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ORIGINAL RESEARCH ARTICLE

A Post Hoc Comparison of the Effects of Lisdexamfetamine Dimesylate and Osmotic-Release Oral System Methylphenidate on Symptoms of Attention-Deficit Hyperactivity Disorder in Children and Adolescents

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Abstract
Introduction There are limited head-to-head data comparing the efficacy of long-acting amfetamine- and methylphenidate-based psychostimulants as treatments for individuals with attention-deficit hyperactivity disorder (ADHD). This post hoc analysis provides the first parallel-group comparison of the effect of lisdexamfetamine dimesylate (lisdexamfetamine) and osmotic-release oral system methylphenidate (OROS-MPH) on symptoms of ADHD in children and adolescents.
Study Design This was a post hoc analysis of a randomized, double-blind, parallel-group, dose-optimized, placebo-controlled, phase III study.
Setting The phase III study was carried out in 48 centres across ten European countries.
Patients The phase III study enrolled children and adolescents (aged 6–17 years) who met *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision* criteria for a primary diagnosis of ADHD and who had a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score of 28 or higher.
Intervention Eligible patients were randomized (1:1:1) to receive a once-daily, optimized dose of lisdexamfetamine (30, 50 or 70 mg/day), placebo or OROS-MPH (18, 36 or 54 mg/day) for 7 weeks.
Main Outcome Measures In this post hoc analysis, efficacy was assessed using the ADHD-RS-IV and Clinical Global Impressions-Improvement (CGI-I) scale. Responders were defined as those achieving at least a 30 % reduction from baseline in ADHD-RS-IV total score and a CGI-I score of 1 (very much improved) or 2 (much improved). The proportion of patients achieving an ADHD-RS-IV total score less than or equal to the mean for their age (based on normative data) was also determined.

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Endpoint was the last on-treatment visit with a valid assessment. Safety assessments included treatment-emergent adverse events (TEAEs) and vital signs.

Results Of the 336 patients randomized, 332 were included in the safety population, 317 were included in the full analysis set and 196 completed the study. The mean (standard deviation) ADHD-RS-IV total score at baseline was 40.7 (7.31) for lisdexamfetamine, 41.0 (7.14) for placebo and 40.5 (6.72) for OROS-MPH. The least-squares (LS) mean change (standard error) in ADHD-RS-IV total score from baseline to endpoint was −24.3 (1.16) for lisdexamfetamine, −5.7 (1.13) for placebo and −18.7 (1.14) for OROS-MPH. The difference between lisdexamfetamine and OROS-MPH in LS mean change (95 % confidence interval [CI]) in ADHD-RS-IV total score from baseline to endpoint was statistically significant in favour of lisdexamfetamine (−5.6 [−8.4 to −2.7]; $p < 0.001$). The difference between lisdexamfetamine and OROS-MPH in the percentage of patients (95 % CI) with a CGI-I score of 1 or 2 at endpoint was 17.4 (5.0–29.8; $p < 0.05$; number needed to treat [NNT] 6), and the difference in the percentage of patients (95 % CI) achieving at least a 30 % reduction in ADHD-RS-IV total score and a CGI-I score of 1 or 2 was 18.3 (5.4–31.3; $p < 0.05$; NNT 6). The difference between lisdexamfetamine and OROS-MPH in the percentage of patients (95 % CI) with an ADHD-RS-IV total score less than or equal to the mean for their age at endpoint was 14.0 (0.6–27.4; $p = 0.050$). The overall frequency of TEAEs and the frequencies of decreased appetite, insomnia, decreased weight, nausea and anorexia TEAEs were greater in patients treated with lisdexamfetamine than in those treated with OROS-MPH, whereas headache and nasopharyngitis were more frequently reported in patients receiving OROS-MPH.

Conclusions This post hoc analysis showed that, at the doses tested, patients treated with lisdexamfetamine showed statistically significantly greater improvement in symptoms of ADHD than those receiving OROS-MPH, as assessed using the ADHD-RS-IV and CGI-I. The safety profiles of lisdexamfetamine and OROS-MPH were consistent with the known effects of stimulant medications.

