for a minimum of 3 days or 5 half-lives, whichever is longer, before the baseline visit. Some medications may require a washout period greater than 3 days or a dose taper, depending on the product labeling recommendations.
3. Baseline Visit: (Day -1): Subject eligibility will be confirmed, and study drug will be initiated at the lowest available dose of Adhansia XR. The starting dose of Adhansia XR will be 12.5 mg in children 4 to <6 years of age and 25 mg in children 6 to 12 years of age.
4. Dose-optimization Period: (Day 1 up to Day 42): Subjects will take their starting dose for one week and will return to the clinic for weekly visits during which, they will be adjusted to the next available dose level at weekly intervals until their optimal dose is reached. Dosing will be discontinued in an individual subject if they have an increase from baseline in pulse rate of ≥30 beats per minute, or an increase from baseline in systolic or diastolic blood pressure of ≥30 mmHg. Subjects who do not reach an optimal dose or cannot tolerate their lowest available dose of Adhansia XR will be discontinued from the study. For subjects enrolled in the 12-month long-term study, once a subject has reached their optimal dose and has been at the optimal dose for one week, they will enter the maintenance period. For subjects enrolled in the PK substudy, once a subject has reached their optimal dose, blood samples for PK analysis will be collected at the times specified in the protocol. Subjects who complete the PK substudy will be eligible to enter the maintenance period and receive their optimized dose for 12 months at the discretion of the investigator after discussion with the medical monitor.
5. Maintenance Period: (12 months): Subjects will receive their optimal dose for up to 12 months. However, the dose level may be adjusted at the discretion of the investigator, as needed, to maintain optimal clinical response. Subjects will be monitored and/or discontinued from treatment if they experience a clinically relevant increase from baseline in liver transaminases, bilirubin, or alkaline phosphatase.
6. End of Study/Early Termination Visit: The end of study assessments will be conducted at the Month 12 visit. If a subject terminates early, the assessments conducted at the early termination visit will be the same as those evaluated at the end of study visit.
7. Follow-up Period: (1 week): Subjects will be contacted for follow-up safety approximately 7 days after the end of study/early termination visit.

It may be preferable to have study visits conducted in the subject's home with home trial support (HTS), also known as home nursing, by qualified, licensed nurses designated by the sponsor. The option to use HTS and the delegation of tasks must always be provided in the

best interest of the subject. Written informed consent specific to HTS must be obtained prior to the subject initiating HTS and before initiation of any study-related procedure in the home.

PK Substudy:

A nested PK substudy will be conducted in children 4 to <6 years of age to characterize the PK profile of methylphenidate hydrochloride following dose optimization. **This nested PK substudy, as well as recruitment and dosing in children 4 to <6 years of age will begin when the 12.5 mg strength of Adhansia XR is available**.

Subjects/parent(s)/legal guardian(s) will be required to provide informed consent/assent to participate in the PK substudy. Subjects who participate in the PK substudy will have a screening period, washout period, baseline visit, and dose-optimization period (as described above) in addition to the following evaluations.

Blood Sample Collection Period: blood samples will be collected at the following time points:

subjects who optimize at a dose level will have 4 blood samples collected within the following sampling windows: Hour 1 to 3, Hour 5 to 8, Hour 11 to 16, and Hour 22 to 26 postdose (this is also considered a predose sample)

Subjects and parent(s)/legal guardian(s)/caregiver will have the option to be admitted to the clinic the evening prior to dosing on the day of blood sample collection and stay at the clinic until the 24-hour blood draw is completed. They will also have the option to have the blood samples collected in the subject's home with HTS. The voluntary decisions to use HTS and the delegation of tasks must always be provided in the best interest of the subject. Written informed consent specific to HTS must be obtained prior to the subject initiating HTS and before initiation of any study-related procedure in the home.

Subjects enrolled in the PK substudy will be eligible to enter the maintenance period (as described above in the 12-month open-label safety study) at their optimized dose at the discretion of the investigator after discussion with the medical monitor. If subjects do not enter the maintenance period, they will complete the end of study/early termination visit (as described above in the 12-month, open-label safety study).

Study duration:

Up to 14 months (not including the screening period of up to 30 days)

Planned number of subjects:

For the 12-month open-label safety study, approximately 159 subjects will be enrolled to allow for 100 subjects to complete to Month 12 at their optimized dose. This sample size is calculated assuming a 10% dropout rate during the dose-optimization period and a 30% dropout rate during the maintenance period.

The PK substudy will enroll up to 12 subjects who optimize at each dose level and provide blood samples for PK evaluation. These subjects may be included in the overall subject count for this safety study if they move to the maintenance period of the open-label safety study.

Target population:

Pediatric subjects who have been diagnosed with ADHD.

General inclusion criteria

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Male and female subjects ≥4 and ≤12 years of age at the time of informed consent/assent.

