ORIGINAL RESEARCH

Methylphenidate Hydrochloride Modified-Release in Adults with Attention Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Trial

Michael Huss · Ylva Ginsberg · Torbjorn Tvedten · Torben Arngrim · Alexandra Philipsen · Katherine Carter · Chien-Wei Chen · Vinod Kumar

ABSTRACT

Introduction: Treatment options for adults with attention deficit hyperactivity disorder (ADHD) are limited. The study was conducted to confirm the clinically effective and safe dose of methylphenidate hydrochloride modified-release (MPH-LA) in adults with ADHD and evaluate the maintenance of effect of MPH-LA.
Methods: The study consisted of three treatment phases. *The double-blind dose-confirmation phase*: 9-week double-blind period (3-week titration period, 6-week fixed dose) with randomization to MPH-LA 40, 60, or 80 mg/day or placebo. *The real-life dose-optimization phase*: a 5-week re-titration period to optimal dose; and the *double-blind maintenance of effect phase*, a 6-month double-blind randomized placebo-controlled *maintenance of effect phase*. The three co-primary endpoints were change in Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale (DSM-IV ADHD RS) and Sheehan Disability Scale (SDS) total scores from baseline to end of 9-week *confirmation phase* and the percentage of treatment failures during the 6-month *maintenance of effect phase*.
Results: 725 of 863 screened patients were randomized to 40 ($N = 181$), 60 ($N = 182$), or 80 mg ($N = 181$) MPH-LA or placebo ($N = 181$),

M. Huss (✉)
Child and Adolescent Psychiatry, University of Medicine, Mainz, Germany
e-mail: michael.huss@unimedizin-mainz.de

Y. Ginsberg
Department of Medical Epidemiology and Biostatistics and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

T. Tvedten
Centre for Therapy and Supervision, Skien, Norway

T. Arngrim
Private Practice, Aarhus, Denmark

A. Philipsen
University Medical Centre, Freiburg, Germany

K. Carter · C.-W. Chen · V. Kumar
Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

and 584 (80.6%) completed. 489 (83.7%) of completers were re-randomized to the double-blinded *maintenance of effect phase* and 235 (48.1%) of them completed. Improvement from baseline in DSM-IV ADHD RS ($P < 0.0001$ for all comparisons) and SDS (40 mg, $P = 0.0003$; 60 mg, $P = 0.0176$; 80 mg, $P < 0.0001$) total scores was significantly greater vs. placebo for all MPH-LA doses. Treatment failure rate was significantly lower with MPH-LA (21.3%) versus placebo (49.6%) during the 6-month *maintenance of effect phase*. Safety profile was consistent with the profile for MPH-LA in children; percentage of serious adverse events was comparable between all MPH-LA arms (1.3%) and placebo (1.5%), while percentage of adverse events was higher in MPH-LA arms.

Conclusion: MPH-LA provided and maintained significant symptomatic and functional improvement in adult ADHD patients.

Keywords: Adult attention deficit hyperactivity disorder (ADHD); Methylphenidate hydrochloride (MPH); Psychiatry; Randomized trial

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder commonly identified and well characterized in children and adolescents, with a worldwide pooled prevalence rate of approximately 5% [1]. The core symptoms of ADHD include attention deficit, hyperactivity, and impulsive disturbances which are often associated with impaired executive functioning [2]. ADHD has been considered as a childhood/adolescent disorder. However, recent epidemiologic studies have highlighted its persistence into adulthood with a prevalence rate of 2–5% of the adult population [3–5]. To date, many adults remain underdiagnosed and/or untreated due to poor diagnosis and suboptimal transition of medical services from childhood/adolescence to adulthood. Adult ADHD is known to be associated with a wide range of clinical and psychosocial challenges including history of school failure, occupational impairment, family problems, substance abuse, traffic violations, and arrests [6, 7]. Furthermore, ineffective treatment of ADHD imposes a socio-economic burden due to elevated healthcare costs, less productivity, and more accidents [8, 9].

Treatment options for ADHD include pharmacotherapy, employing either stimulants or non-stimulants, in addition to psycho-education and cognitive behavioral therapy. Stimulants like methylphenidate (MPH) and dexamphetamine have always been the first-line therapeutic options for the treatment of both childhood and adult ADHD based on their efficacy and safety data [6, 7, 10]. Methylphenidate hydrochloride modified-release (MPH-LA) is an extended-release capsule containing a racemic mixture of *d*- and *l*-threo-MPH that is currently approved for use in children with ADHD aged 6 years and above in over 30 countries worldwide, including many in the European Union (EU).

According to the consensus statement by the European Network Adult ADHD [11], as well as the guidelines of the National Institute for Health and Clinical Excellence [12], pharmacotherapy should be the first-line treatment for adults with ADHD and MPH should be the treatment of first choice. However, approval of such treatments for adult ADHD inside and outside the EU is extremely limited. Currently, only two

medications are approved for treatment of adult ADHD patients in the EU, that is, atomoxetine and an extended-release (ER) MPH in Germany [13]. In the United States (US) and Switzerland, an extended-release formulation of the *d*-threo enantiomer of MPH (dexmethylphenidate HCl) is approved for use in adults with ADHD [11].

Growing recognition of the importance of diagnosis and treatment of ADHD in adults together with the current lack of approved drugs for this indication, represent an unmet medical need. In an effort to address this need, the current phase 3 clinical trial was designed to confirm the clinically effective and safe dose range and evaluate the maintenance effect of MPH-LA in adult patients with ADHD.

METHODS

Study Design and Treatment

This was a 40-week, double-blind, randomized, placebo-controlled, international multicenter efficacy and safety study of MPH-LA in the treatment of adult patients with ADHD conducted between November 24, 2010 and August 7, 2012 in 67 centers including nine countries. The study consisted of the following three treatment phases (Fig. 1): (1) The *double-blind dose-confirmation phase* was a 9-week, double-blind, randomized, placebo-controlled, parallel-group period consisting of a 3-week titration stage and a 6-week fixed-dose stage to confirm the effective dose range of MPH-LA. Any therapies for ADHD, as well as all
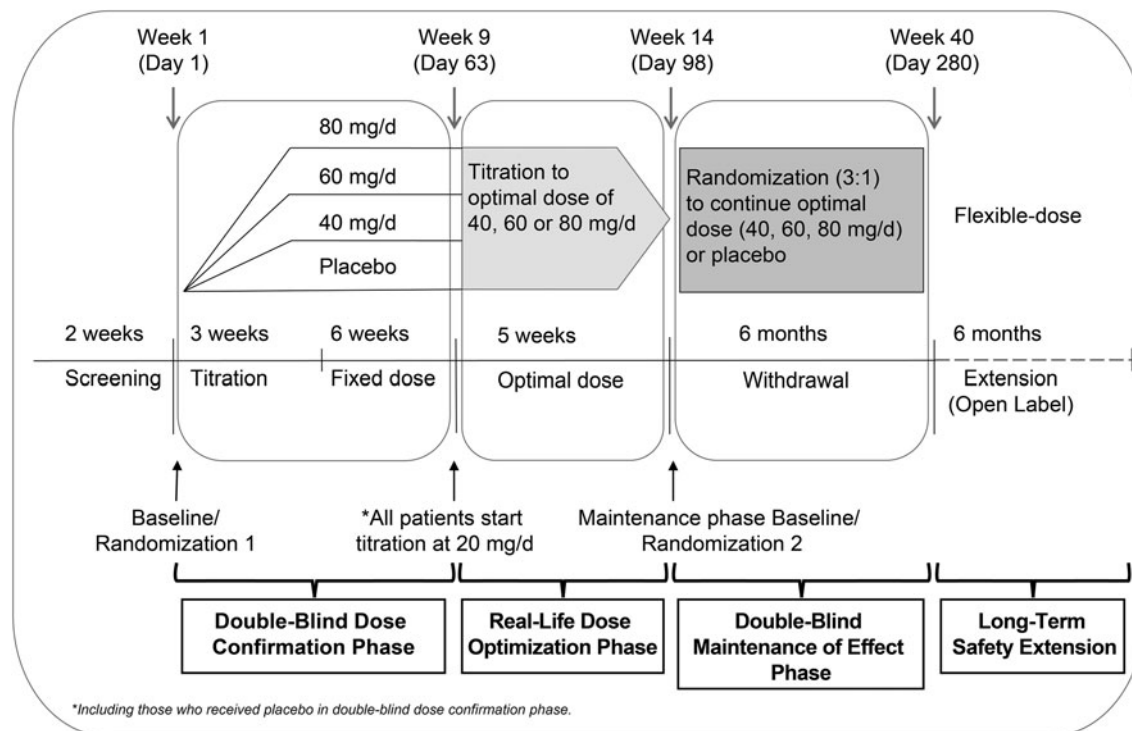

