

# Participant-Perceived Quality of Life in a Long-Term, Open-Label Trial of Lisdexamfetamine Dimesylate in Adolescents With Attention-Deficit/Hyperactivity Disorder

Ann C. Childress, MD<sup>1</sup>; Andrew J. Cutler, MD<sup>2</sup>; Keith Saylor, PhD<sup>3</sup>; Maria Gasior, MD, PhD<sup>4</sup>; Mohamed Hamdani, MS<sup>4</sup>; M. Celeste Ferreira-Cornwell, PhD<sup>4</sup>; Robert L. Findling, MD, MBA<sup>5</sup>

<sup>1</sup>Center for Psychiatry and Behavioral Medicine Inc, Las Vegas, NV; <sup>2</sup>Florida Clinical Research Center, LLC, Bradenton, FL; <sup>3</sup>NeuroScience, Inc, Herndon, VA;

<sup>4</sup>Shire Development Inc., Wayne, PA; <sup>5</sup>University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH

## ABSTRACT

**Objective:** To assess long-term quality of life (QOL), effectiveness, and safety of lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc.) in adolescents with ADHD.

**Methods:** Adolescents with ADHD treated ≥3 weeks in a prior placebo-controlled, 4-week study entered an open-label study. After dose optimization (30-70mg/d LDX over 4 weeks), treatment was maintained 48 additional weeks. ADHD Rating Scale IV (ADHD-RS-IV) assessed effectiveness; Youth QOL-Research Version (YQOL-R) assessed change from baseline (of prior study) in YQOL at week 52 (study completers only), at endpoint (last available assessment for all treated); and post hoc for noncompleters at last available assessment. Safety measures included TEAEs.

**Results:** Of 269 enrolled, 265 were assessed; 113 (42.0%) were discontinued (18 [6.7%] due to AEs). ADHD-RS-IV total scores improved from baseline to endpoint ( $P<.001$ ). Baseline mean (SD) YQOL-R total perceptual score was 79.8 (11.28); improving by 5.0 (9.52) at week 52, 3.9 (9.73) at endpoint ( $P<.001$ ). Mean YQOL-R domain scores improved from baseline at week-52 and endpoint ( $P<.027$  for all). TEAEs (mostly mild to moderate in 230/265 [86.8%]) reported by ≥10% were upper respiratory tract infection (21.9%), decreased appetite (21.1%), headache (20.8%), weight decreased (16.2%), irritability (12.5%), and insomnia (12.1%).

**Conclusions:** QOL perception and ADHD symptoms improved from baseline during LDX treatment in adolescents with ADHD. LDX exhibited a safety profile similar to other stimulants.

## INTRODUCTION

- Prevalence in the United States of parent-reported ADHD diagnosis was 11.2% to 13.6% for those aged 11-17 years<sup>1</sup>
- Untreated vs treated adolescents with ADHD had higher rates of academic failure, emotional problems, delinquency, teenage pregnancy, sexually transmitted infections, earlier onset of substance abuse, and poor driving records<sup>2</sup>
- Stimulants are commonly prescribed for adolescents with ADHD and are considered efficacious<sup>3-5</sup>
- Impact of ADHD and subsequent patient-reported treatment measures such as quality of life (QOL) may be important in the management of ADHD
- During a previously reported randomized, double-blind, placebo-controlled trial<sup>6</sup> of lisdexamfetamine dimesylate (LDX), a long-acting prodrug stimulant indicated for ADHD in children, adolescents, and adults, improvements in participant-perceived QOL based on the Youth QOL-Research Version (YQOL-R) were not noted
- This result was possibly due to the short study duration (4 weeks) and baseline scores that did not indicate poor overall QOL

## OBJECTIVES

- To assess long-term treatment effects of LDX on QOL in adolescents with ADHD, change in participant-perceived QOL was assessed, as well as effectiveness and safety in a long-term (up to 1 year) trial of adolescents with at least moderately severe ADHD symptoms at baseline (of antecedent study)

## METHODS

### Overall Design

- An open-label, multicenter, single-arm extension of a 4-week, randomized, parallel-group, double-blind, placebo-controlled, multicenter study was conducted
- Adolescents (aged 13-17 years) who participated in the antecedent study and met eligibility criteria were evaluated for entry in the present long-term study

### Key Inclusion and Exclusion Criteria

- Eligibility criteria included participants (aged 13-17 years) with a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score ≥28 who completed ≥3 weeks of LDX treatment in the antecedent study and were not terminated because of noncompliance, AEs, or other safety reasons that would preclude continued treatment
- Exclusion criteria included comorbid psychiatric disorders; concurrent chronic or acute or unstable medical condition; serious cardiac abnormalities; and hypersensitivity, intolerance, or nonresponse to amphetamine

