# A phase III, randomised, double-blind, multicentre, parallel-group, placebo- and active-controlled, dose-optimisation safety and efficacy study of Lisdexamfetamine Dimesylate (LDX) in children and adolescents aged 6-17 with attention-deficit/hyperactivity disorder (ADHD)

Published: 08-07-2008
Last updated: 06-05-2024

Primary:The primary objective of this study is to evaluate the efficacy of LDX administered as a daily morning dose (30, 50, and 70mg/day) compared to placebo over the course of 7 weeks. This study will enrol children and adolescents (6-17 years of...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Cognitive and attention disorders and disturbances |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON31918

**Source**
ToetsingOnline

**Brief title**
SPD489-325

### Condition

- Cognitive and attention disorders and disturbances

**Synonym**
ADD, Hyperactivity

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** PRA International
**Source(s) of monetary or material Support:** Shire Pharmaceutical Development Ltd.

## Intervention

**Keyword:** ADHD, Adolescents, Children, Lisdexamfetamine Dimesylate

## Outcome measures

**Primary outcome**

The primary efficacy measure for each subject is defined as the change from Baseline score of the ADHD-RS-IV total score by treatment week. The last on-therapy, post-randomisation treatment week, at which a valid ADHD RS-IV total score is observed is defined as the Endpoint (analogous to Visit 7/ET where a last observation carried forward approach is applied). The Baseline ADHD-RS-IV total score is obtained at the Baseline Visit (Visit 0). The mean ADHD RS IV score and change from Baseline score will be summarised for each visit (using observed data) and for Endpoint by treatment group (LDX, CONCERTA® and placebo) and overall.

The primary efficacy analysis will be performed on the ADHD-RS-IV change score at Endpoint from Baseline for the Full Analysis Set (FAS), using an analysis of covariance (ANCOVA) model. The primary treatment comparison is LDX versus placebo. The ANCOVA model will include treatment group (the effect of interest), the corresponding Baseline score (the covariate), and the blocking

factor age group (6-12 years or 13-17 years). The null hypothesis states that there is no difference between LDX and placebo at Endpoint, with the two-sided alternative of a non-zero difference between groups. The primary treatment comparison will be evaluated at the 0.05 significance level. Treatment effects at each visit will also be assessed by applying the ANCOVA model described above to the observed data at each on-treatment visit (Visits 1 to 7).
Diagnostic residual plots will be evaluated to test for violations of normality. If the normality assumption for the model is not met, a ranked ANCOVA method for testing treatment effects will be used to compare LDX against placebo. This test is the non-parametric equivalent of the two group t-test.
Graphical illustrations will be produced for FAS summaries of the ADHD-RS-IV score by treatment group (LDX, CONCERTA® and placebo).
The primary efficacy measure will be analysed using the same ANCOVA model described above to compare CONCERTA® and placebo.
Additional analyses will be conducted for subgroups, including gender, race, and age.

**Secondary outcome**

Secondary efficacy endpoints of the study are listed below:

• The change from Baseline score of the CPRS-R at Endpoint and each visit for each time point assessed

• The CGI-I at each visit and Endpoint

• The CHIP-CE:PRF at Endpoint

• The HUI-2 at Visit 4 and Endpoint

• The WFIRS-P at Endpoint

Additionally, the safety of LDX in children and adolescents with a diagnosis of

ADHD will be assessed based on TEAEs, specific evaluation of blood pressure and

pulse, ECG results, clinical laboratory test results, and physical examination

findings.

# Study description

**Background summary**

The LDX clinical program has studied the efficacy, safety, and tolerability of LDX in treating core symptoms of ADHD in children aged 6-12 years and adults aged 18-55 years. All of the studies conducted as part of the LDX clinical program have enrolled subjects from the US.
The current Phase III double-blind clinical study is designed to evaluate the safety and efficacy of LDX for the treatment of ADHD in children and adolescents, aged 6-17 years old, in Europe. The doses of LDX in this study were proven safe and effective in the controlled studies. The study includes a reference arm of comparable doses of CONCERTA® to provide reference data on the current standard therapy in Europe.

