Official Title: Real-world Evidence of Duration of Adhansia XR for Treatment of ADHD (RE-DAX): An Open-label Pragmatic Study to Assess the Real-world Effectiveness of Adhansia XR in Treatment of Adult and Adolescent Patients with ADHD in the United States

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Study Synopsis

Full Study Title: Real-world Evidence of Duration of Adhansia XR for treatment of ADHD (RE-DAX): An open-label pragmatic study to assess the real-world effectiveness of Adhansia XR™ in treatment of adult and adolescent patients with ADHD in the United States			
Phase:	Phase IV	**Type**:	Pragmatic Randomized Clinical Study
Number of Patients: ~400; 200 per group		**Duration of Patient Participation**: 6 months	
Number of Sites: 34		**Duration of Study**: 12 months	
Background: Attention-deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. It is usually first diagnosed in childhood, however, often continues through adolescence and into adulthood. In the United States (US), the prevalence of ADHD is estimated to be 8.7% among adolescents (aged 13 to 18 years) and 4.4% among adults (18 to 44 years). Adhansia XR™ is an extended-release (ER) methylphenidate hydrochloride (MPH) product designed for rapid onset of clinical effect (1 hour) and a prolonged duration of effect (up to 16 hours in adolescents and adults) for the treatment of ADHD. Adhansia XR was approved by the Food and Drug Administration (FDA) in February 2019 for the treatment of ADHD in patients 6 years and older; market launch was in July 2019 in the US. Other ER MPH products with different formulations are currently available in the US. An osmotic-controlled release oral delivery system (OROS) MPH, Concerta® (Janssen Pharmaceuticals) is the brand name for an ER MPH with duration of action up to 12 hours approved in August 2000 for the treatment of ADHD. OROS MPH are currently the most commonly dispensed ER MPH treatments in the US. The RE-DAX study is a prospective, phase IV, open-label, randomized, pragmatic study to evaluate the effectiveness of the 2 different ER MPH formulations among patients requiring control of their ADHD symptoms throughout the day. Comparative treatment effectiveness, economic assessments and quality of life analysis will be conducted to demonstrate the benefits of a longer duration therapy window. The RE-DAX study results will provide information on choosing a methylphenidate treatment approach for patients with ADHD requiring prolonged symptom control.			
Rationale: Real-World Data (RWD), such as medical and pharmacy claims, may not be sufficiently robust to provide comprehensive and accurate evidence of the effectiveness of the products being studied, and may not contain the necessary data elements to detail the clinical and economic burden of			

ADHD. Thus, the RE-DAX study plans to investigate the treatment effectiveness of Adhansia XR at Month-2 after initiation, and the effectiveness of Adhansia XR overall and when compared with the active comparator group (OROS MPH or Concerta) over time. Additional outcome assessments for both treatment arms include Health-Related Quality of Life (HRQoL) during the 6-month follow-up period. The burden of illness (BOI) will be investigated by collecting additional measures such as healthcare resource utilization (HCRU), broader treatment patterns, and comorbidities.

Objectives:

Primary Objectives

- To assess the real-world (RW) effectiveness of Adhansia XR among adolescent and adult patients diagnosed with ADHD, by comparing the total score results of the ADHD-Rating Scale 5 (ADHD-RS-5) at Month-2 to the baseline visit among patients receiving Adhansia XR

Secondary Objectives

- To compare the effectiveness of Adhansia XR with the active comparator group among adolescent and adult patients diagnosed with ADHD, measured by the Time-Sensitive ADHD Symptom Scale (TASS), completed at the end of waking hours (14 – 16 hours post-dosing) at Month-2 after the baseline visit
- To describe the RW effectiveness of Adhansia XR among adolescent and adult patients diagnosed with ADHD, measured by the Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Treatment Satisfaction Questionnaire for Medication (TSQM); including results from the TASS and ADHD-RS-5 at other collected time points compared to the baseline visit
- To describe the RW effectiveness of the active comparator medication among adolescent and adult patients diagnosed with ADHD, measured by the CGI-S, CGI-I, TSQM, and ADHD-RS-5; including results from the TASS at other collected time points compared to the baseline visit
- To describe the safety events and safety event rates related to Adhansia XR and the active comparator
- To describe HCRU between patients in the Adhansia XR and active comparator groups
- To describe HRQoL outcomes between patients in the Adhansia XR and active comparator groups, measured by the Adult ADHD QoL (AAQoL-R) - Revised [redacted]

- To describe the treatment patterns for ADHD patients in this study, including but not limited to dose modifications of study treatment or changes in concomitant medications
- To describe the BOI of patients in the Adhansia XR and active comparator groups
- To describe patient sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI) in the Adhansia XR and active comparator groups

