

Functional and symptomatic improvement in adults with ADHD – Data from the open-label extension of the LAMDA trial

M. Casas¹, G.-E. Trott², S. Kooij³, J.A. Ramos-Quiroga⁴, J. Dejonckheere⁵, J. van Oene⁶, B. Schäuble⁷, J. Buitelaar⁸

¹Psychiatry, Universidad Autónoma de Barcelona, Barcelona, Spain; ²Child and Adolescent Psychiatry, Private Practice, Aschaffenburg, Germany; ³Psycho Medical Centre, Parnassia, Den Haag, The Netherlands; ⁴Psychiatry, University Barcelona, Barcelona, Spain; ⁵SGS Life Sciences Services, Antwerpen, Belgium; ⁶EMEA Medical Affairs, Janssen Pharmaceutica, Tilburg, The Netherlands; ⁷EMEA Medical Affairs, Janssen-Cilag GmbH, Neuss, Germany; ⁸Psychiatry, UMC St. Radboud, Nijmegen, The Netherlands

ABSTRACT

Objective: To explore the relationship between symptomatic and functional outcomes in adults with ADHD during open-label treatment with OROS MPH.

Methods: Post hoc analyses of a 7-week open-label extension (OLE) (N = 370) of a 5-week, placebo-controlled double-blind study (DB) which explored safety, efficacy, functional and quality of life outcomes in subjects with a diagnosis of ADHD (DSM-IV). Medication was flexibly dosed (18–90 mg/day) and adjusted individually to best effect during OLE. Regression analyses were performed on the change from DB baseline at OL endpoint in functionality and quality of life as measured by the Sheehan disability scale (SDS) and quality of life (Q-LES-Q). Baseline score, country, randomization group, sex, change from baseline in Conners' adult ADHD rating scale (CAARS) hyperactivity/impulsivity, CAARS inattention and CGI-S at DB endpoint were included as covariates in the analyses.

Results: 337/370 patients completed the 7-week open-label treatment. Improvement on CAARS hyperactivity/impulsivity at DB endpoint was significantly related with improvement in SDS »work«, »social life«, »family life« (at least $p < 0.005$) and »total score« as well as quality of life ($p < 0.05$) at the end of open-label treatment. Change in CGI-S and CAARS inattention at DB endpoint vs. DB baseline were not related with improvements in any of the functional or quality of life scales at OL endpoint ($p > 0.05$).

Conclusion: These results indicate that improvement in daily functioning and quality of life in adults with ADHD during treatment with OROS MPH may be particularly related to improvement in hyperactivity symptoms.

INTRODUCTION

Attention deficit / hyperactivity disorder (ADHD) is a common neuropsychiatric disorder affecting around 4.4 % of the adult population. In adults, ADHD impairs multiple aspects of functioning, such as interpersonal relationships, academic performance and occupational status^{1,2}. Moreover, it increases the risk of motor vehicle accidents³, co-morbid substance abuse⁴, and legal conflicts². Commonly, symptom reduction as measured by Conners' adult ADHD rating scale (CAARS) or adult ADHD investigator symptom rating scale (AISRS) are reported as efficacy outcomes in clinical trials, but the relationship between functional and symptomatic outcomes remains unclear.

Therefore, a post-hoc analysis of the 7-week open-label (OL) extension of a 5-week double blind (DB), fixed-dose, placebo-controlled trial of osmotic-controlled release oral system methylphenidate (OROS MPH) in adult subjects with ADHD was performed to explore the relationship between functional and symptomatic outcomes.