1 Introduction

Amfetamine- and methylphenidate-based stimulants are effective pharmacological treatments for individuals with attention-deficit hyperactivity disorder (ADHD), which is one of the most common neurodevelopmental disorders among school-aged children [1–3]. These pharmacotherapies have consistently been found to reduce the symptoms of inattention, hyperactivity and/or impulsivity, as well as the functional impairments that are associated with ADHD [4, 5].

Long-acting stimulant formulations were developed to provide extended control of ADHD symptoms throughout the day [6]. Lisdexamfetamine dimesylate (lisdexamfetamine) and osmotic-release oral system methylphenidate (OROS-MPH) were both designed to facilitate once-daily dosing. Lisdexamfetamine is the first long-acting prodrug stimulant. It is metabolized primarily in the bloodstream after absorption from the gastrointestinal tract, yielding therapeutically active *d*-amfetamine [7, 8]. OROS-MPH capsules deliver the active drug, racemic methylphenidate, in the gastrointestinal tract in a biphasic manner [9]. Therapeutic benefits have been shown to persist for 13–14 h with lisdexamfetamine [10, 11] and 12.5 h [12] with OROS-MPH. A recent meta-analysis provided indirect evidence that stimulants based on amfetamine may have slightly greater efficacy than those based on methylphenidate in reducing symptoms of ADHD in children and adolescents [1]. However, to date, no published, parallel-group studies have directly compared the efficacy of lisdexamfetamine and OROS-MPH.

Study SPD489-325 was a European, 7-week, phase III, randomized study that evaluated the efficacy and safety of lisdexamfetamine in children and adolescents with ADHD [13]. The study utilised a three-arm design that included a placebo control and an active reference arm, as required by the European Medicines Agency [14]. Lisdexamfetamine and the active comparator, OROS-MPH, were shown to be more effective than placebo in reducing symptoms of ADHD, as assessed using the ADHD Rating Scale IV (ADHD-RS-IV) and the Clinical Global Impressions-Improvement scale (CGI-I) [13]. Improvements in ADHD-RS-IV total score from baseline to endpoint were associated with large effect sizes for lisdexamfetamine (1.80) and OROS-MPH (1.26), indicating robust treatment responses. Although study SPD489-325 was neither planned nor powered for a primary statistical comparison between the two active treatment arms, the present post hoc analysis was conducted to compare the effect of lisdexamfetamine and OROS-MPH on symptoms of ADHD in children and adolescents.

2 Methods

The experimental procedures used in this randomized, double-blind, parallel-group, dose-optimized, placebo-controlled, phase III study have been described previously [13]. The study protocol (ClinicalTrials.gov ID: NCT00763971) was approved by an independent ethics committee/institutional review board and regulatory agency in each centre (as appropriate) before study initiation. The study was conducted in accordance with current international and local applicable regulations, and written

informed consent was obtained from each participant or their legally appointed representative.

2.1 Patients and Study Design

The study was conducted in 48 centres across ten European countries and enrolled male and female children (aged 6–12 years) and adolescents (aged 13–17 years) who met the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision* (DSM-IV-TR) criteria for a primary diagnosis of ADHD. Patients were required to have an investigator-rated, baseline ADHD-RS-IV total score of 28 or higher. Enrolment was managed so that adolescents (aged 13–17 years) accounted for approximately 25 % of the study population.

Eligible patients completed a screening and washout period (3–42 days, depending on previous medication) and were randomized (1:1:1) to receive once-daily lisdexamfetamine, placebo or OROS-MPH. The double-blind evaluation period consisted of a 4-week dose-optimization period, followed by a 3-week dose-maintenance period, and a 1-week washout and safety follow-up.