2. Females of childbearing potential who are not pregnant and not nursing.
3. Females of childbearing potential who agree to practice a clinically accepted method of contraception during the study and for at least 1 month prior to study dosing and 1 month following completion of the study. Acceptable contraceptive methods include abstinence, oral contraception, surgical sterilization (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), intrauterine device, or diaphragm in addition to spermicidal foam and condom on male partner, or systemic contraception (eg, levonorgestrel-releasing implant).
4. Diagnosis of ADHD (any type: combined, predominately hyperactive impulsive type or predominately inattentive type) by a psychiatrist, psychologist, pediatrician, or licensed allied healthcare professional using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and confirmed by administration of a structured diagnostic interview using the Kiddie–Schedule for Affective Disorders and Schizophrenia for School Age Children–Present and Lifetime DSM-5 version (K-SADS-PL).
5. Subjects who have received, or are receiving treatment with medication (amphetamine, methylphenidate, or non-stimulant) for ADHD must be willing to undergo a washout period of a minimum of 3 days or 5 half-lives, whichever is longer, prior to study drug administration. Some medications may require a washout period greater than 3 days or a dose taper, depending on the product labeling.
6. If subjects are currently off treatment, this must be for any reason other than noncompliance, nonresponse, or intolerance to side effects.
7. Ratings on the attention deficit/hyperactivity disorder–Rating Scale, version 5 (ADHD-RS-5) when the subject is not receiving treatment for ADHD must be ≥90th percentile normative value for sex and age in at least 1 of the categories: total score, inattentive subscale, or hyperactive/impulse subscale.
8. Dissatisfied with his or her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD for any reason other than nonresponse, noncompliance, or tolerability issues with stimulants. Newly diagnosed and treatment naïve subjects may be included at the discretion of the investigator.
9. Must be functioning at an age-appropriate level intellectually as determined by an intelligence quotient (IQ) of ≥80 on a documented IQ assessment such as the Wechsler Abbreviated Scale of Intelligence II (WASI-II) vocabulary and matrix reasoning components, or the Kaufman Brief Intelligence Test, Second Edition (KBIT-2).
10. Parent(s)/legal guardian(s) must have the ability to read and understand the language in which the informed consent is written and are mentally and physically competent to provide written informed consent for their child.
11. Written or verbal assent from the subject (as applicable).
12. Subject and parent(s)/legal guardian/caregiver are willing and able to comply with all the protocol requirements and parent(s)/legal guardian/caregiver must be able to provide transportation for the subject to and from the clinic visits.

<u>Specific inclusion criteria for the PK substudy</u>

The following additional inclusion criteria must be met for a subject to be eligible for the PK substudy:

13. Male and female subjects ≥4 and <6 years of age at the time of informed consent/assent.
14. BMI within normal range for age (>3rd percentile and <97th percentile).
15. Parent(s)/legal guardian(s)/ caregiver(s) are willing for their child to remain off prescription or nonprescription medications and over-the-counter preparations (herbal, nutritional

supplements, vitamin and mineral preparations such as omega-3 fatty acids) for the duration of the PK substudy.

16. Parent(s)/legal guardian(s)/ caregiver(s) must be able to accompany the subject for the duration of inpatient stay during the PK substudy.

General exclusion criteria

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Has a known allergy, intolerance, or hypersensitivity to methylphenidate.
2. History of allergic reactions to tartrazine.
3. Known nonresponder to methylphenidate treatment.
4. Subject has received a monoamine oxidase inhibitor within 2 weeks before study treatment.
5. Blood pressure and heart rate outside the 95th percentile for age and sex.
6. Subject has a current or recent history (within the past 6 months) of drug abuse or dependence disorder; or someone in the subject's immediate family has a current or recent history (within the past 6 months) of drug abuse or dependence disorder; or someone living at the subject's home has a current or recent history (within the past 6 months) of drug abuse or dependence disorder; or subject has a positive urine drug screen for stimulant medication (other than currently prescribed stimulant for the treatment of ADHD) or drugs of abuse at the screening visit.
7. Has abnormal thyroid function, glaucoma, Gilles de la Tourette's disorder, a history of seizures (except simple febrile seizures), or a tic disorder. Mild medication-induced tics are not exclusionary.
8. Primary and/or comorbid psychiatric diagnosis other than ADHD with the exception of simple phobias, motor skill disorders, communication disorders, learning disorders, and adjustment disorders so long as such disorder is judged not to interfere with study participation or the safety of the subject.
9. Subjects with a family history (first-degree relatives) of sudden cardiac death require review and approval by the medical monitor for participation in the study.
10. Subject has a history of disorders of the sensory organs, including deafness, blindness or the subject is severely or profoundly developmentally disabled.
11. Any clinically significant abnormality or clinically significant abnormal laboratory test results found during screening or a positive test for hepatitis A, hepatitis B, hepatitis C, or HIV found during screening (subjects who have received a hepatitis A vaccine and test positive for hepatitis A may be included in the study, at the discretion of the investigator).
12. Use of an investigational drug within 30 days (90 days for biologics) or participation in an investigational study within 30 days prior to dosing.
13. Any reason which, in the opinion of the investigator, would prevent the subject from participating in the study.
14. Clinically significant ECG abnormalities (including but not limited to Wolff-Parkinson-White syndrome, supraventricular tachycardia, left ventricular hypertrophy, abnormal conduction defect, or other cardiac arrhythmia), or vital sign abnormalities (normal vital signs should be between 5th and 95th percentile for age) at screening.
15. Known history of cardiovascular disorders including hypertension, angina, arterial occlusive disease, heart failure, hemodynamically significant congenital heart disease,

cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, and channelopathies (disorders caused by the dysfunction of ion channels).