OBJECTIVES

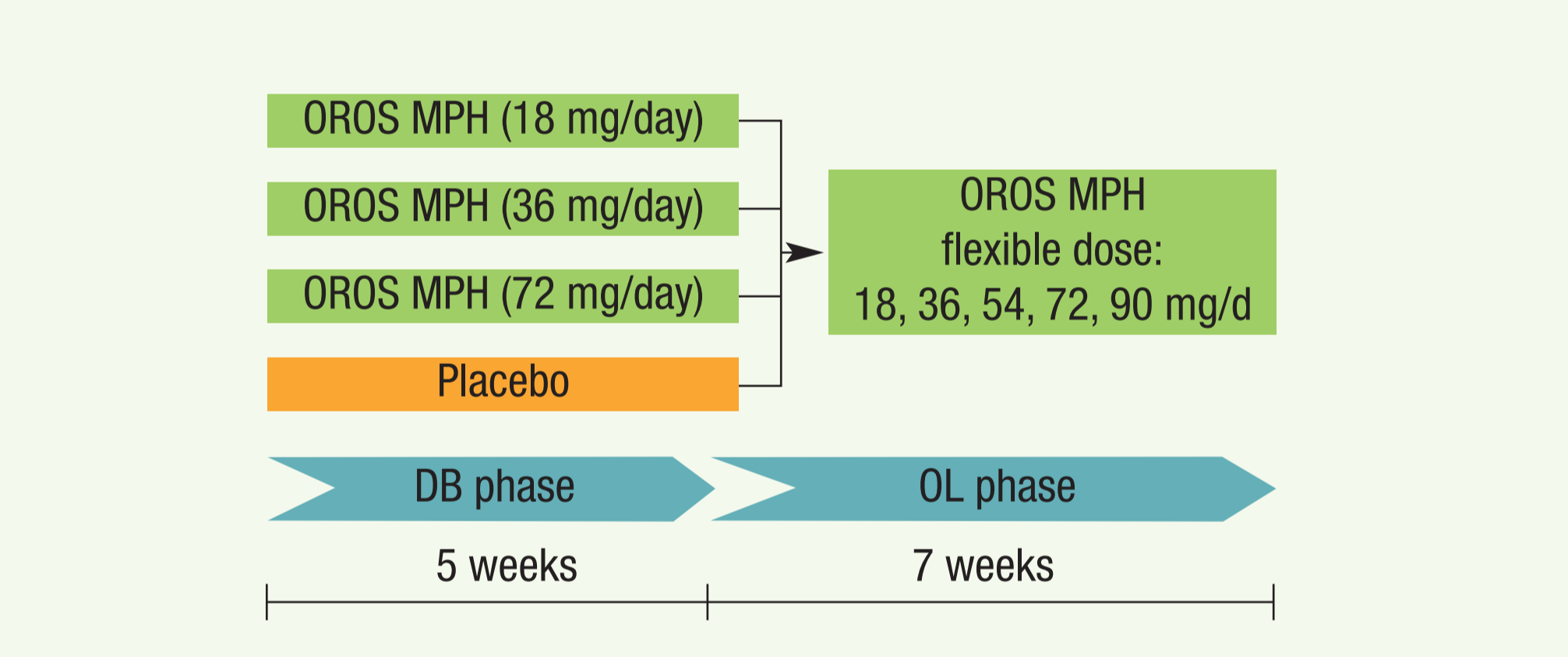
To explore the relationship between symptomatic and functional outcomes in adults (age 18–65 years) with ADHD during OL treatment with OROS MPH following a double-blind, placebo-controlled treatment phase.

METHODS

A. Study Design

This randomized, placebo-controlled, parallel-group, fixed-dose trial (42603ATT3002 or LAMDA I*) was conducted at multiple sites in Europe to evaluate the efficacy and safety of 3 fixed dosages of OROS MPH (18, 36 and 72 mg/day) compared with placebo in adult subjects with ADHD. After the 5-week DB period (results not presented here), subjects continued in a 7-week OL extension that assessed the safety of OROS MPH (18–90 mg/day). Subjects were eligible to enter the OL extension if they completed the 5-week DB phase or had discontinued study medication due to poor tolerability after a minimum of 7 days.