Three doses of lisdexamfetamine (30, 50 and 70 mg/day) and OROS-MPH (18, 36 and 54 mg/day) were used in this study. OROS-MPH was administered according to European regulations (maximum licensed dose, 54 mg/day) [15]. Dosing began at approximately 07:00 h on the morning after completion of the baseline visit. Patients initially received lisdexamfetamine 30 mg/day, placebo or OROS-MPH 18 mg/day. If an acceptable response to treatment was not achieved, adjustments to higher doses were to be made at weekly intervals during the dose-optimization period. An acceptable response was defined as a reduction of at least 30 % in ADHD-RS-IV total score from baseline and a CGI-I score of 1 (very much improved) or 2 (much improved), with tolerable adverse effects. One dose reduction was permitted during the optimization period if a patient experienced an intolerable adverse effect. Doses could not be modified after visit 3; patients unable to tolerate the study drug after visit 3 were withdrawn from the study. Patients achieving an acceptable response continued on their optimal dose for the remainder of the double-blind evaluation period.

2.2 Efficacy Outcomes

The primary efficacy outcome measure of SPD489-325 was the investigator-rated ADHD-RS-IV total score, which was assessed at baseline and at each weekly study visit thereafter. The key secondary efficacy outcome measure was the investigator-rated CGI-I, which was used to assess global improvement at each weekly post-baseline visit. CGI-I scores were categorized as 'improved' (CGI-I of 1 or 2) or 'not improved' (all other scores). A clinically significant response was defined *a priori* as at least a 30 % reduction from baseline in ADHD-RS-IV total score and a CGI-I score of 1 or 2 [16]. The proportions of patients achieving an ADHD-RS-IV total score less than or equal to the mean for their age, based on normative data, were also determined.

2.3 Safety Outcomes

Safety outcomes were assessed for the safety population, defined as all patients who took at least one dose of study drug. Safety assessments included, but were not limited to, evaluation of treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs and electrocardiograms, as well as physical examinations. An adverse event was defined as treatment emergent if the event started or worsened in the period between the first dose of study drug and the third day (inclusive) following cessation of treatment. TEAEs were coded using the current version of the *Medical Dictionary for Regulatory Activities* (version 11.1) and summarized by system organ class, preferred term and treatment group for the number and proportion reporting the event.

2.4 Statistical Analyses

Although not pre-specified in the statistical analysis plan for SPD489-325, a post hoc statistical analysis was conducted to compare the effect of lisdexamfetamine and OROS-MPH on symptoms of ADHD, as assessed using the ADHD-RS-IV and CGI-I.

Efficacy outcomes were assessed for the full analysis set, defined as all patients who were randomized and took at least one dose of study drug. Patients from one site ($n = 15$) were excluded from the full analysis set as a consequence of violations of Good Clinical Practice. The change from baseline in the ADHD-RS-IV total score was analysed using an analysis of covariance (ANCOVA) model. Least squares (LS) means and p values were based on type III sum of squares from the ANCOVA model for the change from baseline, including treatment group (effect of interest), country and age group (randomization blocking factors) and the corresponding baseline score (covariate). Effect sizes based on the change in ADHD-RS-IV total score from baseline were calculated as the difference in LS mean score between treatment arms, divided by the root mean square error obtained from the ANCOVA model. The number and percentage of patients categorized as 'improved' (CGI-I of 1 or 2) at each post-baseline study visit and at endpoint was summarized by treatment group, and each active treatment group compared with placebo using a Cochran–Mantel–Haenszel test stratified by

country and age group. The percentage of patients meeting each responder criterion at endpoint was also analysed using a Cochran–Mantel–Haenszel test stratified by country and age group. The number needed to treat (NNT) was calculated as the inverse of the difference in proportions between the treatment groups. The endpoint for all outcome measures was the last on-treatment, post-baseline visit with a valid assessment.

Safety data are summarized for the safety population using descriptive statistics; no statistical tests were performed.

3 Results

3.1 Patients

Of the 336 patients who were randomized, 332 were included in the safety population (lisdexamfetamine, $n = 111$; placebo, $n = 110$; OROS-MPH, $n = 111$), 317 were included in the full analysis set (lisdexamfetamine, $n = 104$; placebo, $n = 106$; OROS-MPH, $n = 107$) and 196 completed the study (lisdexamfetamine, $n = 80$; placebo, $n = 42$; OROS-MPH, $n = 74$). Patient demographics and baseline characteristics were similar across treatment groups (Table 1).