16. Clinically significant history of neurological, endocrinal (including thyrotoxicosis), pulmonary, hematological, immunologic, gastrointestinal, renal, hepatic or metabolic disease, or psychiatric illness other than ADHD.
17. History of anxiety, tension, agitation, motor tics, Tourette's syndrome or a family history (first-degree relatives) of Tourette's syndrome.
18. History of glaucoma.
19. Has a positive serum pregnancy test (if applicable) at screening.
20. Positive findings on C-SSRS for suicidal ideation or behaviors at screening.
21. Clinically significant illness or surgery within 4 weeks prior to dosing. Subjects who experience vomiting within 24 hours prior to clinic admission will be carefully evaluated for upcoming illness/disease.
22. Hemoglobin <105 g/L or hematocrit <0.310 L/L at screening (subjects with abnormal hemoglobin and/or hematocrit levels deemed not clinically significant may be included in the study, at the discretion of the investigator).
23. Subject has received anticonvulsants (eg, phenobarbital, phenytoin, primidone), coumarin anticoagulants, prescription pressor agents, pressor agents, guanethidine, tricyclic antidepressants (imipramine, desipramine, selective serotonin inhibitors) or herbal remedies within 30 days prior to the first dosing, or melatonin within 3 days prior to the first dosing.

Specific exclusion criteria for the PK substudy

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the PK substudy:

24. Use of beverages and foods containing grapefruit, caffeine or xanthine within 48 hours prior to clinic admission for PK blood sample collection. Xanthine containing beverages or foods are defined as containing caffeine, theophylline or theobromine (eg, coffee, tea, chocolate, cocoa). Allowance for a single incidental consumption may be evaluated and approved by the investigator based on the potential for interaction with the study drug.
25. Use of medication other than topical products (without significant systemic absorption):
26. Prescription medication within 3 days prior to the first dosing (excluding subject's prestudy ADHD medication)
27. Over-the-counter products within 7 days prior to the first dosing with the exception of the occasional use of acetaminophen (up to the daily maximum dose recommended for subject's age)

Test product:

Name: Adhansia XR (methylphenidate hydrochloride extended-release capsules)

Dose: 12.5 (starting dose **only** for children 4 to less than 6 years of age), 25 (starting dose for children 6 to 12 years of age), 35, 45, 55, or 70 mg administered once daily

Mode of administration: oral

Statistical methods:

Analysis datasets

- The safety analysis population is defined as all subjects who are administered at least 1 dose of study drug and have any safety information
- The PK population consists of all individuals who receive at least 1 dose of study drug and have at least 1 valid, quantifiable PK blood sample

Long-term safety study

Continuous variables will be summarized as n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized as the number and percentage of subjects in each category. All analyses will use the safety analysis population.

Demographics and baseline characteristics: Demographic and baseline characteristic will include, but are not limited to age, sex, race, ethnicity, weight, height, BMI, ADHD subtype, and ADHD-RS-5 at baseline. Age will be calculated based on the date of informed consent/assent, and weight and height measurements will be those collected at screening.

Extent of exposure: The exposure to study drug will be summarized separately for the dose-optimization and the maintenance periods. Exposure will be expressed as a function of dose as well as for combined dose levels.

[redacted]

Safety Analysis: For each subject and treatment, AEs, clinical laboratory assessments, vital signs, BMI, physical examinations (including Tanner Staging and growth), ECGs, and C-SSRS will be summarized descriptively. Safety summaries will include the incidence of AEs, and the change over the 12-month maintenance period in other safety parameters, including clinical laboratory assessments, vital signs, BMI, and ECGs. The results of the C-SSRS assessment will be summarized. Physical examination results will be listed by subject. No inferential statistical analysis of safety data is planned.

PK substudy

Demographics and baseline characteristics: Demographic and baseline characteristics will include, but will not limited to age, sex, race, ethnicity, weight, height, BMI, ADHD subtype, and ADHD-RS-5 at baseline. Age will be calculated based on the date of informed consent/assent, and weight and height measurements will be those collected at screening.

[redacted]

Safety Analysis: AEs, clinical laboratory assessments, vital signs, BMI, ECGs, and C-SSRS will be summarized descriptively by study drug dose level. Physical examination results will be listed by subject.

Protocol version and date: version 2, 26 Apr 2021