Study design: The RE-DAX study is a phase IV, prospective, randomized, open-label pragmatic study comparing outcomes of adolescent and adult patients diagnosed with ADHD treated with Adhansia XR or the active comparator (OROS MPH or Concerta). The RE-DAX study will be conducted in approximately 34 sites in the US, with approximately 200 patients (100 adults, 100 adolescents) randomized (1:1) to each treatment group. The enrollment period will be approximately 6 months, and per patient follow-up will also be approximately 6 months, from the study enrollment date of the last patient until treatment discontinuation, lost to follow-up, withdrawal of consent, death, or end of follow-up (whichever occurs first). After the patients are screened for eligibility and provide consent (and assent, if appropriate), they will be randomized 1:1 to the Adhansia XR or the active comparator group, and baseline questionnaires and assessments will be collected. The titration period (conducted per standard of care [SoC]), is estimated to take place over 8 weeks or less to achieve optimal ER MPH dosing; hence the primary comparisons occurring at Month-2 compared to baseline. Patients will receive prescriptions for study treatment for up to 6 months to be obtained from a retail pharmacy per SoC. Both the data from healthcare provider (HCP) visits and patient-reported outcomes (PROs) will be collected and recorded in an electronic data capture (EDC) system. PROs will be completed by the patient or parent/guardian approximately every 1 month during follow-up, while HCP study visits should occur at screening/baseline, and through follow-up at Month-2, -4, and -6.

Study population: Patients who fulfill the following eligibility criteria will be asked to provide informed consent (and assent, if appropriate):

Inclusion criteria

1. Patient with a physician-confirmed diagnosis of ADHD per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, and the HCP has made the decision to prescribe an ER MPH product to the patient for potential improvement of symptoms throughout and later in the day, independent of this study

- Note: The specific DSM-5 criteria satisfied by each patient enrolling will be collected, in addition to the primary reason for starting on an ER MPH treatment.

2. Patient must be 12 years of age or older
3. Patient must be an appropriate patient to receive Adhansia XR or OROS MPH (or Concerta) according to the US product labels; a patient must be appropriate and willing to receive either drug, as randomization will assign them to a specific treatment group. Patient may be treatment-experienced or naïve to pharmacological therapy for ADHD, so long as all inclusion and no exclusion criteria are met.
4. Patient must be willing to take only the assigned study medication per HCP instructions based on FDA label guidance for treatment of their ADHD for the first 2 months of the study (i.e., full titration period). Subjects should not be on any other medication, or starting any new non-medication treatment, proven to have effect on ADHD in the first two months of the study.

Exclusion criteria

1. Concurrent participation in an investigational study in which patient assessment and/or treatment may be dictated by a protocol
2. Patient with a true allergy to MPH, amphetamines (AMP) or sympathomimetic amines, history of serious adverse reactions to MPH or AMP or be known to be non-responsive to MPH or AMP treatment
3. Patient is adequately treated for ADHD on current treatment, and change to a long-acting methylphenidate does not offer a predictable benefit
4. Female patients of child bearing potential who are pregnant, planning on becoming pregnant or breastfeeding
5. Patient with any known conditions that are contraindicated for either Adhansia XR or OROS MPH (or Concerta) use, as documented in the US Full Prescribing Information, including patients with any known serious structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease
    - Refer to the US label/prescription insert for more details on contraindications.
6. Patients with a known sensitivity to the food dye tartrazine (Federal Food, Drug, and Cosmetic Yellow No. 5)

7. Suicidal Ideation
    - The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered at screening and at Month-2, Month-4, and Month-6 but also depends on the judgment of the HCP.
8. Inability or unwillingness of the patient (or parent/guardian if patient is a minor) to complete the study-required electronic questionnaires and provide required information through electronic means

Data collection/Data Sources: The RE-DAX study will collect baseline medical history information and prospectively collect primary data from both healthcare providers (HCPs) and patients/parents using an electronic platform via a website-based system. The RE-DAX study sites will be responsible for enrolling patients, obtaining informed consent, administering HCP questionnaires, and entering data. An electronic case report form (eCRF) will be used to collect data required to address the study objectives. All RE-DAX study data collected from the HCPs will be entered into the eCRF by the site Investigator, or designee. The site Investigator, or designee, will be responsible for ensuring that the required retrospective data (e.g., comorbidities, ADHD treatment history) from the medical chart is extracted and all the prospective data for each patient is collected and all data is entered into the EDC system correctly. Once a patient has been screened and consents (and assents, if appropriate) to participate in the RE-DAX study, there will be a baseline assessment prior to starting study drug at the randomization visit (baseline). After the baseline assessment, HCPs will continue to treat and clinically manage patients according to SoC; study visits have been aligned with expected HCP encounters. PROs will be completed by the patient outside of the HCP visit schedule on an approximately monthly basis using a mobile application or website-based system; however, some PROs may be administered more (or less) often and are shown in the schedule of assessments (SoAs). Follow-up will continue for 6 months until treatment discontinuation, patient withdrawal, lost to follow-up, death or end of study (whichever is first).

