

Effect of Lisdexamfetamine Dimesylate on Parent-Rated Measures of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children Aged 6 to 12 Years With ADHD: A Secondary Analysis

Lawrence D. Ginsberg, MD¹; Jack Schreckengost, PhD²; Suma Krishnan, MS, MBA³

¹Red Oak Psychiatry Associates, PA, Houston, TX; ²Shire Development Inc., Wayne, PA; ³Belvedere, CA, formerly of New River Pharmaceuticals, Inc.

ABSTRACT

Objective: To assess the effect of lisdexamfetamine dimesylate (LDX; Vyvanse™, Shire US Inc) on parent-rated Attention-Deficit/Hyperactivity Disorder (ADHD) Index scores in children aged 6 to 12 years with ADHD.

Methods: The primary study was a phase 3, randomized, double-blind, parallel-group trial with 290 children aged 6 to 12 years with DSM-IV-TR[®]-defined ADHD. Subjects were randomized 1:1:1:1 to 4 weeks' treatment with placebo, 30, 50, or 70 mg/d LDX, with median daily dosing between 7:30 AM and 8 AM. The primary efficacy measure was the ADHD Rating Scale (ADHD-RS). Secondary efficacy measures included the Conners Parent Rating Scale-Revised Short Version ADHD Index Subscale (CPRS ADHD Index) to assess ADHD-related behaviors weekly at 10 AM, 2 PM, and 6 PM.

Results: At endpoint, least squares mean (±SE) percent changes from baseline in CPRS ADHD Index scores at 10 AM, 2 PM, and 6 PM were -51.7% (±3.1%), -51.7% (±3.1%), and -46.0% (±3.1%), respectively, for the 207 LDX-randomized subjects and -3.4% (±5.0%), -3.9% (±5.1%), and -1.9% (±5.1%), respectively, for the 72 placebo-randomized subjects. CPRS ADHD Index improvements for each LDX dose were significantly greater than placebo at all 3 time points (*P*<.0001). LDX was more effective than placebo at all time points measured on the CPRS ADHD Index, regardless of baseline severity (*P*<.0001). Improvements started at the first postbaseline week and persisted throughout the study.

Conclusions: LDX significantly improved CPRS ADHD Index scores in children aged 6 to 12 years. Each dose demonstrated efficacy throughout the day and regardless of baseline severity.

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder, affecting 8% to 12% of children worldwide¹
- Psychostimulants have been shown to be effective in improving symptoms of ADHD and are therefore commonly used to treat subjects with this condition.² Despite the availability of these agents, several therapeutic needs remain unmet, including the consistent delivery of medication throughout the day and adequate duration of action
- Parents of many children with ADHD, especially those aged 6 to 12 years, reported in online interviews that once-daily ADHD medications stop providing relief before 6 PM³
- Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant and is indicated for the treatment of ADHD. A therapeutically inactive prodrug in which d-amphetamine is covalently bound to l-lysine, LDX is converted to the pharmacologically active d-amphetamine by rate-limited hydrolysis. LDX was developed with the goal of providing an extended duration of effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering⁴
- LDX has been shown to have efficacy superior to placebo and a safety profile comparable to existing stimulant medications in the treatment of school-aged children with ADHD^{1,5}:
 - Compared with placebo, LDX significantly reduced symptoms of ADHD
 - LDX is generally well tolerated, with an adverse-event (AE) profile similar to extended-release stimulant products
 - Improvements have been observed as early as the first week of treatment⁴

This secondary analysis of a pivotal clinical trial evaluated the effect of LDX treatment in children with ADHD as evaluated by the ADHD Index scores on the Conners Parent Rating Scale-Revised Short Version (CPRS)

MATERIALS AND METHODS

- This study was a phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled, forced-dose titration trial in children aged 6 to 12 years with DSM-IV-TR[®] criteria diagnosis of ADHD (combined or hyperactive-impulsive subtypes) who may or may not have received prior ADHD treatment
- Following 1-week screening and 1-week washout periods, subjects were randomized 1:1:1:1 to placebo or once-daily doses of 30 mg, 50 mg, or 70 mg LDX for 4 weeks of treatment

- The CPRS was used to assess a cross-section of ADHD-related symptoms and problem behaviors⁶ (Table 1)
 - The CPRS contains 27 questions, grouped into 4 subscales: hyperactivity (6 items), oppositional (6 items), cognitive problems/inattention (6 items), and ADHD Index (12 items; contains items from other subscales)⁶
 - The CPRS total score is the sum of scores on the 4 subscales