Fig. 1 Study design. Study design including the three study phases and extension study: the *double-blind dose-confirmation phase*, the *real-life dose-optimization phase*, the *double-blind maintenance of effect phase*, and the *long-term safety extension*. *d* day

psychotropic medications were required to be discontinued 1–4 weeks prior to randomization. Eligible patients meeting all inclusion criteria at the baseline visit (day 1) and none of the exclusion criteria received either MPH-LA 40, 60, or 80 mg/day or matching placebo in a 1:1:1:1 ratio [study drug (in the formulation of 20 mg or 30 mg) and matching placebo was dispensed as three bottles to eligible patients before start of treatment]. Therapy was started at a dose of 20 mg/day that was increased at weekly intervals in increments of 20 mg/day until the assigned dose of 40, 60, or 80 mg was reached. Following the 3-week titration stage, patients received their allocated dose for a period of 6 weeks. (2) The *real-life dose-optimization phase* was a 5-week period during which all patients, including those treated with placebo in the *double-blind dose-confirmation phase,* were started on a dose of 20 mg/day and titrated each week, in increments of 20 mg/day, to their optimal dose (considered by the investigator to achieve optimum symptom control with good tolerability profile) of MPH-LA (40, 60 or 80 mg/day) within 3 weeks. The optimal dose was maintained for at least 1 week. At the last visit of the *real-life dose-optimization phase,* responders [defined as patients with ≥30% improvement compared to baseline score on the Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale (DSM-IV ADHD RS)] who continued to meet inclusion criteria were re-randomized to enter the *double-blind maintenance of effect phase* in a 3:1 ratio to their optimal dose or placebo. (3) The *double-blind maintenance of effect phase* was a 6-month, double-blind, randomized, placebo-controlled, withdrawal phase to evaluate the maintenance of effect of MPH-LA in adults with ADHD. Patients with ≥30% worsening from baseline during this 6-month *maintenance of effect phase* and <30% remaining improvement

from phase 1 baseline on the DSM-IV ADHD RS were required to discontinue the study due to a lack of therapeutic effect (Fig. 1).

Study Participants

Adult patients (18–60 years) with diagnosis of ADHD, all types, with a confirmed childhood onset according to DSM-IV diagnostic criteria and a DSM-IV ADHD RS total score of ≥30 at screening and baseline were included in the study. Exclusion criteria were: pre-existing cardiovascular or cerebrovascular diseases, or any other co-morbid psychiatric disorder requiring medical intervention/therapy or that might interfere with the study conduct at the time of enrollment; patients demonstrating a ≥30% improvement in DSM-IV ADHD RS total score at baseline relative to that at screening were also excluded from this study. Any psychological or behavioral therapies for the treatment of ADHD were discontinued at least 1 month prior to the screening visit. Patients who initiated these therapies within 3 months prior to screening visit for reasons other than ADHD were excluded from the trial.

Additionally, patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgment were excluded from this study. Patients with use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment (whichever was longer), were excluded from the study. In patients receiving any psychotropic medications the minimum discontinuation period varied according to drug class as follows: 1 week prior to the screening visit for stimulants including MPH, antidepressants other than fluoxetine, antipsychotics, anticonvulsants for non-epilepsy uses, mood stabilizing medications

such as lithium, and herbal preparations with psychotropic potential; 2 weeks prior to the screening visit for benzodiazepines, barbiturates, all other sedatives or hypnotics, and monoamine oxidase inhibitors and 4 weeks prior to the screening visit for fluoxetine. Other exclusion criteria included pregnancy, seizures, recent alcohol or drug abuse and patients with body mass index <18.5 kg/m^2 or >35 kg/m^2.

The study protocol was designed in accordance with the EU guideline on studies in ADHD which requires that "two primary endpoints should be stipulated reflecting the symptomatic and the functional domain" [14]. Ethics approval was received before the start of the study in compliance with global and local guidelines by ethic committees of the respective countries. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study.

Randomization and Blinding

Randomization was performed at the beginning of the double-blind dose-confirmation phase and the double-blind maintenance of effect phase upon fulfillment of the inclusion/exclusion criteria mentioned above. Patients were randomized to one of the treatment arms using a validated Interactive Voice/Web Response System (IVRS/IWRS). A unique, confidential randomization number was assigned to each patient and IVRS/IWRS allocated medication accordingly, as assigned, throughout the respective treatment periods. An unbiased, confidential patient randomization list was produced by the IVRS/IWRS provider using a validated system that

automated the random assignment of patient numbers to randomization numbers. A separate medication randomization list was produced under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs. The randomization scheme was reviewed and approved by a member of the Biostatistics Quality Assurance Group. All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, in line with Consort guidelines.

Prior to study enrollment, the investigator and the patient jointly decided the most appropriate time of administration of study medication. The investigator promoted compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance was necessary for the patient's safety and the validity of the study. The patient was instructed to contact the investigator if he/she was unable for any reason to take the study drug as prescribed. After the start of the study, drug patients were not allowed to take psychotropic drugs or other medications that would have interfered with the study assessments. The use of rescue medication was not permitted during the study. Patients whose symptoms were not adequately controlled on study medication were discontinued from the study and treated at the discretion of the investigator. Compliance was assessed by the investigator

and/or study personnel at each visit using pill counts and information provided by the patient.

Efficacy and Safety Endpoints

The primary objectives of this study were to confirm the clinically effective and safe dose of MPH-LA in adults with ADHD and to evaluate the maintenance of effect of MPH-LA in this population. Symptomatic and functional domains were evaluated using the change from baseline to the end of the *double-blind dose-confirmation phase* (week 9) total score on the physician-rated DSM-IV ADHD RS (range 0–54) [15] and self-rated SDS (range 0–30) [16] as co-primary endpoints. SDS total is composed out of three sub-scores: work, family and social life sub-score. DSM-IV ADHD RS consisted of 18 items directly adapted from the ADHD symptom list according to the DSM-IV, wherein the clinician recorded the frequency of each symptom as reported by the patient for the past week. SDS is a five-item, self-rated questionnaire which measured the extent to which a patient's disability due to an illness or health problem (e.g., anxiety disorder, painful conditions, depression) interferes with three sub-scores assessing work/school, social life/ leisure, and family life/home responsibilities. Patients were asked to indicate how much their symptoms have disrupted their regular activities over the past week in each of these areas using a scale for each item ranging from 0 ('not at all') to 10 ('extremely'). The SDS scale has been validated for use in adult patients [Coles T, Coon C, DeMuro C, L McLeod, Gnanasakthy A. Psychometric Evaluation of the Sheehan Disability Scale in Adult Patients With Attention-Deficit/Hyperactivity Disorder. Neuropsychiatr Dis Treat. (submitted)]. Additionally, the percentage of MPH-LA-versus placebo-treated treatment failures at the end of the 6-month *maintenance of effect phase* (week 40) was used as a third primary endpoint to assess the maintenance of effect of MPH-LA. Treatment failures were withdrawn from the study if they fulfilled both of the lack of therapeutic effect discontinuation criteria: (1) 30% or more worsening from baseline of this study phase on DSM-IV ADHD rating scale score AND; (2) less than 30% remaining improvement from the phase 1 baseline score on DSM-IV ADHD rating scale. The denominator for calculating percentage of treatment failures was the number of patients randomized at the start of *maintenance of effect phase*.