Table 1 Baseline characteristics and demographic data (safety population)[a]

Characteristic	LDX ($n = 111$)	Placebo ($n = 110$)	OROS-MPH ($n = 111$)
Age, years, mean (SD)	10.9 (2.9)	11.0 (2.8)	10.9 (2.6)
Sex, male, *n* (%)	87 (78.4)	91 (82.7)	90 (81.1)
Race, white, *n* (%)	107 (96.4)	108 (98.2)	107 (96.4)
BMI, kg/m^2, mean (SD)	19.3 (3.7)	19.0 (3.3)	19.1 (3.2)
Baseline ADHD-RS-IV total score, mean (SD)[b]	41.0 (7.3)	41.2 (7.2)	40.4 (6.8)
ADHD subtype, *n* (%)[c]			
Predominantly inattentive	23 (20.7)	16 (14.5)	14 (12.7)
Predominantly hyperactive-impulsive	2 (1.8)	7 (6.4)	1 (0.9)
Combined	86 (77.5)	87 (79.1)	95 (86.4)
Concomitant psychiatric diagnosis, *n* (%)[d]			
Any	19 (17.1)	20 (18.2)	29 (26.1)
Oppositional defiant disorder	8 (7.2)	8 (7.3)	10 (9.0)

[a] Demographic and baseline characteristics have previously been reported in detail [13]

[b] Five patients had no baseline ADHD-RS-IV total score

[c] One patient in the OROS-MPH group was not evaluated for ADHD subtype. Percentages are based on the number of patients in each treatment group

[d] Patients with at least one ongoing definite psychiatric diagnosis based on the Kiddie Schedule for Affective Disorders and Schizophrenia for school age children—present and lifetime diagnostic interview. A patient could have more than one diagnosis

ADHD attention-deficit hyperactivity disorder; *ADHD-RS-IV* ADHD Rating Scale IV, *BMI* body mass index, *LDX* lisdexamfetamine dimesylate, *OROS-MPH* osmotic-release oral system methylphenidate, *SD* standard deviation

3.2 Efficacy Outcomes

At baseline, mean ADHD-RS-IV total scores (standard deviation [SD]) were similar across treatment groups (lisdexamfetamine 40.7 [7.31]; placebo 41.0 [7.14]; OROS-MPH 40.5 [6.72]) [13]. The LS mean change (standard error) in ADHD-RS-IV total score from baseline to endpoint was −24.3 (1.16) for lisdexamfetamine, −5.7 (1.13) for placebo and −18.7 (1.14) for OROS-MPH [13]. The difference (active drug minus placebo) in the LS mean change in ADHD-RS-IV total score was statistically significant for lisdexamfetamine ($p < 0.001$; effect size 1.80) and OROS-MPH ($p < 0.001$; effect size 1.26) (Table 2) [13]. The percentage of patients (95 % CI) with a CGI-I score of 1 or 2 at endpoint was 78.0 % (69.9–86.1) for lisdexamfetamine, 14.4 % (7.7–21.2) for placebo and 60.6 % (51.2–70.0) for OROS-MPH. The difference (active drug minus placebo) in the percentage of patients with a CGI-I score of 1 or 2 was statistically significant for lisdexamfetamine ($p < 0.001$; NNT 2) and OROS-MPH ($p < 0.001$; NNT 3) (Table 2) [13].

A clinically significant response to treatment was defined *a priori* as at least a 30 % reduction from baseline in ADHD-RS-IV total score and a CGI-I score of 1 or 2. At endpoint, the percentage of patients (95 % CI) categorized as responders was 74.2 % (65.5–82.9) for lisdexamfetamine, 10.7 % (4.7–16.6) for placebo and 55.9 % (46.2–65.5) for OROS-MPH. The difference (active drug minus placebo) in the percentage of responders was statistically significant for lisdexamfetamine ($p < 0.001$; NNT 2) and OROS-MPH ($p < 0.001$; NNT 3) (Table 2).