Table 1. CPRS Revised Short Version ADHD Index Subscale Items⁶

- Inattentive, easily distracted
- Short attention span
- Fidgets with hands or feet or squirms in seat
- Messy or disorganized at home or school
- Only attends if it is something he/she is very interested in
- Distractibility or attention span a problem
- Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)
- Gets distracted when given instructions to do something
- Has trouble concentrating in class
- Leaves seat in classroom or in other situations in which remaining seated is expected
- Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- Easily frustrated in efforts

Conners CK. *Conners' Rating Scales-Revised Technical Manual*. North Tonawanda, NY: Multi-Health Systems Inc; 2001. © 2001 Multi-Health Systems Inc. 3770 Victoria Park Avenue, Toronto, ON, M2H 3M6. All rights reserved.

- Parents rated their child's behavior for the 2-hour period immediately preceding assessment times at 10 AM, 2 PM, and 6 PM
- At baseline, the investigator performed a Clinical Global Impression-Severity (CGI-S) assessment, rating severity on a scale of 1 (no symptoms) to 7 (very severe symptoms)
- Post hoc analysis was also conducted to compare the degree of improvement in CPRS ADHD Index scores with varying CGI-S assessments at baseline

RESULTS

Subject Demographics

- In the primary study, 290 subjects were randomized: 72 to placebo, 71 to 30 mg/d LDX, 74 to 50 mg/d LDX, and 73 to 70 mg/d LDX
- Of the 290 randomized subjects, 230 (79%) completed the trial
- <1% of LDX-treated subjects (2/218) discontinued for lack of efficacy, compared with 16.7% of placebo-treated subjects
- Demographics were similar across treatment groups (Table 2)

Efficacy

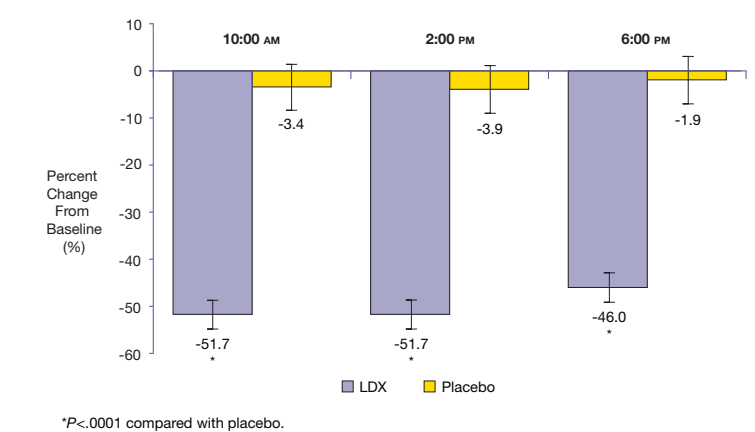
- For each of the 3 dose groups (30 mg/d, 50 mg/d, and 70 mg/d), improvement in CPRS total score at endpoint was significantly greater than placebo at 10 AM, 2 PM, and 6 PM (*P*<.0001)

Table 2. Demographic and Baseline Characteristics of the Randomized Population (N=290)

Characteristics	Placebo (n=72)	30 mg/d (n=71)	50 mg/d (n=74)	70 mg/d (n=73)
Age (y)				
Mean ± SD	9.4 ± 1.7	9.0 ± 1.9	8.9 ± 1.8	8.7 ± 1.8
Sex, n (%)				
Male	50 (69.4)	53 (74.6)	46 (62.2)	52 (71.2)
Female	22 (30.6)	18 (25.4)	28 (37.8)	21 (28.8)
Ethnicity, n (%)				
White	43 (59.7)	37 (52.1)	34 (45.9)	41 (56.2)
Black	16 (22.2)	18 (25.4)	19 (25.7)	17 (23.3)
Hispanic	9 (12.5)	10 (14.1)	17 (23.0)	12 (16.4)
Other	4 (5.6)	6 (8.5)	4 (5.4)	3 (4.1)
Weight (lb)				
Mean ± SD	82.6 ± 22.8	80.9 ± 27.2	80.7 ± 25.4	79.0 ± 23.7
CGI-S at Baseline, n (%)				
CGI-S 3 to 4	27 (37.5)	26 (36.6)	26 (35.2)	25 (34.2)
CGI-S 5 to 7	45 (62.5)	45 (63.4)	48 (64.9)	48 (65.8)