Figure 1. Overview of study design of the LAMDA study (42603ATT3002)



B. Subject Eligibility

Subjects were eligible for this study if they were aged 18–65 years inclusive with a diagnosis of ADHD according to the diagnostic and statistical manual of mental disorders-IV (DSM IV)^{1,5}, confirmed by Conners' adult ADHD diagnostic interview for the DSM-IV (CAADID). Subjects had a described chronic course of ADHD symptomatology from childhood (< 7 years) to adulthood and a Conners' adult ADHD rating scale (CAARS) score of ≥ 24 at screening for the DB phase.

Excluded were subjects who were known non-responders to MPH, had a child known to be non-responding to MPH, had received MPH within 1 month of screening, had any clinically unstable psychiatric condition, a family history of schizophrenia or affective psychosis, autism, Asperger's syndrome, motor tics, history or family history of Tourette's syndrome, or who had a diagnosis of substance use disorder (DSM-IV) within 6 months prior to screening.

C. Assessments

Symptomatic outcomes were assessed using the investigator-rated Conners' adult ADHD rating scale (CAARS) and clinical global impression-severity (CGI-S) scale; functional outcomes were assessed using Sheehan's disability scale (SDS) and quality of life was assessed using the quality of life enjoyment and satisfaction questionnaire (Q-LES-Q) short form. Assessment time points were DB baseline, end of DB phase and end of OL phase for all scales except the CAARS, which was assessed at every visit during the DB and OL phases.

• CAARS: 18-item investigator-rated scale with a scoring range of 0 (no symptoms) to 54 (frequent symptoms). It has 2 subscales, the hyperactivity/impulsivity subscale and the inattention subscale, each with a scoring range of 0 to 27.

• CGI-S: investigator-rated scale measuring the severity of a subject's illness on a 7 point scale ranging from 1 (not ill) to 7 (extremely severe).

• SDS: self-administered non-disease specific instrument measuring the impairment of subject's work, social life/leisure activities, and home life/family responsibilities on a 10-point visual analogue scale. The SDS total score ranges from 0 (unimpaired) to 30 (highly impaired). It has 3 subscales: work, social life, and family life.

• The Q-LES-Q short form is a 16-item self-administered quality of life questionnaire with total score ranging from 0 (worst) to 100 (best).

Safety assessments included adverse event (AE) reporting, clinical laboratory tests, and vital signs.

D. Statistical Analysis

Regression analysis was performed for the OL intent-to-treat (ITT) population, which included all subjects who had received at least 1 dose of OL study medication and had at least 1 efficacy assessment in the OL phase.

For every dependent variable (change from DB baseline at OL endpoint of functional [SDS] and quality of life [Q-LES-Q] scales), a separate regression analysis was performed. The change in symptomatic scores (CAARS subscales and CGI-S) from DB baseline to DB endpoint, baseline score, country, randomisation group (DB phase), and sex were included as independent variables. Given the high correlation of the CAARS total score with the CAARS subscale score, only the CAARS hyperactivity/impulsivity and inattention subscale scores were included in these regression models.

The CAARS scores were assessed at multiple time points during the DB phase and were analysed according to the last-observation-carried-forward (LOCF) principle. All other scales were assessed only once during each treatment phase: at last scheduled visit or early termination. Symptomatic outcomes were measured as changes from DB baseline to DB endpoint and functional and quality of life outcomes were measured as changes from DB baseline to OL endpoint of the relevant scale scores (total score or subscale scores).