Responders were also defined *a posteriori* as those achieving an ADHD-RS-IV total score less than or equal to the mean for their age. At endpoint, the percentage of patients (95 % CI) meeting this second responder criterion was 65.0 % (55.7–74.3) for lisdexamfetamine, 14.4 % (7.7–21.2) for placebo and 51.0 % (41.4–60.6) for OROS-MPH. The difference (active drug minus placebo) in the percentage of responders was statistically significant for lisdexamfetamine ($p < 0.001$; NNT 2) and OROS-MPH ($p < 0.001$; NNT 3) (Table 2).

The post hoc analysis showed a statistically significant difference between lisdexamfetamine and OROS-MPH, in favour of lisdexamfetamine, in the LS mean change in

Table 2 Summary of efficacy outcomes for lisdexamfetamine dimesylate and osmotic-release oral system methylphenidate in children and adolescents with attention-deficit hyperactivity disorder (full analysis set)

	LDX minus placebo	OROS-MPH minus placebo	LDX minus OROS-MPH
ADHD-RS-IV[a]			
Difference in LS mean change in ADHD-RS-IV total score from baseline to endpoint	−18.6	−13.0	−5.6
95 % CI	−21.5 to −15.7	−15.9 to −10.2	−8.4 to −2.7
p value	<0.001	<0.001	<0.001
Effect size	1.80	1.26	0.54
CGI-I			
Difference in percentage of patients 'improved' at endpoint (%)[b]	63.6	46.2	17.4
95 % CI	53.0–74.1	34.6–57.7	5.0–29.8
p value	<0.001	<0.001	<0.05
NNT	2	3	6
Responders (≥30 % reduction from baseline in ADHD-RS-IV total score and CGI-I of 1 or 2)			
Difference in percentage of responders at endpoint (%)	63.5	45.2	18.3
95 % CI	53.0–74.1	33.9–56.5	5.4–31.3
p value	<0.001	<0.001	<0.05
NNT	2	3	6
Responders (ADHD-RS-IV total score ≤ mean for age)[c]			
Difference in percentage of responders at endpoint (%)	50.6	36.5	14.0
95 % CI	39.0–62.1	24.8–48.3	0.6–27.4
p value	<0.001	<0.001	0.050
NNT	2	3	8

p values are based on the difference between active drug and placebo (predefined comparison) and the difference between LDX and OROS-MPH (post hoc comparison). Data are provided for the full analysis set: LDX ($n = 104$); placebo ($n = 106$); OROS-MPH ($n = 107$). All percentages are based on the number of patients with data at that visit in each treatment group. Endpoint was the last on-treatment, post-baseline visit with a non-missing assessment

[a] A decrease from baseline in the ADHD-RS-IV total score indicates an improvement in ADHD symptoms

[b] Improvement was defined as a CGI-I score of 1 (very much improved) or 2 (much improved)

[c] Responder analysis based on normative data

ADHD attention-deficit hyperactivity disorder; *ADHD-RS-IV* ADHD Rating Scale IV, *CGI-I* Clinical Global Impressions-Improvement, *CI* confidence interval, *LDX* lisdexamfetamine dimesylate, *LS* least squares, *NNT* number needed to treat, *OROS-MPH* osmotic-release oral system methylphenidate

ADHD-RS-IV total score from baseline to endpoint ($p < 0.001$; effect size 0.54), in the percentage of patients with a CGI-I score of 1 or 2 at endpoint ($p < 0.05$; NNT 6) and in the percentage of patients achieving at least a 30 % reduction from baseline in ADHD-RS-IV total score and a CGI-I score of 1 or 2 at endpoint ($p < 0.05$; NNT 6) (Table 2). At endpoint, the difference between lisdexamfetamine and OROS-MPH in the percentage of patients with an ADHD-RS-IV total score less than or equal to the mean for their age was not statistically significant ($p = 0.050$; Table 2).