The key secondary endpoint was the proportion of patients with clinical improvement at the end of the initial *double-blind dose-confirmation phase* on the physician-rated Clinical Global Impression-Improvement Scale (CGI-I) [17]. CGI-I scale was used to assess the overall change in illness relative to the baseline. The CGI-I scale consisted of seven ratings ranging from 1 ('very much improved') to 7 ('very much worse'). Improvement on CGI-I scale was defined as a visit rating of 1 ('very much improved') or 2 ('much improved'). Other secondary efficacy measurements included the improvement from baseline to end of the *double-blind dose-confirmation phase* on the physician-rated Clinical Global Impression-Severity scale (CGI-S) [17], the observer-rated Conner's Adult ADHD Rating Scale-Observer (CAARS-O:S) [18], and on the Adult Self-Report Scale (ASRS) total scores [19]. CGI-S scale was used to rate globally, the severity of symptoms on a 7-point scale, ranging from 1 ('normal, not at all ill') to 7 ('among the most extremely ill patients'). The ASRS scale assessed ADHD symptoms in adults comprised 18 items (which reflect the DSM-IV

diagnostic criteria for ADHD) and is rated from 0 ('never') to 4 ('very often'). CAARS-O:S scale consisted of 26 items and 6 subscales: Inattention/Memory Problems, Hyperactivity/ Restlessness, Impulsivity/Emotional Lability, Problems with Self-Concept, ADHD Index (to distinguish ADHD adults from non-clinical adults), and Inconsistency Index (to identify random or careless responding).

DSM-IV ADHD RS, CGI-I, and CGI-S are physician-rated scales, SDS and ASRS are self-rated scales, and CAARS-O:S is an observer-rated scale (assessments made by a friend, family member, or a colleague).

DSM-IV ADHD RS and CGI-I scores were assessed at weeks 1, 2, 3, 5, 7, and 9 during the *double-blind dose-confirmation phase*; at every week during the 5-week *real-life dose-optimization phase;* and every 4 weeks during the 6-month *maintenance of effect phase*. SDS, CGI-S, CAARS-O:S, and ASRS scores were assessed at the end of each of the three study phases.

Safety assessments included the recording of all adverse events (AEs) and serious adverse events (SAEs). Additionally, cardiac safety parameters [blood pressure, heart rate, notable electrocardiogram (ECG) intervals] were closely monitored. Laboratory parameters were examined at baseline, the end of the *real-life dose-optimization phase*, and the end of the study.

Statistical Analysis

Statistical Analysis Software (SAS®) 9.2 (SAS Institute Inc., Cary, NC, USA) was used to conduct the analyses. The sample size and power calculation was based on DSM-IV ADHD RS total score and SDS total score individually as those two endpoints were tested first and simultaneously. It also ensured sufficient patients and power to detect the difference in treatment failure rates in phase 3.

For change from baseline in SDS total score at the end of the *double-blind dose-confirmation phase*, Medori et al. [20] and Michelson et al. [21] indicated a likely difference from placebo to be in the range 2.5–3.0 points, with a standard deviation in the range 4.0–8.0. The power to detect such differences at a two-sided alpha-level of 0.0167, given a sample size of 140 patients per treatment group is shown in Table 1. For change from baseline in DSM-IV ADHD RS total score in the *double-blind dose-confirmation phase*, to detect a difference with an effect size of 0.5 at a two-sided alpha-level of 0.0167, 140 patients per treatment group would give approximately 96% power. Assuming a 20% dropout rate in this initial *dose-confirmation phase*, a total of 700 randomized patients were required.

Assuming a responder rate of 80% and a dropout rate of 15% during the *real-life dose-optimization phase*, approximately 380 patients were expected to be re-randomized to placebo and MPH-LA with an allocation ratio of 1:3. Allowing 40% dropout rate in the *double-blind maintenance of effect phase*, a total of approximately 230 patients were expected to complete the 6-month *double-blind maintenance of effect phase*. Assuming a two-sided alpha-level of 0.0083, this number of patients could detect a 30% difference in treatment failure

Table 1 Power estimation for change from baseline in Sheehan Disability Scale total score

Clinically relevant difference	2.5	3	2.5	3	2.5	3
SD	7	7	6	6	5	5
Power (%)	71	88	86	96	96	>99

rate between MPH-LA and placebo with 89% power.

The co-primary efficacy endpoints including change from baseline to the end of the *dose-confirmation phase* in the total DSM-IV ADHD RS and SDS scores were evaluated by analysis of covariance (ANCOVA) model with treatment group and center as factors and baseline DSM-IV ADHD RS or SDS scores as covariates as applicable. They were tested in composite hypotheses. The effect size d was calculated as $(M1 - M2)/SD$, where M1 and M2 are the mean values of the endpoints in the MPH-LA or placebo group and SD is the pooled standard deviation of the MPH-LA and placebo group [22]. The third primary efficacy endpoint, the comparison of the percentage of treatment failures in the MPH-LA group versus the placebo group in the 6-month *double-blind maintenance of effect phase* and the key secondary endpoint (improvement on the CGI-I scale) at the end of the 9-week *double-blind dose-confirmation phase* were analyzed using a logistic regression model with treatment as the factor and baseline as covariate. Missing post-baseline scores were imputed based on last observation carried forward (LOCF) or based on the multiple imputation approach if data were not available for LOCF for the third primary efficacy endpoint. The analyses were performed on the intent-to-treat population. The significance levels for the three primary and the key secondary endpoints were determined by a gate-keeping procedure based on the graphical approach to sequentially rejective multiple test procedures [23]. For other secondary endpoints, CGI-S was analyzed using a logistic regression model, and CAARS-O:S and ASRS were evaluated by the ANCOVA model.

RESULTS

A total of 863 adult patients (18–60 years) were screened, of which 725 patients were randomized in a ratio of 1:1:1:1 to one of the following arms: MPH-LA 40, 60, or 80 mg, or placebo; with per country enrollment as: Belgium ($n = 32$), Colombia ($n = 26$), Denmark ($n = 10$), Germany ($n = 362$), Norway ($n = 24$), Singapore ($n = 5$), South Africa ($n = 8$), Sweden ($n = 28$), USA ($n = 230$).

Of the 725 patients randomized at phase 1 baseline, 584 (80.6%) patients completed the 9-week *double-blind dose-confirmation phase* and entered the *real-life dose-optimization phase*. Of these patients, 489 (83.7%) completed the 5-week *dose-optimization phase* with ≥30% improvement compared to the baseline 1 on the DSM-IV ADHD RS, thus re-randomized to the *double-blind maintenance of effect phase* (Fig. 2). During this 6-month *maintenance of effect phase*, patients with unsatisfactory therapeutic effect were required to discontinue the study. Altogether, 235 (48.1%) out of 489 defined responders of the *dose-optimization phase* completed the 6-month *double-blind maintenance of effect phase* (Fig. 2).

