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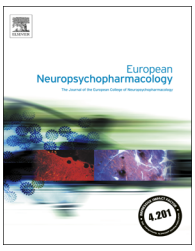

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European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder

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Abstract
This study evaluated the efficacy and safety of lisdexamfetamine dimesylate (LDX) compared with placebo in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in Europe. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference arm. Patients (6–17 years old) with a baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score ≥28 were randomized (1:1:1) to dose-optimized LDX (30, 50, or 70 mg/day), OROS-MPH (18, 36, or 54 mg/day) or placebo for 7 weeks. Primary and key secondary efficacy measures were the investigator-rated ADHD-RS-IV and the Clinical Global Impressions-Improvement (CGI-I) rating, respectively. Safety assessments included treatment-emergent adverse events (TEAEs), electrocardiograms, and vital signs. Of 336 patients randomized, 196 completed the study. The difference between LDX and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was −18.6 (95% confidence interval [CI]:

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−21.5 to −15.7) ($p<0.001$; effect size, 1.80). The difference between OROS-MPH and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was −13.0 (95% CI: −15.9 to −10.2) ($p<0.001$; effect size, 1.26). The proportions (95% CI) of patients showing improvement (CGI-I of 1 or 2) at endpoint were 78% (70–86), 14% (8–21), and 61% (51–70) for LDX, placebo, and OROS-MPH. The most common TEAEs for LDX were decreased appetite, headache, and insomnia. Mean changes in vital signs were modest and consistent with the known profile of LDX. LDX was effective and generally well tolerated in children and adolescents with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders diagnosed in children, with an estimated worldwide prevalence of 5.29% (Polanczyk et al., 2007). ADHD is characterized by persistent core symptoms of hyperactivity, impulsivity, and/or inattention, and is associated with impairments in academic, social, and interpersonal functioning (American Academy of Pediatrics, 2011a; Gordon et al., 2006). Stimulant medications are commonly recommended as part of a comprehensive multimodal treatment plan for ADHD that will often also include behavioral, psychoeducational, and psychological interventions (American Academy of Pediatrics, 2011b; Banaschewski et al., 2006; National Institute for Health and Clinical Excellence, 2009; Taylor et al., 2004). Stimulants are available in long-acting and short-acting formulations. In addition to reducing or eliminating the need for multiple daily dosing, the suggested benefits of long-acting stimulants also include improved adherence and lower abuse potential compared with their short-acting counterparts (Banaschewski et al., 2006).

Lisdexamfetamine dimesylate (LDX) is the first long-acting, prodrug stimulant. The intact parent molecule requires enzymatic hydrolysis to yield the therapeutically-active metabolite *d*-amfetamine (Pennick, 2010). After oral administration, LDX is readily absorbed from the gastrointestinal tract. As the metabolic conversion of LDX to *d*-amfetamine occurs primarily in the blood, it is unlikely to be affected by changes in gastric pH or variations in gastrointestinal transit time (Pennick, 2010). Pharmacokinetic studies in children with ADHD have shown that, following oral administration of LDX, exposure to *d*-amfetamine is long lasting and dose proportional, with low intrapatient and interpatient variability (Biederman et al., 2007a; Boellner et al., 2010).

All clinical trials of LDX reported to date have been conducted in the United States. These studies have shown LDX to be an effective once-daily treatment for ADHD in children (Biederman et al., 2007b), adolescents (Findling et al., 2011), and adults (Adler et al., 2008). Studies in a laboratory school setting and in a simulated adult workplace environment have demonstrated that the therapeutic benefits of LDX are ongoing at 13 h post-dose in children (Wigal et al., 2009) and 14 h post-dose in adults (Wigal et al., 2010). The present European, phase 3 trial evaluated the efficacy and safety of LDX over the course of 7 weeks in children and adolescents (6–17 years old) diagnosed with ADHD of at least moderate severity. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference arm.

2. Experimental procedures

This randomized, double-blind, parallel-group, dose-optimized, placebo-controlled study (ClinicalTrials.gov Identifier: NCT00763971) was conducted in accordance with the current applicable regulations, the International Conference on Harmonisation of Good Clinical Practice, and local ethical and legal requirements. The study protocol was approved by an independent ethics committee/institutional review board and regulatory agency in each center (as appropriate) before study initiation. Each patient's parent or legal guardian provided written, informed consent, and assent was obtained from each participant, as applicable, before commencing study-related procedures.

2.1. Study population

The study enrolled male and female children (6–12 years old) and adolescents (13–17 years old) who satisfied the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria for a primary diagnosis of ADHD (American Psychiatric Association, 2000). Patients had ADHD of at least moderate severity, as defined by a baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score of 28 or higher. Additional inclusion criteria included: age-appropriate intellectual functioning; blood pressure measurements within the 95th percentile for age, sex, and height; and ability to swallow a capsule. Girls of childbearing potential had to have a negative urine pregnancy test at baseline and to comply with any contraceptive requirements of the protocol.

Key exclusion criteria included: failure to respond to previous OROS-MPH therapy; presence of a comorbid psychiatric diagnosis with significant symptoms (based on Kiddie-Schedule for Affective Disorders and Schizophrenia for school age children – Present and Lifetime – diagnostic interview); conduct disorder (excluding oppositional defiant disorder); pregnancy or lactation; weight below 22.7 kg; body mass index (BMI, kg/m^2) greater than the 97th percentile for age and sex; positive urine drug test (with the exception of the patient's current ADHD therapy); clinically significant electrocardiogram or laboratory abnormalities; suspected substance abuse or dependence disorder (excluding nicotine) within the previous 6 months; history of seizures; tics or Tourette's disorder; known structural cardiac abnormality; or any other condition that might increase vulnerability to the sympathomimetic effects of a stimulant drug. Patients whose current ADHD medication provided effective control of symptoms with acceptable tolerability were also excluded.

2.2. Study drug administration

Eligible patients completed a screening and washout period (3–42 days) and were randomized in a 1:1:1 ratio at baseline (visit 0) to receive once-daily LDX, OROS-MPH, or placebo for a 7-week double-blind evaluation period (4-week stepwise dose-optimization period