3.3 Safety Outcomes

Safety outcomes have been reported in detail previously [13]. Most patients in the safety population reported one or more TEAEs (Table 3). Of the TEAEs reported in at least 10 % of patients in any treatment group, those that occurred at a numerically greater frequency in the lisdexamfetamine group than in the OROS-MPH group were decreased appetite, insomnia, decreased weight, nausea and anorexia; headache and nasopharyngitis were more frequently reported in the OROS-MPH group than in the lisdexamfetamine group (Table 3). The proportion of patients reporting serious adverse events was low across all treatment groups (lisdexamfetamine 2.7 %; placebo 2.7 %; OROS-MPH 1.8 %). Few patients experienced TEAEs leading to discontinuation of study drug (lisdexamfetamine 4.5 %; placebo 3.6 %; OROS-MPH 1.8 %).

Patients treated with lisdexamfetamine and OROS-MPH reported modest increases from baseline to endpoint in mean (SD) pulse rate (lisdexamfetamine +5.5 [13.2] bpm; placebo −0.6 [10.6] bpm; OROS-MPH +3.4 [13.2] bpm), heart rate (lisdexamfetamine +5.7 [15.3] bpm; placebo −1.1 [9.6] bpm; OROS-MPH +5.0 [12.8] bpm), systolic blood pressure (lisdexamfetamine +1.0 [9.8] mmHg; placebo +1.0 [9.6] mmHg; OROS-MPH +0.3 [11.1] mmHg), and diastolic blood pressure (lisdexamfetamine +0.2 [9.6] mmHg; placebo +1.2 [8.7] mmHg; OROS-MPH +1.7 [9.9] mmHg) [13]. Changes in mean (SD) body weight from baseline to endpoint were as follows: lisdexamfetamine −2.1 [1.9] kg; placebo +0.7 [1.0] kg; OROS-MPH −1.3 [1.4] kg) [13]. Of the 47 patients (lisdexamfetamine, $n = 35$; OROS-MPH, $n = 12$) who had a potentially clinically significant decrease in weight at endpoint (defined as ≥7 % from baseline), three patients (lisdexamfetamine, $n = 2$; OROS-MPH, $n = 1$) moved from a body mass index (BMI) category of healthy weight low (BMI from 5th to 25th percentile) or healthy weight high (BMI from 25th to 85th percentile) to underweight (BMI less than the 5th percentile).

Table 3 Treatment emergent adverse effects reported by ≥5 % of patients in any treatment group (safety population)[a]

TEAE, preferred term, *n* (%)	LDX (*n* = 111)	Placebo (*n* = 110)	OROS-MPH (*n* = 111)
Any TEAE	80 (72.1)	63 (57.3)	72 (64.9)
TEAEs (≥5 % of patients in any treatment group)[b]			
Decreased appetite	28 (25.2)	3 (2.7)	17 (15.3)
Headache	16 (14.4)	22 (20.0)	22 (19.8)
Insomnia	16 (14.4)	0	9 (8.1)
Decreased weight	15 (13.5)	0	5 (4.5)
Nausea	12 (10.8)	3 (2.7)	8 (7.2)
Anorexia	12 (10.8)	2 (1.8)	6 (5.4)
Nasopharyngitis	8 (7.2)	8 (7.3)	14 (12.6)
Upper abdominal pain	8 (7.2)	6 (5.5)	9 (8.1)
Abdominal pain	6 (5.4)	6 (5.5)	4 (3.6)
Sleep disorder	6 (5.4)	1 (0.9)	2 (1.8)
Cough	3 (2.7)	0	8 (7.2)
Initial insomnia	3 (2.7)	1 (0.9)	7 (6.3)

[a] Safety outcomes have previously been reported in detail [13]

[b] TEAEs are presented in order of decreasing frequency in the LDX treatment group

LDX lisdexamfetamine dimesylate, *OROS-MPH* osmotic-release oral system methylphenidate, *TEAE* treatment-emergent adverse event

4 Discussion

In this post hoc analysis of data from a European, 7-week, phase III study (SPD489-325), children and adolescents treated with lisdexamfetamine showed statistically significantly greater improvements in ADHD-RS-IV total score and CGI-I score from baseline to endpoint than those treated with OROS-MPH. In addition, a greater proportion of patients receiving lisdexamfetamine were categorized as responders at study endpoint than those receiving OROS-MPH. These findings suggest that, at the doses tested, lisdexamfetamine produced greater improvements in the symptoms of ADHD in children and adolescents than OROS-MPH.