A total of 22 patients enrolled from one site were excluded from the efficacy analysis due to serious non-compliance with International Conference on Harmonization-Good Clinical Practices at the site. Patients without study drug intake were excluded from the safety analysis set. Patient demographics and background characteristics were similar across all treatment groups (Table 2). Most of the study participants were Caucasian (89.5%; Table 2). 13.3% of the patients had received stimulants previously, most frequently used treatments were MPH/methylphenidate (9.1%), mixed amphetamine salts (2.5%), and lisdexamfetamine dismesylate (1.1%).
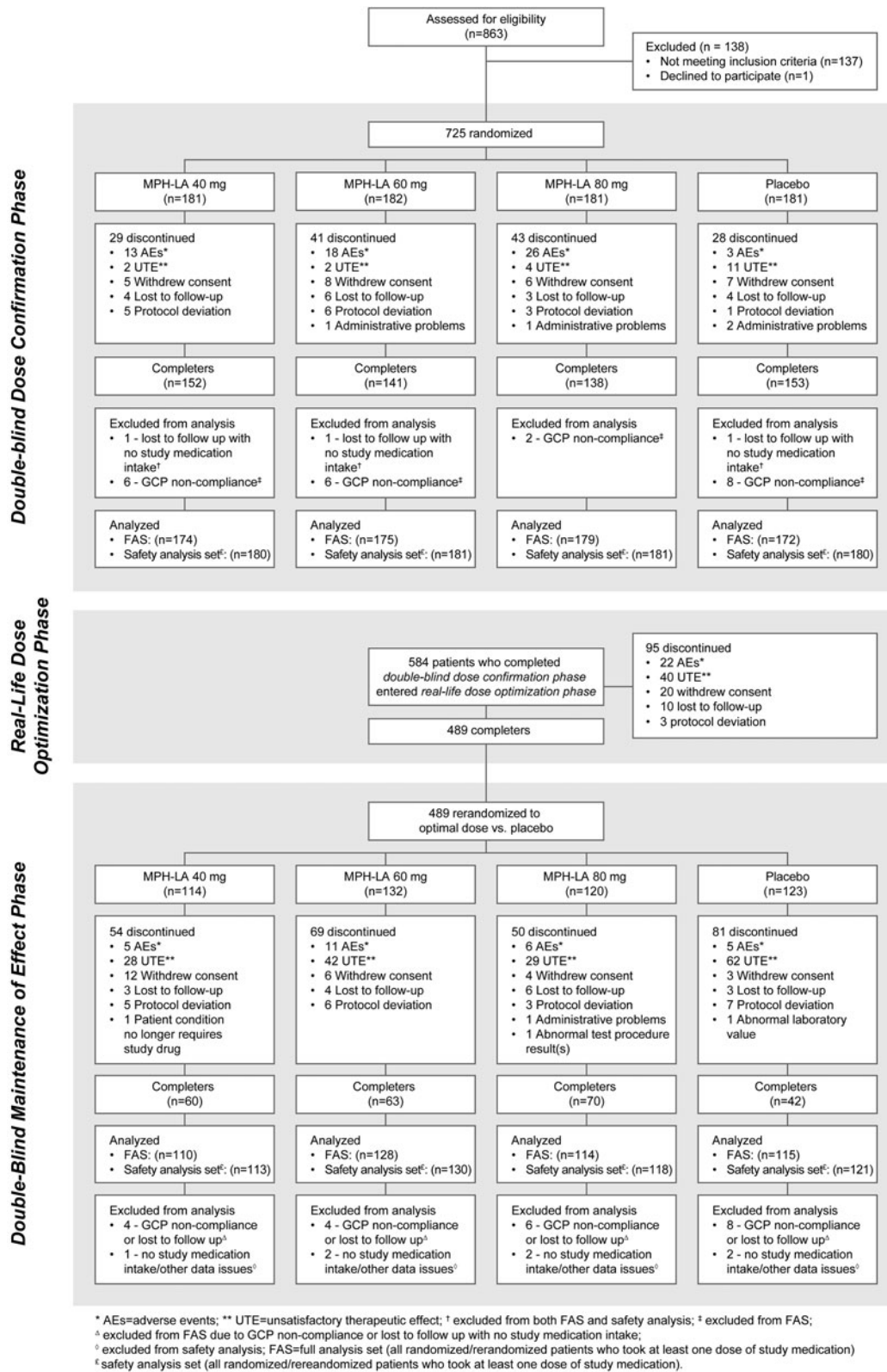
Fig. 2 Patient disposition. *FAS* full analysis set, *GCP* good clinical practice, *MPH-LA* methylphenidate hydrochloride modified-release

Table 2 Baseline and demographic characteristics

	MPH-LA 40 mg (N = 181)*	MPH-LA 60 mg (N = 182)*	MPH-LA 80 mg (N = 181)*	All MPH-LA (N = 544)*	Placebo (N = 181)*	All (N = 725)*
Age (years)						
Mean ± SD	35.1 ± 11.37	34.8 ± 10.79	34.9 ± 11.13	34.9 ± 11.08	36.8 ± 12.15	35.4 ± 11.38
Sex, n (%)						
Male	94 (51.9)	105 (57.7)	95 (52.5)	294 (54.0)	101 (55.8)	395 (54.5)
Female	87 (48.1)	77 (42.3)	86 (47.5)	250 (46.0)	80 (44.2)	330 (45.5)
Race, n (%)						
Caucasian	160 (88.4)	155 (85.2)	165 (91.2)	480 (88.2)	169 (93.4)	649 (89.5)
Black	5 (2.8)	7 (3.8)	4 (2.2)	16 (2.9)	4 (2.2)	20 (2.8)
Asian	6 (3.3)	7 (3.8)	4 (2.2)	17 (3.1)	1 (0.6)	18 (2.5)
Other	10 (5.5)	13 (7.1)	8 (4.4)	31 (5.7)	7 (3.9)	38 (5.2)
Height (cm)						
Mean ± SD	172.6 ± 9.66	173.7 ± 9.36	173.6 ± 9.68	173.3 ± 9.56	172.8 ± 9.87	173.2 ± 9.64
Weight						
Mean ± SD	76.5 ± 15.35	77.1 ± 14.92	76.8 ± 14.82	76.8 ± 15.01	77.8 ± 16.64	77.0 ± 15.42
BMI (kg/m^2)						
Mean ± SD	25.5 ± 3.55	25.5 ± 4.08	25.4 ± 3.80	25.4 ± 3.81	25.9 ± 4.12	25.6 ± 3.89
DSM-IV ADHD RS total score	39.6	39.1	39.3	39.3	39.0	39.2
SDS total score	20.7	19.4	19.7	19.9	19.9	19.9
CAARS-O:S	48.0	46.1	46.7	46.9	45.9	46.7
ASRS	52.7	51.3	52.4	52.1	51.7	52.0
Smoking status						
Current smoker (yes)	55 (30.4)	66 (36.3)	50 (27.6)	171 (31.4)	56 (30.9)	227 (31.3)

ASRS Adult Self-Reporting Scale, *CAARS-O:S* Conner's Adult ADHD Rating Scale-Observer Short Version, *DSM-IV ADHD RS* Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release, *SD* standard deviation, *SDS* Sheehan Disability Scale

* N represents the randomized set for the *double-blind dose-confirmation phase*

Efficacy

Double-Blind Dose-Confirmation Phase

Responder analysis showed that over 75% of all MPH-LA treated patients demonstrated greater than 30% improvement in the DSM-IV ADHD RS total score versus placebo. An increased number of responders were noted for 40 (75.8%), 60 (80.5%) and 80 mg (81.0%) groups as compared to placebo (Fig. 3). MPH-LA (40, 60, and 80 mg) was shown to be statistically and clinically superior to placebo for all three co-primary efficacy endpoints. By the end of the 9-week *double-blind dose-confirmation phase*, improvement from baseline in DSM-IV ADHD RS total score for all MPH-LA dose levels was significantly greater than placebo (all comparisons: $P < 0.0001$; Fig. 4a; Table 3). Similarly, functional improvement, as assessed by change from baseline in the SDS total score, was significantly greater for all MPH-LA dose levels compared to placebo (40 mg, $P = 0.0003$; 60 mg, $P = 0.0176$; 80 mg, $P < 0.0001$; Fig. 4b; Table 3). Figure 5 shows the improvement of all dose levels of MPH-LA versus placebo on DSM-IV ADHD RS over the 9-week treatment period. The effect size Cohen's d of all MPH-LA three dose levels combined was 0.55 for DSM-IV ADHD RS (0.55, 0.47, and 0.64 for MPH-LA 40, 60, and 80 mg, respectively) and was 0.39 for