RESULTS

A. Subjects

• 370 subjects of the 401 subjects who participated in the DB phase continued in the OL extension (Table 1)

– 93 had received placebo in the DB phase (referred to as the placebo/OROS MPH group)

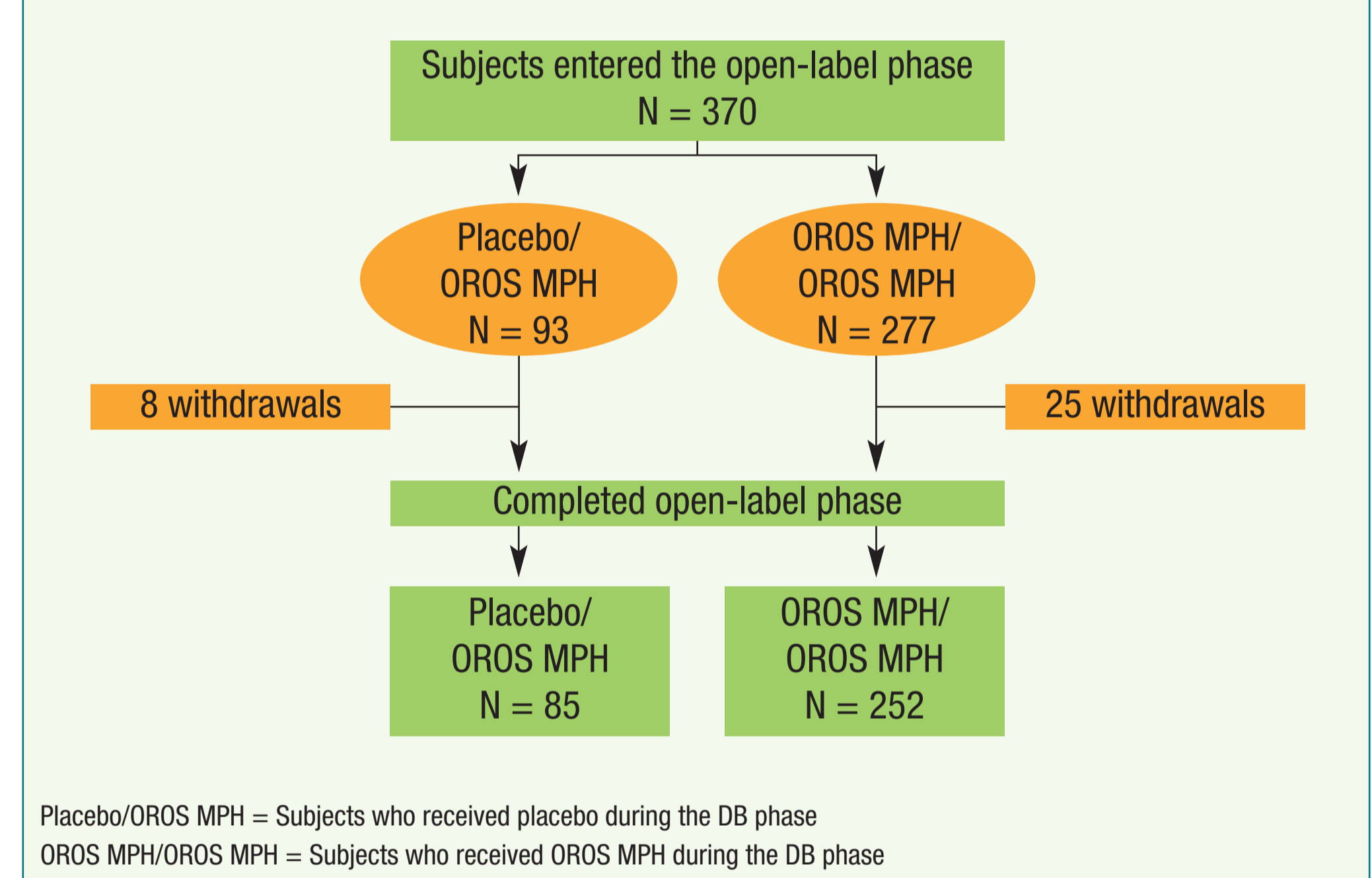
– 277 had received 18, 36 or 72 mg/day OROS MPH in the DB phase (referred to as the OROS MPH/OROS MPH group).