### Study Design

- The current study was designed to assess effectiveness and safety and QOL in adolescents with ADHD receiving LDX as a daily morning dose (30-70 mg/d)
- During the 4-week dose-optimization phase, participants were evaluated every 7 days (±2 days) for dose titration
  - Participants enrolled from the antecedent study were initiated at LDX 30 mg/d and titrated (in 20-mg/d increments) weekly to an optimal dose (30-70 mg/d based on investigator's clinical judgment)
- During the maintenance phase (48 additional weeks), evaluations occurred every 28 days (±5 days) and optimized LDX dose was continued or adjusted
- Efficacy was assessed with comparisons to baseline of the antecedent study

### Efficacy Measures

#### Primary Effectiveness Measure

- Primary efficacy endpoint: change from baseline in the ADHD-RS-IV total score at endpoint (ie, last available assessment for each participant); similar to last observation carried forward (LOCF)/early termination (ET)

- ADHD-RS-IV scores were also assessed for all postbaseline visits, including week-52 assessment (ie, last study visit; study completers)

#### Secondary Effectiveness Measures

##### CGI

- Clinical Global Impressions-Severity (CGI-S) assessed baseline global illness severity based on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill)
- CGI-Improvement (CGI-I) evaluated global improvement over time (weeks 1 to 52) vs baseline based on a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse)

##### YQOL-R

- The YQOL-R, a participant-completed, 56-item generic instrument for adolescents with physical/psychiatric disabilities, but not specifically validated for ADHD,<sup>7,8</sup> measured QOL for the overall LDX group
- This instrument consists of contextual (potentially verifiable by others) and perceptual (known only to participants) questions, with perceptual items data presented here
- An overall perceptual score comprises 4 domain scores that include the following:
  - Self (assessing adolescents' sense of self)
  - Relationships (assessing family and peer relationships)
  - Environment (assessing engagement and participation in life activities)
  - General (assessing overall enjoyment and satisfaction with life)

- YQOL-R raw scores are each transformed to a 100-point scale to aid interpretation; higher scores indicated better QOL

- YQOL data were assessed at baseline (of antecedent study), week 28, week 52 (for study completers), and at endpoint, which included both completers (week 52) and ET visit for noncompleters of the present study

### Post Hoc Analyses

- Participants were classified as those having "poor" baseline YQOL-R (≥1 SD below study population mean) vs all others
- YQOL-R was examined for noncompleters of the present study
- YQOL-R results were examined to compare those for poor baseline QOL vs all others, and for completers vs noncompleters
- These analyses were done because:
  - A ceiling effect from those with normal YQOL-R scores at baseline could mask improvements in those with poor baseline QOL
  - Endpoint analysis that included both completers and noncompleters could conceal any signal that failure to improve QOL contributed to the decision to discontinue
  - ADHD-RS-IV scores were also analyzed for those with poor QOL at baseline vs all others, and for completers vs noncompleters
- For these post hoc analyses, only descriptive statistics are provided

### Safety Measures

- Safety data were previously reported<sup>6</sup> including:
  - AEs and vital signs evaluated at all study visits
  - 12-lead ECG evaluated at weeks 12, 24, 36, and 52/endpoint/ET
  - Physical examinations at week 52/endpoint/ET
  - Laboratory evaluations at week 20 and week 52/endpoint/ET
- All safety measures were assessed at last visit of the antecedent study (also entry visit of the present study)