SDS total score (0.47, 0.25, and 0.43 for MPH-LA 40, 60, and 80 mg, respectively). The percentage of patients with improvement on the CGI-I scale (key secondary efficacy endpoint) for all
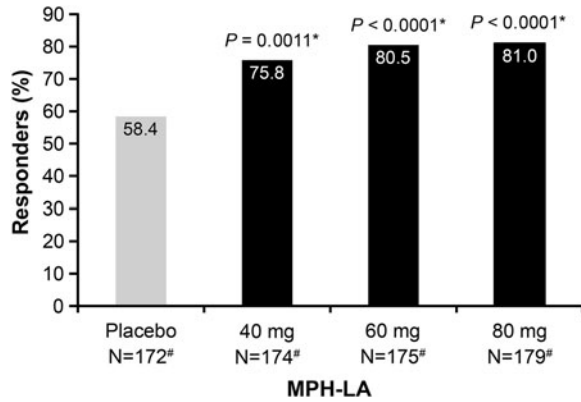

Fig. 3 Response rate on DSM-IV ADHD RS total score at the end of the 9-week *double-blind dose-confirmation phase*. Responders = patients with at least 30% improvement from baseline to end of the 9-week *double-blind dose-confirmation phase*. *P values refer to two-sided *P* value based on the difference between MPH-LA group and placebo. #Full analysis set (all randomized/re-randomized patients who took at least one dose of study medication) for the *double-blind dose-confirmation phase*. *DSM-IV ADHD RS* Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release
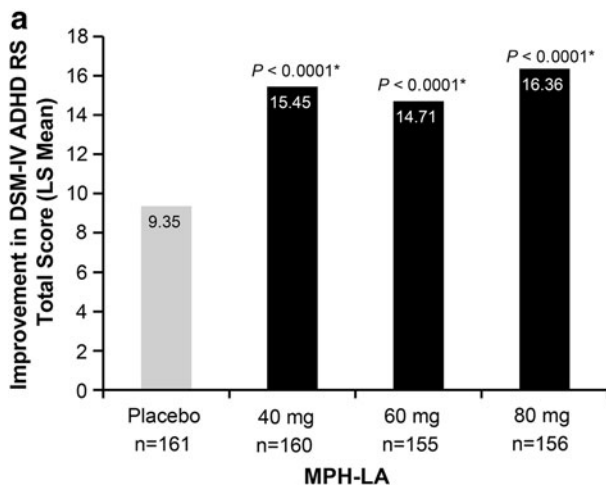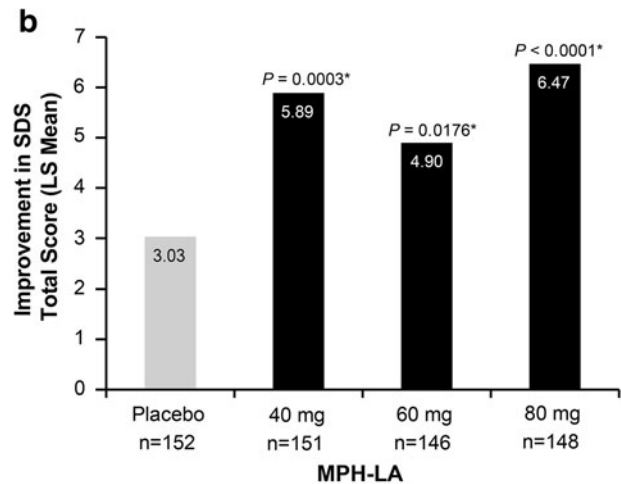
three MPH-LA dose levels was significantly higher compared to placebo (Table 4). Similarly, the percentage of patients with improvement for all three MPH-LA dose levels on CGI-S was significantly higher compared to the placebo group. Consistent results were seen for the observer-rated CAARS-O:S and self-rated ASRS: improvement from baseline for all dose levels of MPH-LA was significantly greater than placebo (Table 4).

Real-Life Dose-Optimization Phase

At the end of the 5-week *real-life dose-optimization phase*, a comparable number of patients had been optimized, as per investigator's assessment, at each of the dose levels: 152, 177, and 160 patients for 40, 60, and 80 mg/day, respectively.

Double-Blind Maintenance of Effect Phase

During the *double-blind 6-month maintenance of effect phase*, significantly less patients treated with MPH-LA were required to discontinue the study due to treatment failure (21.3%, $n = 75$) compared to those treated with placebo

Fig. 4 Primary efficacy endpoints: improvement in DSM-IV ADHD RS (**a**) and SDS total scores (**b**) from baseline to the end of the *double-blind dose-confirmation phase*. *DSM-IV ADHD RS* Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release, *SDS* Sheehan Disability Scale

Table 3 Analysis of co-primary endpoints during the 9-week *double-blind dose-confirmation phase*

Primary efficacy endpoints

	MPH-LA 40 mg (N = 160)[#]	MPH-LA 60 mg (N = 155)[#]	MPH-LA 80 mg (N = 156)[#]	Placebo (N = 161)[#]
(1) DSM-IV ADHD RS total score (improvement from baseline to end of *double-blind dose-confirmation phase*)				
Mean ± SD	16.0 ± 12.18	14.7 ± 10.12	16.8 ± 11.36	9.7 ± 11.05
Least-square means	15.45	14.71	16.36	9.35
Least-square means difference from placebo (95% CI)*	6.10 (3.68, 8.53)	5.36 (2.92, 7.79)	7.01 (4.59, 9.42)	
P value	<0.0001	<0.0001	<0.0001	
Significance level	0.0167	0.0208	0.0313	
	MPH-LA 40 mg (N = 151)[#]	MPH-LA 60 mg (N = 146)[#]	MPH-LA 80 mg (N = 148)[#]	Placebo (N = 152)[#]
(2) SDS total score (improvement from baseline to end *of double-blind dose-confirmation phase*)				
Mean ± SD	6.4 ± 7.54	4.7 ± 7.08	6.1 ± 7.31	2.9 ± 7.47
Least-square means	5.89	4.90	6.47	3.03
Least-square means difference from placebo (95% CI)*	2.86 (1.33, 4.39)	1.87 (0.33, 3.41)	3.44 (1.91, 4.97)	
P value	0.0003	0.0176	<0.0001	
Significance level	0.0167	0.0208	0.0313	

DSM-IV ADHD RS Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release *SD* standard deviation *SDS* Sheehan Disability Scale
* 95% CI based on adjusted SD; [#]*N* represents the number of patients in full analysis set with available baseline and post-baseline measurements (in the 6-week fixed-dose period of *double-blind dose-confirmation phase*)

(49.6%, *n* = 57; Fig. 6). Patients treated with placebo had more than three times higher chance of being required to discontinue the study due to treatment failure compared to patients treated with MPH-LA [odds ratio (95% CI) 0.3 (0.2, 0.4); Fig. 6].