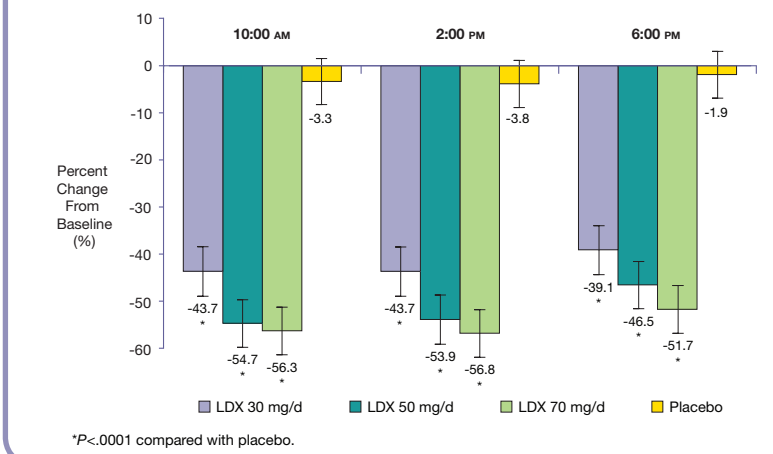
- Least squares (LS) mean (±SE) percent changes in CPRS total scores from baseline to endpoint at 10 AM, 2 PM, and 6 PM were -51.9% (±3.0%), -50.9% (±3.3%), and -45.3% (±3.1%), respectively, for the LDX-treated group, and -4.5% (±4.8%), -3.3% (±5.3%), and -1.7% (±5.1%) for the placebo group
 - The improvements in the CPRS total score in the LDX-treated group were statistically significantly greater than the placebo group at all 3 time points (*P*<.0001)
- LS mean (±SE) percent changes in CPRS ADHD Index scores from baseline to endpoint at 10 AM, 2 PM, and 6 PM were -51.7% (±3.1%), -51.7% (±3.1%), and -46.0% (±3.1%), respectively, for the LDX-treated group, and -3.4% (±5.0%), -3.9% (±5.1%), and -1.9% (±5.1%) for the placebo group (Figure 1)
 - The improvements in the CPRS ADHD Index score in the LDX-treated group were significantly greater than the placebo group at all 3 time points (*P*<.0001)

Figure 1. Percent changes in CPRS ADHD Index score from baseline to endpoint.



- For each LDX dose, LS mean percent change from baseline CPRS ADHD Index score was also significantly greater than placebo at all 3 time points (*P*<.0001) (Figure 2)

Figure 2. Percent change in CPRS ADHD Index score by dose throughout the day at endpoint.

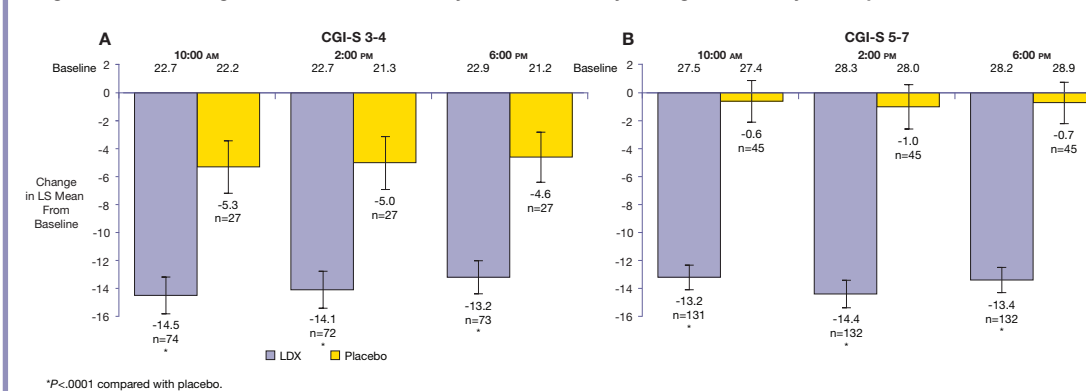


- Significant improvement in CPRS ADHD Index scores compared with placebo occurred in both the baseline CGI-S 3 to 4 (mildly to moderately ill) group and the baseline CGI-S 5 to 7 (markedly to extremely ill) group (Figure 3)
- In both groups, improvement in CPRS ADHD Index score was significantly greater with LDX treatment than with placebo at all time points (*P*<.0001)
- Improvements started at the first postbaseline week and persisted throughout the study

Tolerability

- Overall, AEs were experienced by 72% of subjects in the 30-mg/d group, 68% in the 50-mg/d group, and 84% in the 70-mg/d group, compared with 47% in the placebo group (Table 3)

Figure 3. Mean change in CPRS ADHD index by baseline severity throughout the day at endpoint.