• All subjects in the OL phase started on OROS MPH 36 mg daily. Median last dose in the OL phase was 54 mg/day.

• 337 out of 370 subjects (91 %) completed the 7-week OL treatment.

• Adverse events were the main reason for trial discontinuation (5 %) during OL treatment; one subject discontinued due to lack of efficacy.

Figure 2. Subject disposition of the OL extension phase of the LAMDA I study (42603ATT3002)



Placebo/OROS MPH = Subjects who received placebo during the DB phase
OROS MPH/OROS MPH = Subjects who received OROS MPH during the DB phase

B. Efficacy

• During the DB phase, statistically significant improvements in CAARS and CGI-S were observed in both the placebo and OROS MPH groups (Tables 2 and 3).

• During the OL phase, when all subjects received an individually optimized OROS MPH dose between 18 and 90 mg per day, scores in SDS and Q-LES-Q continued to improve, regardless of the subjects' treatment during the DB phase (Table 4; Figures 3, 4, and 5).

C. Regression Analysis

• The improvement on the CAARS hyperactivity/impulsivity subscale at DB endpoint was significantly related with improvement in SDS »work«, »social life«, »family life« (at least $p < 0.005$) and »total score« as well as quality of life total score ($p < 0.05$) at the end of OL treatment.

• Change in CGI-S and the CAARS inattention subscale at DB endpoint versus DB baseline were not related with improvements in any of the functional or quality of life scales at OL endpoint ($p > 0.05$) (Table 5).

D. Safety

• The safety profile of OROS MPH was in line with that reported in other OL studies of MPH in adult subjects with ADHD.

• The most frequently reported treatment-emergent adverse events during the OL phase were:

– headache (placebo/OROS MPH: 17.2 %; OROS MPH/OROS MPH: 16.6 %),

– decreased appetite (placebo/OROS MPH: 22.6 %; OROS MPH/OROS MPH: 9.4 %),

– insomnia (placebo/OROS MPH: 17.2 %; OROS MPH/OROS MPH: 9.0 %).

STUDY LIMITATIONS

• Open-label design.

• Comparatively short duration (12 weeks), which may have prevented documentation of the full extent of improvement in functional and quality of life outcomes possible during treatment over a longer period.

• Flexible dose based on clinical judgement; patients might have experienced more improvement with higher doses (forced titration or fixed dosing).

CONCLUSIONS

• These results suggest that improvement in the CAARS hyperactivity/impulsivity subscale at the end of 5 weeks of DB treatment was predictive of functional improvement as assessed by SDS and improvement of quality of life over a 12-week DB/OL treatment period.

• Furthermore, these results indicate that functional improvement at work, in social and family life in adult subjects with ADHD during treatment with OROS MPH may be particularly related to improvement in hyperactivity symptoms.

• Improvements on the CAARS hyperactivity/impulsivity subscale were also associated with an improved quality of life at endpoint.

• Of note, the improvement in inattention was neither associated with improved quality of life, nor with increased functionality at work, in social interaction or at home. A possible explanation might be that hyperactivity/impulsivity may be more disruptive in daily interactions than inattention.

REFERENCES

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Table 1. Demographic and baseline characteristics for OL ITT population at start of LAMDA I study

Characteristic	Placebo/ OROS MPH N = 93	OROS MPH/ OROS MPH N = 276	All Subjects N = 370
Age (years)			
mean (SD)	34.8 (9.55)	34.2 (10.54)	34.3 (10.29)
range	18 – 57	18 – 63	18 – 63
Sex, n (%)			
Female	35 (37.6)	136 (49.1)	171 (46.2)
Male	58 (62.4)	141 (50.9)	199 (53.8)
ADHD subtype childhood [§] , n (%)			
Combined type	65 (69.9)	209 (75.5)	274 (74.1)
Predominantly inattentive type	21 (22.6)	52 (18.8)	73 (19.7)
Predominantly hyperactive-impulsive type	5 (5.4)	14 (5.1)	19 (5.1)
Not otherwise specified	2 (2.2)	0	2 (0.5)
ADHD subtype adulthood, n (%)			
Combined type	65 (69.9)	194 (70.0)	259 (70.0)
Predominantly inattentive type	23 (24.7)	68 (24.5)	91 (24.6)
Predominantly hyperactive-impulsive type	2 (2.2)	14 (5.1)	16 (4.3)
Not otherwise specified	3 (3.2)	1 (0.4)	4 (1.1)