To date, there has only been one published parallel-group comparison of stimulant medications for the treatment of individuals with ADHD [17]. In this study, mixed amfetamine salts were found to produce significantly greater improvements in teacher ratings and CGI-I scores than short-acting methylphenidate [17]. Several crossover studies have investigated the comparative efficacies of short-acting methylphenidate- and amfetamine-based stimulants, but no consistent differences have emerged [2]. However, a meta-analysis of randomized controlled trials of both short- and long-acting formulations found that effect sizes for amfetamine-based stimulants were moderately, but statistically significantly, greater than those for methylphenidate [1]. While SPD489-325 was not prospectively designed or powered to compare the clinical profiles of the two active treatment arms, this post hoc analysis has provided the first parallel-group comparison of the efficacy of the long-acting stimulants, lisdexamfetamine and OROS-MPH. Although both treatments produced robust responses, improvements in symptoms were greater for lisdexamfetamine than for OROS-MPH.

In the present study, patients who were randomized to the lisdexamfetamine treatment group received 30, 50 or 70 mg/day. OROS-MPH was administered according to European regulations (maximum licensed dose, 54 mg/day). The study included a 3-week dose-optimization period, suggesting that the doses of lisdexamfetamine and OROS-MPH were less likely to have influenced their relative efficacy. However, it is notable that a higher proportion of patients was optimized to the highest available dose of OROS-MPH (18 mg/day, 9.9 %; 36 mg/day, 19.8 %; 54 mg/day, 53.2 %) than to the highest available dose of lisdexamfetamine (30 mg/day, 18.0 %; 50 mg/day, 29.7 %; 70 mg/day, 33.3 %) [13]. Furthermore, the proportion of patients who were discontinued from the study due to lack of efficacy was greater for OROS-MPH than for lisdexamfetamine [13]. Therefore, it is possible that treatment responses were dose limited in more patients receiving OROS-MPH than in those receiving lisdexamfetamine.

There is little evidence to suggest that differences in the baseline patient characteristics contributed to the observed differences in treatment responses to lisdexamfetamine and OROS-MPH. Patients were randomized to receive lisdexamfetamine, placebo or OROS-MPH, and patient demographics and baseline disease characteristics were similar across treatment groups [13]. Although the proportion of patients with the predominantly inattentive subtype was numerically greater for lisdexamfetamine than for OROS-MPH, most patients across all treatment groups had the combined ADHD subtype, and previous analyses revealed that improvements in both the hyperactivity/impulsivity and the inattention subscale scores of the

ADHD-RS-IV in response to lisdexamfetamine and OROS-MPH treatment were similar [13]. The proportion of patients with a concomitant, non-exclusionary psychiatric diagnosis was greater for OROS-MPH than for lisdexamfetamine. However, there was a minimal difference in the proportions of patients with oppositional defiant disorder, which has been shown to influence responses to stimulant treatment [18].