The most frequently reported AEs among LDX subjects were typical side effects of stimulant products: decreased appetite (39% with active treatment vs 4% with placebo); insomnia (19% vs 3%), abdominal pain upper (12% vs 6%), headache (12% vs 10%), irritability (10% vs 0%), vomiting (9% vs 4%), weight decreased (9% vs 1%), and nausea (6% vs 3%)

- More than 95% of treatment-emergent AEs were mild or moderate in intensity
- A total of 21 randomized and treated subjects were withdrawn from the study due to AEs: 1 subject (1%) in the placebo group, 6 (9%) in the LDX 30-mg/d group, 4 (5%) in the 50-mg/d group, and 10 (14%) in the 70-mg/d group

Table 3. Treatment-Emergent Adverse Events With Subject Incidence Greater Than 5% in Any Dose Group

Adverse Events	Placebo (n=72)	30 mg/d (n=71)	50 mg/d (n=74)	70 mg/d (n=73)	LDX Doses (n=218)
Any events, n (%)	34 (47)	51 (72)	50 (68)	61 (84)	162 (74)
Abdominal pain upper	4 (6)	10 (14)	5 (7)	11 (15)	26 (12)
Cough	4 (6)	2 (3)	1 (1)	0 (0)	3 (1)
Decreased appetite	3 (4)	26 (37)	23 (31)	36 (49)	85 (39)
Dizziness	0 (0)	5 (7)	4 (5)	2 (3)	11 (5)
Dry mouth	0 (0)	2 (3)	2 (3)	6 (8)	10 (5)
Headache	7 (10)	7 (10)	7 (10)	12 (16)	26 (12)
Irritability	0 (0)	8 (11)	6 (8)	7 (10)	21 (10)
Insomnia	2 (3)	11 (16)	12 (16)	18 (25)	41 (19)
Nasal congestion	4 (6)	3 (4)	0 (0)	0 (0)	3 (1)
Nasopharyngitis	4 (6)	4 (6)	3 (4)	4 (6)	11 (5)
Nausea	2 (3)	3 (4)	2 (3)	8 (11)	13 (6)
Vomiting	3 (4)	5 (7)	4 (5)	10 (14)	19 (9)
Weight loss	1 (1)	4 (6)	2 (3)	14 (19)	20 (9)

CONCLUSIONS

- Treatment with 30, 50, and 70 mg/d LDX significantly improved CPRS ADHD Index scores in children aged 6 to 12 years with ADHD compared with placebo at all time points measured (10 AM, 2 PM, and 6 PM). Significant improvements were also observed for CPRS total scores
- Improvements in CPRS ADHD Index scores were observed at the first postbaseline week and persisted throughout the study
- Significant improvement in CPRS ADHD Index scores compared with placebo occurred in both the baseline CGI-S 3 to 4 (mildly to moderately ill) group and the baseline CGI-S 5 to 7 (markedly to extremely ill) group
- LDX was generally well tolerated, with most AEs being mild to moderate in nature

REFERENCES

- Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366:237-248.
- Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. *JAMA*. 1998;279:1100-1107.
- Findling RL. Parental perceptions of the duration of effectiveness of prescription medications used to treat attention-deficit/hyperactivity disorder in children and adolescents. Poster presented at: 20th Annual U.S. Psychiatric and Mental Health Congress; October 11-14, 2007; Orlando, FL.
- Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose parallel-group study. *Clin Ther*. 2007;29:450-463.
- Biederman J, Boellner SW, Childress A, Lopez F, Krishnan S, Hodgkins P. Improvements in symptoms of attention-deficit/hyperactivity disorder in school-aged children with lisdexamfetamine (NRP104) and mixed amphetamine salts, extended-release versus placebo. Abstract presented at: 159th Annual Meeting of the American Psychiatric Association; May 25-28, 2006; Toronto, Ontario, Canada.
- Conners CK. *Conners' Rating Scales-Revised Technical Manual*. North Tonawanda, NY: Multi-Health Systems Inc; 2001.