## RESULTS

### Demographics and Baseline Characteristics

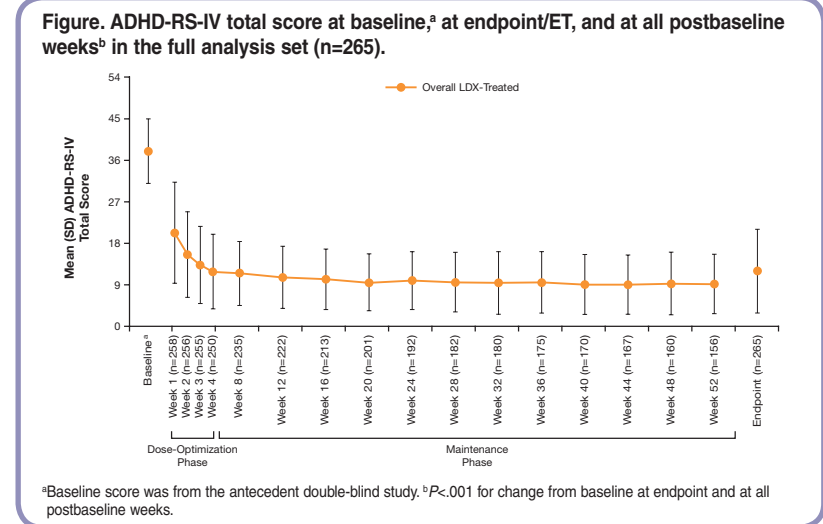
- Overall, 310 participants were included in the safety population (of the antecedent study)
- In the present study, of 269 participants enrolled, 113 (42.0%) were discontinued (18/269 [6.7%] and 15/265 [5.7%] because of AEs and TEAEs, respectively); 156 (58.0%) were completers; 265 (98.5%) included in safety/efficacy populations
- Majority of the safety population was male (187 [70.6%]), white (211 [79.6%]), and non-Hispanic (229 [86.4%])

- At baseline, the majority of the safety population was moderately or markedly ill (252/265 [95.1%]) based on CGI-S ratings

### Effectiveness

#### Primary Effectiveness Measure

- ADHD-RS-IV total score changes from baseline were significantly improved at endpoint/ET (primary efficacy endpoint;  $P<.001$ ) and at all postbaseline weeks starting at week 1 ( $P<.001$ ) (Figure)



### Secondary Effectiveness Measure

- The percentage of participants improved (CGI-I rating of 1 [very much improved] or 2 [much improved]) with LDX was 91.2% at week 4 (dose-optimization phase) and 87.2% at endpoint/ET
- With LDX treatment, mean (SD) CGI-I score at endpoint/ET was 1.6 (0.86)

### QOL

- At all weeks assessed, YQOL-R total transformed perceptual scores ( $P<.001$  for each vs baseline) and domain scores ( $P<.027$ ) improved from baseline with LDX (Table 1)

Table 1. YQOL-R Transformed <sup>a</sup> Total and Domain Scores and Change From Baseline <sup>b</sup> Scores							
Variables	Visit	Observed Value		Change From Baseline Score		P Value <sup>c</sup>	
		n	Mean (SD)	n	Mean (SD)		
		<b>YQOL-R Transformed Total Perceptual Score</b>					
	Baseline	264	79.8 (11.28)	–	–	–	
	Week 28	181	84.6 (9.36)	180	4.6 (9.31)	<.001	
	Endpoint/ET	238	83.9 (11.00)	237	3.9 (9.73)	<.001	
<b>YQOL-R Transformed Domain Scores</b>	<b>Self</b>	Baseline	264	68.3 (10.77)	–	–	–
		Week 28	181	74.5 (9.07)	180	6.0 (9.61)	<.001
		Endpoint/ET	238	74.2 (9.77)	237	5.7 (10.37)	<.001
	<b>Relationship</b>	Baseline	264	81.0 (13.77)	–	–	–
		Week 28	181	85.8 (12.28)	180	4.6 (12.12)	<.001
		Endpoint/ET	238	84.8 (13.21)	237	3.7 (11.85)	<.001
	<b>Environment</b>	Baseline	264	82.7 (12.64)	–	–	–
		Week 28	181	88.2 (10.16)	180	5.0 (10.36)	<.001
		Endpoint/ET	238	87.2 (12.22)	237	4.1 (10.68)	<.001
	<b>General</b>	Baseline	264	87.1 (15.99)	–	–	–
		Week 28	181	90.0 (13.23)	180	2.9 (15.14)	.012
		Endpoint/ET	238	89.6 (14.26)	237	2.3 (15.59)	.027

<sup>a</sup>The YQOL-R raw score is transformed to a 0- to 100-point scale to assist in result interpretation; higher scores indicate improvement in QOL. Both mean and SD values were derived from the study cohort.  
<sup>b</sup>Baseline is from the antecedent 4-week study.  
<sup>c</sup>P values are based on a 2-sided, one-sample t test.