Safety Assessments

Overall, the MPH-LA group had approximately five times greater exposure to study drug than the placebo group (95,449 days versus 20,992 days, respectively). No deaths occurred during study drug exposure. The percentage of SAEs was comparable between all MPH-LA arms (1.3%) and placebo (1.5%). AEs were more frequently observed in each of the MPH-LA-treated groups compared to placebo during the *double-blind dose-confirmation phase* and the 6-month *double-blind maintenance of effect phase* (Table 5). The most common AEs observed during the initial 9-week *dose-confirmation phase* for all three MPH-LA dose groups were decreased appetite, headache, and dry mouth (Tables 5, 6, 7). During the 5-week *real-life dose-optimization phase*, the MPH-LA AE
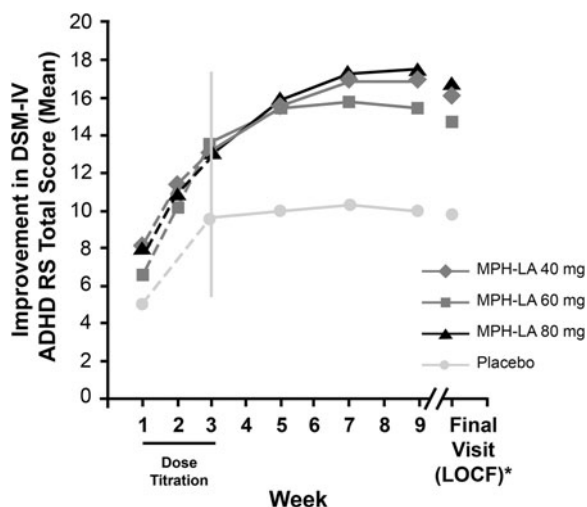
Fig. 5 Progression of improvement on DSM-IV ADHD RS total score from baseline to the end of the *double-blind dose-confirmation phase* by week. *LOCF, last observation carried forward using the final visit for each patient with data in the 6-week fixed-dose phase of *double-blind dose-confirmation phase*. *DSM-IV ADHD RS* Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release

profile was similar to that observed during the initial phase. The overall incidence of AEs was lower during the 6-month *double-blind maintenance of effect phase* compared to the 9-week *dose-confirmation phase* or 5-week *optimization phase*. The most frequent AEs in all treatment groups during the *maintenance of effect phase* were nasopharyngitis and headache. Overall, there was no apparent relationship between the dose of MPH-LA and the incidence of AEs. During the 9-week *double-blind dose-confirmation phase*, anxiety and decreased appetite each led to discontinuation in 2.2% of patients in the MPH-LA 60 and 80 mg groups, respectively. Otherwise, all AEs leading to discontinuation were reported in less than 2.0% of patients in any treatment group. No clinically meaningful differences were observed between treatment groups with respect to laboratory findings, vital signs or

ECGs (Table 7b); none of the patients had a QT, QTcB or QTcF ≥500 ms during the study. One death (51-year-old male patient) was reported 21 days after patient completed the study (21 days after receiving last dose of study medication) due to aortic dissection rupture. The patient had a history of aortic aneurysm not requiring any medical intervention according to the investigator, and was under the observation of another physician. The investigator did not suspect any relationship to drug.

DISCUSSION

Main Findings

In this large 40-week, randomized, double-blind, placebo-controlled trial, the efficacy and safety of MPH-LA was demonstrated in adult patients (18–60 years). Statistical and clinical significance for MPH-LA 40, 60, and 80 mg/day relative to placebo were seen for all three primary efficacy endpoints. The results confirmed a clinically effective dose range of 40–80 mg MPH-LA daily as measured by the change from baseline to the end of the 9-week, fixed-dose *double-blind dose-confirmation phase* in DSM-IV ADHD RS and SDS total scores. Furthermore, patients treated with MPH-LA had a significantly lower treatment failure rate compared to those receiving placebo during the study's 6-month *double-blind maintenance of effect phase*. Patients treated with placebo had more than three times higher chance of treatment failure compared to patients treated with MPH-LA. During this 6-month *maintenance of effect phase*, 50.4% of patients in the placebo group did not meet the criteria for treatment failure. The fact that all these patients were exposed to MPH-LA for 5–14 weeks before being

Table 4 Analysis of secondary endpoints during the 9-week *double-blind dose-confirmation phase*

Secondary efficacy endpoints

	MPH-LA 40 mg (N = 174)*	MPH-LA 60 mg (N = 175)*	MPH-LA 80 mg (N = 179)*	Placebo (N = 172)*
(1) CGI-I scale (proportion of patients with improvement from baseline to end of *double-blind dose-confirmation phase*)				
n/evaluable patients (%)	90/160 (56.3)	85/155 (54.8)	89/156 (57.1)	51/161 (31.7)
Odds ratio	2.44	2.25	2.51	
95% CI for odds ratio	(1.52, 3.93)	(1.40, 3.64)	(1.56, 4.05)	
P value	0.0002	0.0009	0.0002	
Significance level	0.0167	0.0250	0.0500	
	MPH-LA 40 mg (N = 174)*	**MPH-LA 60 mg (N = 175)***	**MPH-LA 80 mg (N = 179)***	**Placebo (N = 172)***
(2) CGI-S scale (proportion of patients with improvement from baseline to end of *double-blind dose-confirmation phase*)				
n/evaluable patients (%)	112/157 (71.3)	112/152 (73.7)	112/151 (74.2)	77/159 (48.4)
Odds ratio	2.79	3.20	3.24	
95% CI for odds ratio	(1.73, 4.48)	(1.97, 5.22)	(1.98, 5.28)	
P value	<0.0001	<0.0001	<0.0001	
	MPH-LA 40 mg (N = 136)#	**MPH-LA 60 mg (N = 135)#**	**MPH-LA 80 mg (N = 137)#**	**Placebo (N = 147)#**
(3) CAARS-O:S total score (improvement from baseline to end of *double-blind dose-confirmation phase*)				
Mean ± SD	10.1 ± 13.91	9.0 ± 12.22	10.4 ± 15.66	4.6 ± 11.94
Least-square means	9.45	9.20	10.12	4.50
Least-square means difference from placebo (95% CI)	4.95 (2.08, 7.81)	4.69 (1.83, 7.56)	5.61 (2.79, 8.44)	
P value	0.0008	0.0014	0.0001	
	MPH-LA 40 mg (N = 154)#	**MPH-LA 60 mg (N = 150)#**	**MPH-LA 80 mg (N = 151)#**	**Placebo (N = 159)#**
(4) ASRS total score (improvement from baseline to end of *double-blind dose-confirmation phase*)				
Mean ± SD	14.5 ± 14.11	12.6 ± 13.15	15.8 ± 13.90	6.8 ± 12.20
Least-square means	13.76	13.11	15.87	6.81
Least-square means difference from placebo (95% CI)	6.95 (4.04, 9.85)	6.30 (3.39, 9.21)	9.05 (6.17,11.94)	
P value	<0.0001	<0.0001	<0.0001	

ASRS Adult Self-Reporting Scale, *CAARS-O:S* Conner's Adult ADHD Rating Scale-Observer Short Version, *CGI-I* Clinical Global Impression-Improvement Scale, *CGI-S* Clinical Global Impression-Severity Scale, *MPH-LA* methylphenidate hydrochloride modified-release, *SD* standard deviation
* Full set analysis. # N represents the number of patients in full analysis set with available baseline and post-baseline measurements (in the 6-week fixed-dose period of *double-blind dose-confirmation phase*)

randomized to receive placebo is especially interesting. This finding indicates that re-evaluation of the need to continue drug therapy after a certain period of time may be warranted.