N = number of subjects with data; n = number of subjects with observation
§ Based on CAADID

Table 2. CAARS scores during DB phase for OL ITT population (LOCF)

CAARS score, mean (SD)	Placebo/ OROS MPH N = 93	OROS MPH/ OROS MPH N = 276
Total score		
Baseline	37.2 (7.15)	36.5 (6.89)
DB endpoint	29.5 (10.6)	24.3 (10.92)
Change from DB baseline at DB endpoint	-7.7 (9.94)*	-12.3 (10.64)*
Hyperactivity/impulsivity subscale scores		
Baseline	17.1 (5.52)	16.9 (5.09)
DB Endpoint	13.1 (6.38)	11.5 (5.58)
Change from DB baseline at DB endpoint	-4.0 (5.47)*	-5.3 (5.69)*
Inattention subscale scores		
Baseline	20.0 (4.31)	19.7 (4.09)
DB endpoint	16.4 (6.03)	12.8 (6.17)
Change from DB baseline at DB endpoint	-3.6 (5.19)*	-6.9 (6.05)*

N = number of subjects with data
* statistically significant change from baseline, $p < 0.001$ (2-sided paired t-test)

Table 3. CGI-S during DB phase for OL ITT population

CGI-S, median (range)	Placebo/ OROS MPH N = 93	OROS MPH/ OROS MPH N = 276
Baseline	5.0 (3 – 7)	5.0 (1 – 7)
DB endpoint	5.0 (2 – 6)	4.0 (1 – 7)
Change from DB baseline at DB endpoint	0.0 (-3 – 1)*	-1.0 (-4 – 1)*

N = number of subjects with data
* statistically significant change from baseline, $p < 0.001$ (2-sided Wilcoxon signed rank test)

Table 4. SDS and Q-LES-Q during OL phase

Change from DB baseline at end of OL phase	Placebo/ OROS MPH		OROS MPH/ OROS MPH	
	N	mean (SD)	N	mean (SD)
SDS total score	70	-7.0 (5.92)	207	-7.6 (6.80)
SDS work subscale	70	-2.5 (2.21)	207	-2.7 (2.62)
SDS social life subscale	89	-2.0 (2.54)	255	-2.4 (2.61)
SDS family life subscale	89	-2.4 (2.45)	255	-2.6 (2.85)
Q-LES-Q total score	71	9.7 (17.16)	226	10.8 (16.18)

N = number of subjects with data

Table 5. Overview of estimates and p-values of improvement on symptomatic scales at DB endpoint as predictors of functional improvement at end of OL phase

Symptomatic improvement at DB endpoint	Functional improvement at end of OL phase				
	SDS: Work	SDS: Social life	SDS: Family life	SDS: Total score	Q-LES-Q Total score
Inattention	0.0349 (0.3207)	0.0182 (0.5602)	-0.0059 (0.8588)	0.0604 (0.5121)	-0.3729 (0.1040)
Hyperactivity/impulsivity	0.0919 (0.0048)	0.0849 (0.0037)	0.1151 (0.0003)	0.2778 (0.0011)	-0.4865 (0.0205)
CGI-S	0.1893 (0.3315)	0.2301 (0.1804)	0.1696 (0.3559)	0.4788 (0.3484)	-0.3776 (0.7640)