- Participants who were stratified at baseline with poor participant-perceived QOL vs others had a greater change in YQOL-R scores at all time points assessed (Table 2)

Table 2. YQOL-R Transformed <sup>a</sup> Perceptual Scores and Change From Baseline <sup>b</sup> Scores, Stratified by Participant-Perceived QOL at Baseline										
Variables	Visit	Stratification YQOL-R Scores at Baseline								
		Poor QOL <sup>c</sup>			Others <sup>d</sup>					
		Observed Value	Change From Baseline Score	Observed Value	Change From Baseline Score					
<b>YQOL-R Transformed Total Perceptual Score</b>	Baseline	32	57.6 (9.84)	–	–	232	82.8 (7.38)	–	–	
	Week 28	20	75.2 (10.63)	20	17.6 (9.51)	160	85.9 (8.49)	160	3.0 (7.93)	
	Week 52	17	70.9 (14.24)	17	14.7 (11.16)	136	86.7 (7.89)	136	3.8 (8.59)	
	Endpoint/ET	26	70.0 (15.29)	26	12.5 (13.02)	211	85.6 (9.03)	211	2.9 (8.72)	
<b>YQOL-R Transformed Domain Scores</b>	<b>Self</b>	Baseline	32	53.6 (10.96)	–	–	232	70.4 (9.05)	–	–
		Endpoint/ET	26	63.7 (11.77)	26	9.8 (13.55)	211	75.5 (8.72)	211	5.1 (9.83)
	<b>Relationship</b>	Baseline	32	58.0 (16.11)	–	–	232	84.2 (9.89)	–	–
		Endpoint/ET	26	69.0 (17.73)	26	11.4 (16.43)	211	86.8 (11.16)	211	2.7 (10.83)
<b>Environment</b>	Baseline	32	62.2 (14.15)	–	–	232	85.5 (9.44)	–	–	
	Endpoint/ET	26	72.8 (16.62)	26	11.4 (12.63)	211	88.9 (10.33)	211	3.3 (10.09)	
<b>General</b>	Baseline	32	56.6 (17.79)	–	–	232	91.3 (10.10)	–	–	
	Endpoint/ET	26	74.4 (22.45)	26	17.6 (22.26)	211	91.4 (11.73)	211	0.4 (13.48)	

<sup>a</sup>The YQOL-R raw score is transformed to a 0- to 100-point scale to assist in result interpretation; higher scores indicate improvement in QOL. Both mean and SD values were derived from the study cohort.  
<sup>b</sup>Baseline is from the antecedent 4-week study.  
<sup>c</sup>Poor QOL = participants with YQOL-R scores ≤ (mean – 1SD).  
<sup>d</sup>Others = participants with YQOL-R scores > (mean – 1SD).

- Mean (SD) ADHD-RS-IV total scores at baseline, stratified by baseline participant-perceived QOL, was 38.1 (6.57) for those with poor baseline YQOL-R scores and for others was 38.1 (7.06)
  - Change scores at endpoint were -25.0 (8.72) and -26.5 (9.89), respectively
- Participants who were study completers vs noncompleters were noted to have greater numerical improvements in YQOL-R scores at endpoint from baseline (Table 3)

Table 3. YQOL-R Transformed <sup>a</sup> Perceptual Scores and Change From Baseline <sup>b</sup> Scores, as Stratified by Completers <sup>c</sup> vs Noncompleters <sup>d</sup> of Present Study											
Variables	Visit	Study Completers				Study Noncompleters					
		Observed Value		Change From Baseline Score		Observed Value		Change From Baseline Score			
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
<b>YQOL-R Transformed Total Perceptual Score</b>	Baseline	155	79.9 (11.66)	–	–	109	79.6 (10.76)	–	–		
	Week 52	154	84.9 (10.04)	153	5.0 (9.52) <sup>e</sup>	Endpoint/ET	82	82.1 (12.55)	82	1.9 (9.64)	
<b>YQOL-R Transformed Domain Scores</b>	<b>Self</b>	Baseline	155	68.4 (11.24)	–	–	Baseline	109	68.3 (10.12)	–	–
		Week 52	154	74.6 (9.45)	153	6.2 (10.38) <sup>e</sup>	Endpoint/ET	82	73.6 (10.32)	82	4.9 (10.18)
	<b>Relationship</b>	Baseline	155	81.1 (14.45)	–	–	Baseline	109	80.9 (12.79)	–	–
		Week 52	154	85.8 (12.59)	153	4.7 (11.58) <sup>e</sup>	Endpoint/ET	82	83.0 (14.27)	82	1.8 (12.03)
	<b>Environment</b>	Baseline	155	83.3 (12.93)	–	–	Baseline	109	81.8 (12.22)	–	–
		Week 52	154	88.4 (11.03)	153	5.1 (10.42) <sup>e</sup>	Endpoint/ET	82	84.9 (14.02)	82	2.4 (10.86)
<b>General</b>	Baseline	155	86.8 (16.06)	–	–	Baseline	109	87.5 (15.95)	–	–	
	Week 52	154	90.9 (12.00)	153	4.0 (14.47) <sup>e</sup>	Endpoint/ET	82	86.9 (17.65)	82	-1.4 (16.64)	

<sup>a</sup>The YQOL-R raw score is transformed to a 0- to 100-point scale to assist in result interpretation; higher scores indicate improvement in QOL.  
<sup>b</sup>Baseline is from the antecedent 4-week study.  
<sup>c</sup>Study completers = participants who completed the present study.  
<sup>d</sup>Study noncompleters = participants who did not complete the present study.  
<sup>e</sup> $P<.001$  based on a 2-sided, one-sample t test.