Analysis of the key secondary variable (CGI-I scale) and for the other secondary variables (CGI-S scale, CAARS-O:S, and ASRS) showed significantly greater improvement for all three

MPH-LA dose levels compared to placebo at the end of the 9-week *double-blind dose-confirmation phase*. The clinical significance of these primary and secondary efficacy results is reinforced by the fact that the statistically significant superiority for all three dose levels of MPH-LA compared to placebo was consistent across physician-, observer-, and self-rated scales.
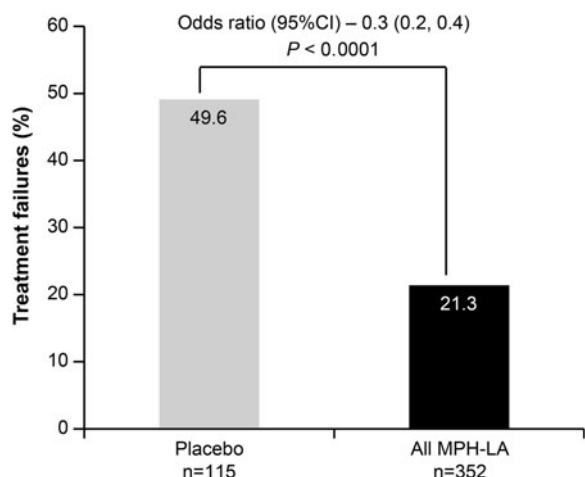
Fig. 6 Primary efficacy endpoint: percentage of treatment failures during the *double-blind maintenance of effect phase*. Treatment failures: patient with ≥30% worsening from baseline during the 6-month *double-blind maintenance of effect phase* and <30% remaining improvement from phase 1 baseline on DSM-IV ADHD RS. Treatment failures were analyzed using a logistic regression model with treatment as the factor and baseline as covariate. Missing post-baseline scores were imputed based on last observation carried forward (LOCF) or based on the multiple imputation approach if data were not available for LOCF. Significance level = 0.05. *DSM-IV ADHD RS* Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale, *MPH-LA* methylphenidate hydrochloride modified-release

No new or unexpected safety concerns unique to adults treated with MPH-LA were observed in the current study. The safety results are comparable with the available data from recent studies for MPH in children and adults with ADHD [24–26]. The types and frequencies of the AEs reported during the study are consistent with the pharmacologic activity and known safety profile of MPH established during more than 50 years of clinical use in childhood ADHD. Except for headache, which was reported in a similar percentage of patients in the placebo group and the MPH-LA 80 mg group, the rates of the most frequently reported AEs were higher for all three MPH-LA dose levels compared to placebo.

Safety analysis showed that reducing the dose of MPH-LA from 80 mg/day to 20 mg/day, or suddenly stopping doses of 40, 60, or 80 mg/day had no impact on safety, indicating that the common practice of gradually tapering the dose of MPH-LA prior to discontinuation is unnecessary.

ADHD symptoms persist into adulthood in 40–80% of children with ADHD and the prevalence of ADHD in adults is 2–5% [24, 27, 28]. With the increasing recognition of ADHD in adults [29, 30] and few countries with drugs approved for this indication, efficacy and safety data from well-controlled clinical trials such as the present study are essential for meeting this unmet medical need. Beyond being a well-controlled trial, this is the first phase 3 study in adult patients with ADHD, designed to comply with the European Medicines Agency 'Guideline on the clinical investigation of medicinal products for the treatment of ADHD'. The guideline, released in 2010, calls for the inclusion of co-primary endpoints to evaluate both the symptomatic and functional domains in ADHD trials [14]. Therefore, the DSM-IV ADHD RS and the SDS were included as co-primary outcome measures. This is also the first study with MPH in adults with ADHD including a withdrawal design to evaluate maintenance of effect for 6 months, thus providing evidence supporting the management of adult ADHD patients requiring long-term treatment.

Research in Context

From a design perspective, the inclusion of co-primary endpoints to evaluate symptomatic and functional improvement in adult ADHD, together with a third primary endpoint to measure maintenance of treatment effect through a 6-month *maintenance of effect phase*

Table 5 Adverse events and serious adverse events during the *double-blind dose-confirmation phase*

Preferred term	All MPH-LA (N = 542)*	MPH-LA 40 mg (N = 180)*	MPH-LA 60 mg (N = 181)*	MPH-LA 80 mg (N = 181)*	Placebo (N = 180)*
Number (%) of patients with AEs (>5% in any group)					
Any preferred term	401 (74.0)	131 (72.8)	134 (74.0)	136 (75.1)	108 (60.0)
Decreased appetite	136 (25.1)	39 (21.7)	49 (27.1)	48 (26.5)	8 (4.4)
Headache	111 (20.5)	39 (21.7)	42 (23.2)	30 (16.6)	30 (16.7)
Dry mouth	110 (20.3)	34 (18.9)	39 (21.5)	37 (20.4)	4 (2.2)
Nausea	58 (10.7)	15 (8.3)	20 (11.0)	23 (12.7)	9 (5.0)
Nasopharyngitis	54 (10.0)	22 (12.2)	15 (8.3)	17 (9.4)	17 (9.4)
Insomnia	44 (8.1)	13 (7.2)	18 (9.9)	13 (7.2)	7 (3.9)
Hyperhidrosis	43 (7.9)	12 (6.7)	14 (7.7)	17 (9.4)	5 (2.8)
Palpitations	39 (7.2)	8 (4.4)	15 (8.3)	16 (8.8)	1 (0.6)
Fatigue	38 (7.0)	11 (6.1)	16 (8.8)	11 (6.1)	11 (6.1)
Dizziness	32 (5.9)	12 (6.7)	9 (5.0)	11 (6.1)	5 (2.8)
Irritability	32 (5.9)	11 (6.1)	12 (6.6)	9 (5.0)	8 (4.4)
Anxiety	29 (5.4)	8 (4.4)	11 (6.1)	10 (5.5)	1 (0.6)
Initial insomnia	28 (5.2)	9 (5.0)	4 (2.2)	15 (8.3)	2 (1.1)
Restlessness	26 (4.8)	9 (5.0)	10 (5.5)	7 (3.9)	5 (2.8)
Tachycardia	26 (4.8)	6 (3.3)	10 (5.5)	10 (5.5)	0 (0.0)
Abdominal pain upper	22 (4.1)	6 (3.3)	3 (1.7)	13 (7.2)	7 (3.9)
SAEs					
Goiter	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Infected bites	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Loss of consciousness	1 (0.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Ovarian cyst ruptured	1 (0.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Sudden hearing loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Eye infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

Table 5 continued

Preferred term	All MPH-LA ($N = 542$)*	MPH-LA 40 mg ($N = 180$)*	MPH-LA 60 mg ($N = 181$)*	MPH-LA 80 mg ($N = 181$)*	Placebo ($N = 180$)*
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
	All MPH-LA	**Placebo**			
AEs leading to discontinuation	61 (11.3)	4 (2.2)			

AEs adverse events, *MPH-LA* methylphenidate hydrochloride modified-release, *SAEs* serious adverse events
* Safety analysis set for the *double-blind dose-confirmation phase*

Table 6 Adverse events and serious adverse events during the *real-life dose-optimization phase*

Preferred term	All MPH-LA ($N = 580$)*
Number (%) of patients with AEs >5% in any group	
Any preferred term	378 (65.2)
Headache	78 (13.4)
Decreased appetite	62 (10.7)
Dry mouth	50 (8.6)
Nasopharyngitis	43 (7.4)
Nausea	37 (6.4)
Insomnia	34 (5.9)
SAEs	
Concussion	1 (0.2)
Rib fracture	1 (0.2)
Panic attack	1 (0.2)
AEs leading to discontinuation	22 (3.8)

AEs adverse events, *MPH-LA* methylphenidate hydrochloride modified-release, *SAEs* serious adverse events
* Safety analysis set for the *real-life dose-optimization phase*

sets this study apart from all other studies in adult ADHD. The efficacy results of this unique study were consistent with results from three recently published studies [20, 24, 25] showing significant improvements with

MPH in adult ADHD across physician- and patient-rated scales. However, the fact that each of these studies included a single primary endpoint, a smaller patient population, and did not include an assessment of maintenance of effect does not allow for more quantitative cross-study comparison of efficacy outcomes. As observed for MPH-LA in the present study, the overall safety profile for MPH in both studies was consistent with that observed in children. A meta-analysis of 18 adult ADHD studies, which included patients with co-morbid substance use disorders, demonstrated efficacy for MPH in adults [31], as well as in a recently published randomized controlled trial on MPH conducted in adult criminal offenders with ADHD and coexistent amphetamine dependence [32]. However, unlike in the present study, efficacy was shown to be dose-dependent.