Figure 3. Mean (SD) SDS total score

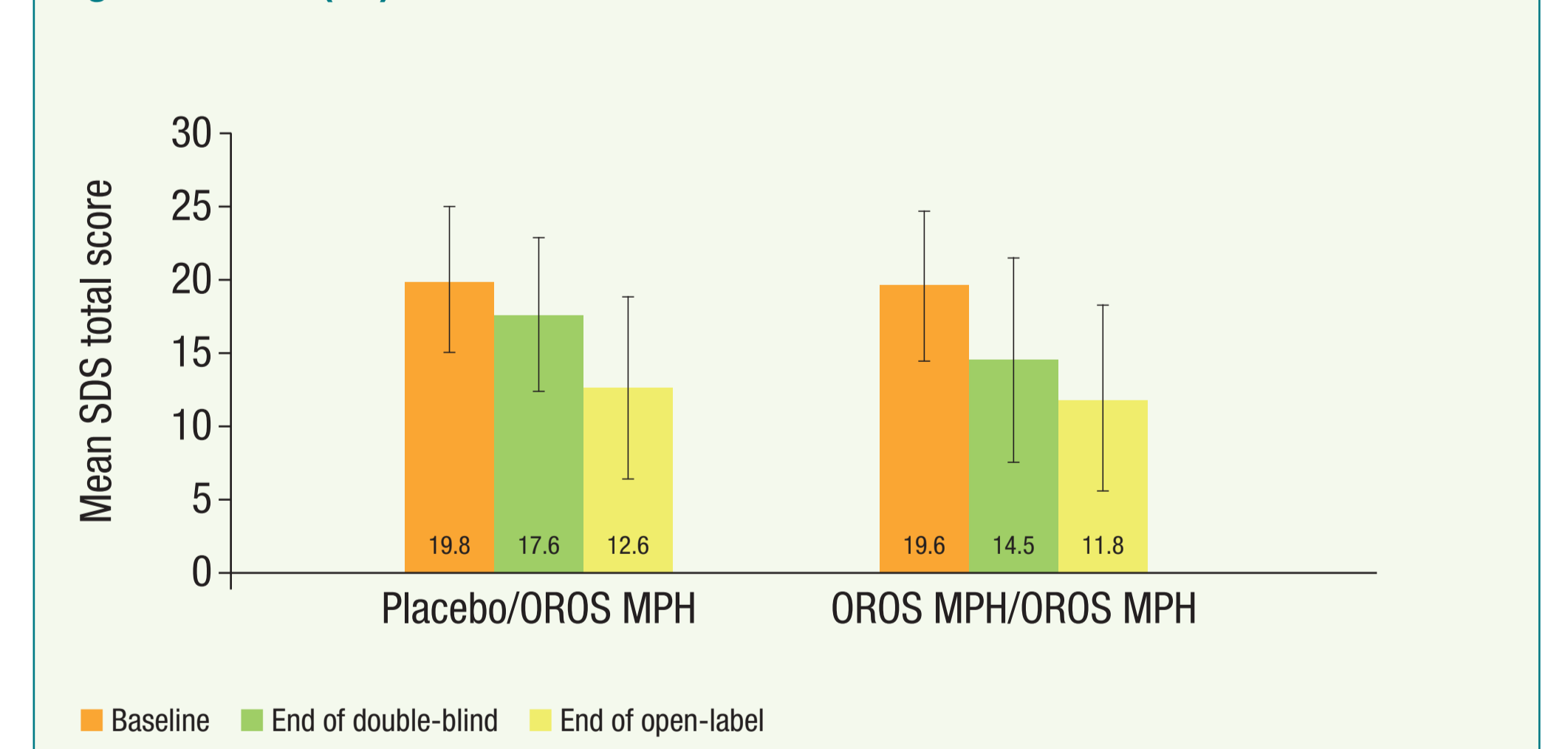


Figure 4. Mean (SD) SDS