- At baseline, the mean (SD) ADHD-RS-IV total score for study completers (n=156) was 37.5 (6.72) and for noncompleters (n=109) was 38.8 (7.35)
  - Change scores were -28.6 (8.53) at week 52 ( $P<.001$ ) and -22.9 (10.45) at endpoint/ET

**Dr Childress** has the following disclosures: Shire Pharmaceuticals, Inc. – Consultant, Speaker, Research Support; Novartis Pharmaceutical Corporation – Consultant, Speaker, Research Support; Bristol-Myers Squibb – Speaker, Research Support; Somerset Pharmaceuticals, Inc. – Research Support; NextWave Pharmaceuticals – Consultant, Research Support; Abbott Laboratories – Research Support; Lilly USA, LLC – Research Support; Ortho-McNeil Janssen Scientific Affairs – Research Support; Johnson & Johnson Pharmaceutical Research & Development, LLC – Research Support; GlaxoSmithKline – Speaker, Sponsor Inc. – Research Support; Otsuka – Research Support. **Dr Cutler** receives/receives research grant support from Abbott, Adrenex, AstraZeneca, Bristol-Myers Squibb, Cephalon, Jazz Pharmaceuticals, Johnson & Johnson PRD, Lilly, McNeil Pharmaceuticals, Memory Pharmaceuticals, Merck, Novartis, Ortho-McNeil, Otsuka, Pfizer, Sanofi (incl. Sanofi-Synthelabo, Sanofi-Aventis), Shionogi, Sepracor, Shire, Solway, Supernus, Targacept; is/has been a consultant to Abbott, Adrenex, AstraZeneca, Bristol-Myers Squibb, Cephalon, Johnson & Johnson PRD, Lilly, Merck, Novartis, Ortho-McNeil, Otsuka, Pfizer, Shionogi, Sepracor, Shire, Supernus, Targacept; and is/has been a speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, Lilly, Novartis, Ortho-McNeil, Otsuka, Pfizer, Shionogi, Sepracor, and Shire. **Dr Saylor** is/has been a consultant for Eli Lilly, Supernus Pharmaceuticals, and Company, and Shire; receives/receives research support from Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Otsuka, Shire, and Supernus. **Dr Gasior** is an employee of Shire and holds stock and/or stock options in Shire. **Mr Hamdani** is an employee of Shire and holds stock and/or stock options in Shire. **Dr Ferreira-Cornwell** is an employee of Shire and holds stock and/or stock options in Shire. **Dr Findling** has 1) received grant/research support from Abbott, Adrenex, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, Merck, Neuropharm, Otsuka, Pfizer, Rhoads Pharmaceuticals, Schering-Plough, Shire, Supernus, and Wyeth; 2) served as a consultant to Abbott, Adrenex, Alkerm, AstraZeneca, Biogen, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KermPharm, Lilly, Lundbeck, Merck, Novartis, Noven, Organon, Otsuka, Pfizer, Sanofi Aventis, Schering-Plough, Seaside Therapeutics, Sepracor, Shire, Solway, Sunovion, Supernus, Targacept, Valldis, and Wyeth; and 3) served as a speaker for Bristol-Myers Squibb, Johnson & Johnson, and Shire.

### Safety

- In the safety population (n=265), 15 (5.7%) participants had 19 TEAEs that led to discontinuation; 10 (3.8%) had serious TEAEs
- 230 (86.8%) participants experienced TEAEs (Table 4); most TEAEs were mild to moderate in severity

Table 4. TEAEs With an Incidence ≥5% in the Safety Population (n=265)	
Preferred Terminology (MedDRA version 11.1)	LDX Overall, n (%) (n=265)
Any TEAE	230 (86.8)
Decreased appetite	56 (21.1)
Dizziness	14 (5.3)
Dry mouth	14 (5.3)
Headache	55 (20.8)
Influenza	18 (6.8)