Data Management and Quality Assurance:

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. Remote and on-site monitoring will be performed to examine compliance with the protocol and adherence to the data

collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

Safety: All adverse events (AEs), regardless of relationship to the study treatment or intervention, will be monitored and reported throughout the entire course of the study. The AE reporting period begins when the patient is included into the study (date of first signature of informed consent and assent, if appropriate) and continues through the follow-up period. All AE verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs assessed as non-serious will be reported through the 7 days following the patient's last study drug dose. Serious AEs (SAEs) that are ongoing at the patient's last study visit must be followed until resolution or for 30 days after the patient's last study drug dose, whichever comes first. Additional details will be described in the study Safety Monitoring Plan (SMP).

Statistical Considerations: All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA). Adult and adolescent patient treatment groups will be analyzed separately, but pooling of the age groups may be considered if appropriate. Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected, and the characteristics of the sample studied.

Primary Objective Analysis:

Primary treatment effectiveness will be determined by the mean improvement in ADHD symptoms based on the ADHD-RS-5 total score at Month-2 compared to baseline for Adhansia XR-treated patients. Note that the ADHD-RS-5 will also be collected for patients in the active comparator arm at the same time points but will be used for analysis of secondary objectives only.

Secondary Objective Analyses:

The key secondary purpose of the RE-DAX study is to compare effectiveness at Month-2 after the baseline visit between Adhansia XR and the active comparator, using the TASS questionnaire. The TASS will be completed at the end of waking hours (14 – 16 hours post-dosing) on a once monthly basis starting at Month-2. Patients will have the opportunity to complete the TASS each month within a 5-day window (excluding weekend days or holidays). A longitudinal regression approach such as linear mixed-model (LMM) or general estimating equation (GEE) will be used and fully described in the statistical analysis plan (SAP). Assessments of comparative effectiveness utilizing TASS will be performed at Month-2 through Month-6 during follow-up. Month-2 will be the key/primary comparison, with Month-3 through Month-6 as part of the secondary study objectives.

Further secondary outcomes will be analyzed to compare treatment groups, with appropriate prespecified tests of statistical significance. The analysis plan will be fully described in a written and approved SAP.

Sample size

The sample size is calculated for the key secondary purpose (effectiveness at Month-2 after the baseline visit between Adhansia XR and active comparator group, using the TASS questionnaire) to ensure adequate power for non-inferiority and superiority testing. A total sample size of 400 patients has been planned, with 200 patients in each treatment group and 200 patients within each age group. Randomization will be stratified by age group, with 100 adults and 100 adolescents per treatment group. Treatment group sizes of 80 patients per treatment group would be needed to achieve 81% power to detect non-inferiority using a one-sided, Mann-Whitney test assuming that the actual distribution is normal. The margin of non-inferiority is 6.60 points. The true difference between the score means is assumed to be null, with a significance level (alpha) of 0.05. The data are drawn from populations with Standard deviation (SD) of 16.0 points in each treatment group (calculated by PASS 11.0.4 Statistical Software. NCSS, LLC. Kaysville, Utah, USA. 2016).

Thus, within each age category (adolescents and adults), 80 patients are needed in each treatment arm, plus 20% additional patients enrolled to account for assumed supplemental ADHD medication use after Month-2 and attrition. This results in a total of 96 patients in each treatment arm and each age category, or a total of 384 patients for the entire study. The planned sample size of 400 patients is adequately planned for 10% anticipated attrition, 10% exclusion for supplemental ADHD medication use after Month-2, and to sufficiently power the comparative analysis.

Interim and Final Analyses: An abbreviated interim data look may be performed to assess overall data quality and completeness; it will not estimate primary or secondary outcomes. A final analysis report will be prepared at closure of the study database, when all data collection procedures are completed. The final report will encompass all planned analyses, including a description of the complete RE-DAX study population and patient outcomes, as described in the written SAP.

Ethical and Regulatory Considerations: The RE-DAX study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Clinical Practices (GCP), Good Pharmacoepidemiology Practices (GPP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on

the protection of individuals, and in compliance with Safe Harbor privacy principles. An Institutional Review Board/Independent Ethics Committee (IRB/IEC) must review and approve the protocol and informed consent form before any patients are enrolled. Before any protocol-directed data collection is performed, the patient must sign and date the IRB/IEC-approved informed consent form.