**Study objective**

Primary:
The primary objective of this study is to evaluate the efficacy of LDX administered as a daily morning dose (30, 50, and 70mg/day) compared to placebo over the course of 7 weeks. This study will enrol children and adolescents (6-17 years of age inclusive) diagnosed with moderately-symptomatic ADHD.
The primary measure of efficacy will be the clinician-administered ADHD rating scale-IV (ADHD RS IV).

Secondary:
The key secondary objective of this study is to assess the efficacy of LDX compared to placebo using a global clinical measure of improvement, the Clinical Global Impressions - Global Improvement (CGI-I).
The other secondary objectives of this study are listed below:
1. To assess the duration of therapeutic response to LDX compared to placebo using the Conners* Parent Rating Scale - Revised (CPRS-R) performed in the morning (around 10:00AM), afternoon (around 2:00PM), and evening (around 6:00PM).
2. To assess the impact of LDX compared to placebo on the perception of health state preferences and quality of life (QoL) using the Health Utilities Index -

Mark 2 (HUI-2) and the Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP CE:PRF), respectively.
3. To assess the relationship of change in the core symptoms of ADHD with the changes in functional outcomes, as assessed by the Weiss Functional Impairment Rating Scale - Parent (WFIRS-P), in subjects treated with LDX compared to placebo.
4. To evaluate the safety of LDX based on occurrence of treatment-emergent adverse events (TEAEs), specific evaluation of blood pressure and pulse, electrocardiogram (ECG) results, clinical laboratory test results, and physical examination findings.
5. To assess the safety and efficacy of CONCERTA® compared to placebo.

## Study design

This study is a Phase III, randomised, double-blind, multicentre, parallel-group, placebo- and active-controlled, dose optimisation safety and efficacy study. Children and adolescents (6-17 years of age inclusive) diagnosed with ADHD will be randomised to LDX, CONCERTA® or placebo and treated for 7 weeks to evaluate safety and efficacy, followed by an immediate 1-week post-treatment washout. The study will be conducted at approximately 54 sites in Europe and the US. Approximately 333 subjects will be randomised in a 1:1:1 ratio (LDX:CONCERTA®:placebo).
The study will have four periods: (1) screening and washout; (2) baseline; (3) 7-week double-blind evaluation of LDX, CONCERTA® and placebo; and (4) post-treatment washout and safety follow-up.
Subjects will be required to visit the sites up to 10 times over a 9-14 week period.

## Intervention

NA

## Study burden and risks

Questionnaires to be completed by the parents. Children must be awake at 7:00 in the morning to take a capsule. There will be a physical examination at 3 visits. A fourth physical examination will be required at baseline if more than 30 days have elapsed since the screening. ECG will be conducted at each visit, with the exeption of the baseling, where 3 ECGs will be conducted. Blood will be taken at 2 visits for routine laboratory tests. For females of child bearing potential a part of this sample will be used to conduct a serum pregnancy test. A third blood draw will be required at baseline if more than 30 days have elapsed since screening. Urine will be collected at 2 visits for routine laboratory tests and urine drug screen. A third urine sample will be required for routine laboratory tests at baseline if more than 30 days have elapsed since screening. For females of child bearing potential a urine sample will be

collected at 3 visits for a urine pregnancy test. Weight and vital signs will be collected at 10 visits. Height will be collected at screening. Participation in this trial can involve certain risks and discomfort. The patient can have adverse events or reactions. Taking blood can provoke pain, swelling, bleeding or bruises. Taking blood can provoke infection. The patient might become dizzy or might faint.