subscale score

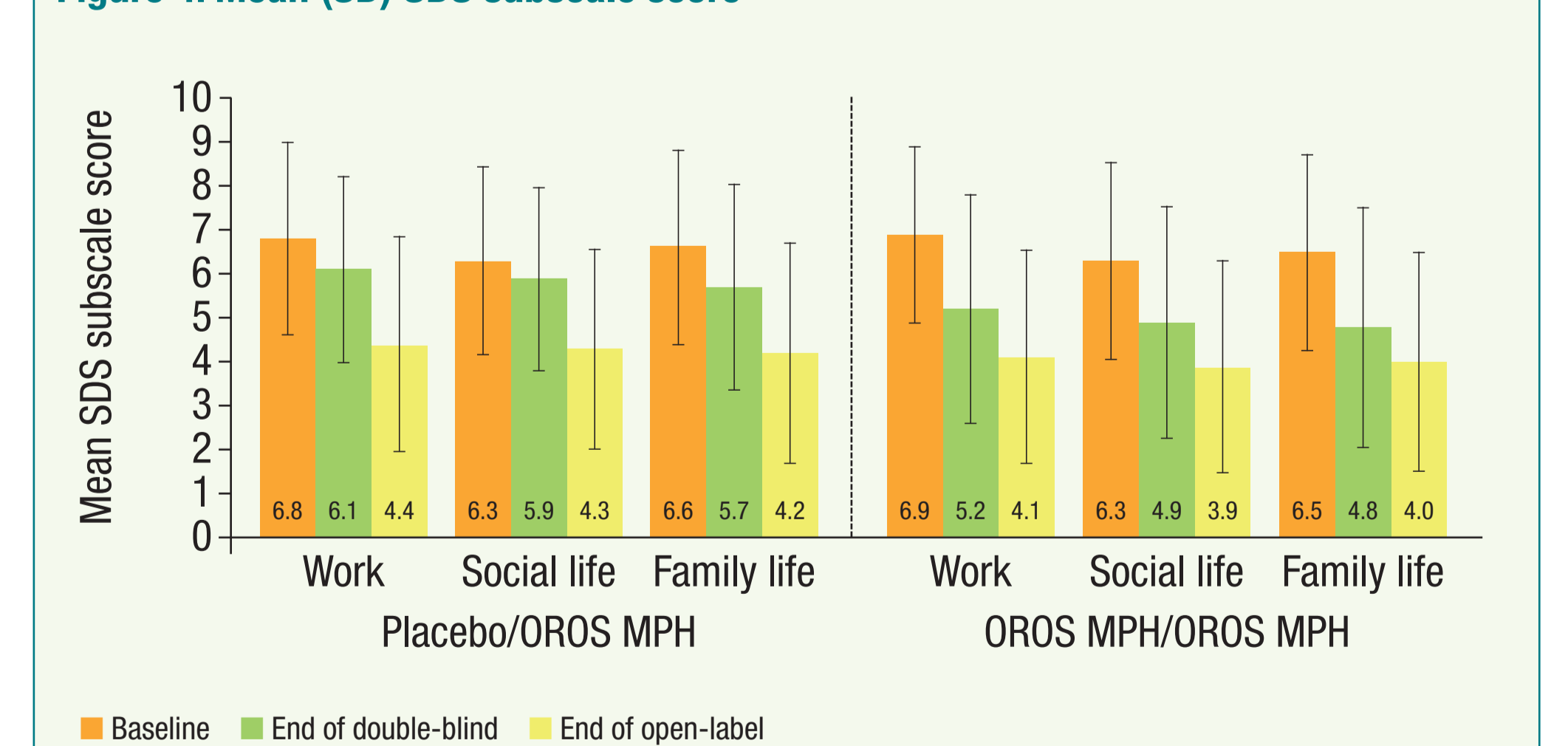


Figure 5. Mean (SD) Q-LES-Q total score