Although the mechanisms of action of stimulants in the treatment of ADHD remain to be fully established, it is possible that differences in the pharmacologies of methylphenidate- and amfetamine-based stimulants contributed to the differential treatment responses observed for lisdexamfetamine and OROS-MPH [19]. Differences in formulation and the resulting pharmacokinetic profiles of these long-acting stimulants may also have influenced their therapeutic activity. The pharmacokinetic profile of *d*-amfetamine following administration of lisdexamfetamine is monophasic, sustained and dose proportional [20]. The time to maximum observed plasma concentration (T_{max}) and half-life ($t_{½}$) for *d*-amfetamine following administration of lisdexamfetamine (30, 50 or 70 mg/day) are 3.41–3.58 h and 8.61–8.90 h, respectively [20]. These pharmacokinetic properties are reflected in the clinical duration of action of lisdexamfetamine, which extends to at least 13 h post-dose in children and 14 h post-dose in adults [10, 11]. As the metabolism of lisdexamfetamine occurs mostly in the bloodstream [7], it is unlikely to be affected by variations in gastric pH or gastrointestinal transit time [9]. The intra- and inter-patient variability in pharmacokinetic parameters is low, reflecting predictable and consistent exposure to *d*-amfetamine following administration of lisdexamfetamine [21]. OROS-MPH uses a mechanical mode of delivery, releasing methylphenidate in a biphasic manner as it transits through the gastrointestinal tract [9]. Approximately 22 % of the overall dose of methylphenidate is immediately released from the drug overcoat of the capsule, providing a rapid onset of clinical efficacy. This is followed by the sustained, osmotically driven release of methylphenidate. In contrast to lisdexamfetamine, alterations in gastrointestinal transit time and first pass metabolism in the liver may have an impact on the delivery of methylphenidate from OROS-MPH to sites of action [9]. Emerging evidence suggests that genetic factors may also influence treatment responses. To date, most pharmacogenetic studies of stimulants for ADHD have focused on genetic variability associated with their potential mechanism of action and have failed to yield consistent, clinically relevant findings [22–24]. It is now also being recognized that genetic variability in carboxylesterase 1A, the principal enzyme responsible for the metabolism of *d,l*-methylphenidate to the inactive metabolite, ritalinic acid, may have an impact on dose requirements [25]. Overall, inter- and intra-patient variability in pharmacokinetic parameters appears to be higher for OROS-MPH than for lisdexamfetamine [9]. Consistent with this, although the therapeutic benefits of OROS-MPH have been shown to last at least 12.5 h [12], clinical experience suggests that there is considerable variation in the duration of response [6].

In this study, no new safety signals of concern were observed and the safety profiles of lisdexamfetamine and OROS-MPH were similar to the known effects of stimulant medications [26]. However, it is notable that the overall frequency of TEAEs and the proportion of patients who were discontinued from the study due to TEAEs was numerically greater for lisdexamfetamine than for OROS-MPH. In addition, certain TEAEs, including decreased appetite, insomnia, decreased weight, nausea and anorexia, occurred more frequently in patients treated with lisdexamfetamine than in those who received OROS-MPH; none of these TEAEs were serious [13]. The modest mean increases from baseline in heart rate, pulse rate, and systolic and diastolic blood pressure in patients receiving lisdexamfetamine and OROS-MPH were also consistent with the known safety profiles of stimulant medications [26]. Finally, the decrease in mean weight was numerically greater in the lisdexamfetamine treatment group than in the OROS-MPH group. However, most patients in both active treatment groups remained within their baseline BMI category and few participants had potentially clinically important weight changes that resulted in a shift to the underweight BMI category. Overall, decisions regarding the choice of ADHD medication for individual patients should take into account the balance between the benefits and risks associated with each treatment.

5 Conclusions

In this post hoc analysis of data from a European, randomized, phase III study, children and adolescents with ADHD who were treated with lisdexamfetamine showed statistically significantly greater improvements in ADHD-RS-IV total score and CGI-I score from baseline to endpoint than those treated with OROS-MPH. This suggests that, at the doses tested, patients treated with lisdexamfetamine showed greater improvements in symptoms of ADHD than those who received OROS-MPH. The results of ongoing parallel-group clinical studies (ClinicalTrials.gov: NCT01552915 and NCT01552902) [27, 28] will provide definitive evidence of the comparative therapeutic efficacy of lisdexamfetamine and OROS-MPH. Meanwhile, the results of the present post hoc analysis support lisdexamfetamine as a valuable treatment option for the management of children and adolescents with ADHD.

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