# Contacts

**Public**
PRA International

Business Park E19; Battelsesteenweg 455B
2800 Mechelen
BE
**Scientific**
PRA International

Business Park E19; Battelsesteenweg 455B
2800 Mechelen
BE

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

1. Subject*s parent or legally authorised representative (LAR) must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject indicating that the subject is aware of the investigational nature of the study and the required

procedures and restrictions, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations before completing any study-related procedures.
2. Subject and parent/LAR are willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dosing. Specifically, the parent/LAR must be available upon awakening, at approximately 7:00AM, to dispense the dose of study drug for the duration of the study.
3. Subject is a male or female aged 6-17 years inclusive at the time of consent.
4. Subject must meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSM IV TR) criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation.
5. Subject must have a Baseline ADHD-RS-IV total score >=28.
6. Subject, who is a female of childbearing potential (FOCP), must have a negative serum beta human chorionic gonadotropin (HCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline and agree to comply with any applicable contraceptive requirements of the protocol.
7. Subject has blood pressure measurements within the 95th percentile for age, gender, and height at Screening and Baseline.
8. Subject is functioning at an age-appropriate level intellectually, as deemed by the study investigator.
9. Subject is able to swallow a capsule.

## Exclusion criteria

1. Subject has failed to respond to more than one adequate course (dose and duration) of stimulant therapy. One course must have been a long-acting formulation.
2. Subject has a current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms such as any severe comorbid Axis II disorder or severe Axis I disorder (such as Post Traumatic Stress Disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, anorexia nervosa, severe depressive or severe anxiety disorder) or other symptomatic manifestations, such as agitated states, marked anxiety, or tension that, in the opinion of the examining physician, will contraindicate treatment with LDX or CONCERTA® XL or confound efficacy or safety assessments. Comorbid psychiatric diagnoses will be established with the Screening interview of the Kiddie-SADS-Present and Lifetime - Diagnostic Interview (K SADS-PL) and additional modules if warranted by the results of the initial interview. Subjects may continue participating in behavioural therapy during this study as long as they have been receiving the therapy for at least 1 month at the time of the Baseline Visit.
3. Subject has a conduct disorder. Oppositional Defiant Disorder is not exclusionary.
4. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject. Similarly, the subject will be excluded if he or she has any additional condition(s) that, in the Investigator*s opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional condition(s) would include any

significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma is not exclusionary.
5. Subject is currently considered a suicide risk, has previously made a suicide attempt or has a prior history of, or is currently, demonstrating active suicidal ideation.
6. Subject is female and is pregnant or lactating.
7. Subject has glaucoma.
8. Subject weighs less than 22.7kg (50lbs).
9. Subject is significantly overweight based on Centre for Disease Control and Prevention Body Mass Index (BMI)-for-age gender specific charts at Screening. Significantly overweight is defined as a BMI >97th percentile for this study.
10. Subject has a positive urine drug result at Screening (with the exception of subject*s current ADHD therapy).
11. Subject has current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) at Screening. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
12. Subject has any clinically significant ECG or laboratory abnormalities at Screening and/or Baseline.
13. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or methylphenidate.
14. Subject has a documented allergy, hypersensitivity, or intolerance to any excipients in the test or reference product.
15. Subject has a recent history (within the past 6 months) of suspected substance abuse or dependence disorder (excluding nicotine) in accordance with DSM-IV-TR* criteria.
16. Subject has a history of seizures (other than infantile febrile seizures), a tic disorder, or a current diagnosis and/or a known family history of Tourette*s Disorder.
17. Subject has a known history of symptomatic cardiovascular disease, advance arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.
18. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
19. Subject is taking any medication that is excluded.
20. Subject is taking other medications that have central nervous system (CNS) effects, affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are monoamine oxidase inhibitors (during or within 14 days of test or reference product administration). Stable use of bronchodilator inhalers is not exclusionary.
21. Subject is well-controlled on their current ADHD medication with acceptable tolerability.
22. Subject has taken another investigational product or taken part in a clinical trial within 30 days prior to Screening.
23. Subject has a pre-existing severe gastrointestinal tract narrowing (pathologic or iatrogenic).

## Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-10-2008 |
| Enrollment: | 50 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Registration: | No |
| Product type: | Medicine |
| Brand name: | CONCERTA® |
| Generic name: | Methylphenidate |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | NA |
| Generic name: | Lisdexamfetamine Dimesylate (LDX) |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 08-07-2008 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 10-06-2009 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 13-07-2009 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 25-08-2009 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 02-12-2009 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 18-05-2010 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-08-2010 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-10-2010 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2008-000679-90-NL |
| CCMO | NL23494.091.08 |