In the present study, the combined effect size for all MPH-LA dose levels was 0.55 and 0.39 for DSM-IV ADHD RS and SDS total scores, respectively. These results are in line with the overall effect size ($d = 0.42$) reported by Koesters et al. [33] from the meta-analysis of 18 studies comparing MPH with placebo in the treatment of adult ADHD. Koesters et al. [33] also reported that regression analysis showed no significant influence of mean daily dose on effect size.

Table 7 (a) Adverse events and serious adverse events during the 6-month *double-blind maintenance of effect phase*. (b) Mean change in blood pressure and heart rate from baseline of the *double-blind dose-confirmation phase* to the end of the *maintenance of effect phase*

Preferred term	All MPH-LA (N = 361)*	MPH-LA 40 mg (N = 113)*	MPH-LA 60 mg (N = 130)*	MPH-LA 80 mg (N = 118)*	Placebo (N = 121)*
(a) Number (%) of patients with AEs (>5% in any group)					
Any preferred term	197 (54.6)	64 (56.6)	75 (57.7)	58 (49.2)	44 (36.4)
Nasopharyngitis	44 (12.2)	11 (9.7)	18 (13.8)	15 (12.7)	6 (5.0)
Headache	37 (10.2)	12 (10.6)	14 (10.8)	11 (9.3)	9 (7.4)
SAEs					
Cholecystitis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Cholelithiasis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Localized infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Adjustment disorder	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Suicide attempt	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Nephrolithiasis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Tonsillar hypertrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

	All MPH-LA		Placebo		
AEs leading to discontinuation	18 (5)		4 (3.3)		

	All MPH-LA	MPH-LA 40 mg	MPH-LA 60 mg	MPH-LA 80 mg	Placebo
b. Mean change from *double-blind dose confirmation phase* baseline to end of *maintenance of effect phase*					
Systolic blood pressure (mmHg)	2.7	3.5	0.3	4.3	−1.0
Diastolic blood pressure (mmHg)	1.9	2.4	1.1	2.3	−0.3
Heart rate (bpm)	4.0	3.3	3.2	5.2	−1.7

AEs adverse events, *bpm* beats per minute, *MPH-LA* methylphenidate hydrochloride modified-release, *SAEs* serious adverse events

* Safety analysis set for the *double-blind maintenance of effect phase*

Limitations

A limitation of the study is the limited external validity, as the protocol did not allow the inclusion of patients with psychiatric co-morbidities. At least one co-morbid condition like anxiety, affective, substance use, or antisocial personality disorder is known to occur in nearly 80% of adults with ADHD [34–36]; however, patients with these conditions

requiring treatment were not included in this study. The intentional exclusion of co-morbidities helped to avoid confounding factors and allowed for clear comparisons that were necessary to meet the defined objectives of the study. Nonetheless, the efficacy and safety of MPH has been evaluated in ADHD patients with co-morbid conditions in other studies [24, 34, 37].

As many clinicians prefer to use twice-daily dosing to extend coverage for their patients [11], the once-daily dosage regimen used in this study may be considered a limitation. However, the robust efficacy results of this study, particularly the significant patient-rated outcome for functional improvement, do not indicate that once-daily dosing with MPH-LA limited treatment benefit for the majority of patients.

Another limitation due to the design of the study was that the study was not powered to differentiate between the different dose levels, but powered to differentiate between the respective dose and placebo. However, during the second part of the study, which assessed "optimal dose" and individualized treatment, a comparable number of patients were optimized, upon the discretion of the investigator, with each of the dose levels, which demonstrates the need for individualized treatment and the need for all three of the dose levels studied.

Diagnosis of childhood onset ADHD (all types) was performed as per the international DSM-IV diagnostic criteria [38]. Semi-structured interviews like Conner's Adult ADHD Diagnostic Interview for DSM-IV or Diagnostic Interview for ADHD in adults were not employed, due to their limited validation in several countries participating in this multi-centered study. For future studies, it would be beneficial to cross-validate this with semi-structured interviews, as soon as those have been validated in the majority of countries.

CONCLUSION

As far as we are aware, this is the first study in adults with ADHD to include the assessment of both symptoms and function as co-primary endpoints. The results show that MPH-LA can provide significant symptomatic and functional improvement for adults with ADHD and a maintained treatment effect for at least 6 months. The data also demonstrate that there is no new safety concern uniquely associated with the administration of MPH to adult patients with ADHD. The present study addresses an unmet medical need for robust dose range, efficacy, and safety data on the use of MPH in this currently underserved population.

ACKNOWLEDGMENTS

data collection, data interpretation, and writing the manuscript. Torbjorn Tvedten contributed to data collection and protocol amendments, and also contributed to the manuscript's content and form. Torben Arngrim contributed to data collection, data interpretation, and writing the manuscript. Alexandra Philipsen contributed to data collection, data interpretation, and writing the manuscript. Katherine Carter was the trial head employed by Novartis Pharmaceutical Corporation and was accountable for the delivery of the trial. She completed, contributed to or created literature searches, figures, study design, data collection, data analysis, data interpretation, and writing the manuscript. Chien-Wei Chen contributed to data analysis and data interpretation. Vinod Kumar contributed to the design of the study and helped conduct the study, as well as contributing to data analysis, data interpretation, and the preparation of the manuscript. All authors approved the final draft of the manuscript. Michael Huss is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Compliance with ethics guidelines. The study protocol was designed in accordance with the EU guideline on studies in ADHD which requires that "two primary endpoints should be stipulated reflecting the symptomatic and the functional domain" [14]. Ethics approval was received before the start of the study in compliance with global and local guidelines by ethic committees of the respective countries. All procedures followed were in accordance with the ethical standards of

the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study.

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164:942–8.

2. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet. 2005;366:237–48.

3. Lara C, Fayyad J, de Graaf R, et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biol Psychiatry. 2009;65:46–54.

4. Lie N. Follow-ups of children with attention deficit hyperactivity disorder (ADHD). Review of literature. Acta Psychiatr Scand Suppl. 1992;368:1–40.

5. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry. 2009;194:204–11.

6. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry. 1996;37:393–401.

7. Knouse LE, Bagwell CL, Barkley RA, Murphy KR. Accuracy of self-evaluation in adults with ADHD: evidence from a driving study. J Atten Disord. 2005;8:221–34.

8. Secnik K, Swensen A, Lage MJ. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. Pharmacoeconomics. 2005;23:93–102.

9. Kessler RC, Adler L, Ames M, et al. The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. J Occup Environ Med. 2005;47:565–72.

10. Kendall T, Taylor E, Perez A, Taylor C. Diagnosis and management of attention-deficit/hyperactivity disorder in children, young people, and adults: summary of NICE guidance. BMJ. 2008;337:a1239.

11. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry. 2010;10:67.

12. National Institute of Clinical Excellence (NICE). Attention Deficit Hyperactivity Disorder: The NICE guideline on diagnosis and management of ADHD in children, young people and adults. NICE. 2008.

13. Ramos-Quiroga JA, Montoya A, Kutzelnigg A, Deberdt W, Sobanski E. Attention deficit hyperactivity disorder in the European adult population: prevalence, disease awareness, and treatment guidelines. Curr Med Res Opin. 2013;29:1093–104.

14. European Medicines Agency (EMA). Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD). EMEA/CHMP/EWP/431734/2008.

15. Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. Int J Methods Psychiatr Res. 2005;14:186–201.

16. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27:93–105.

17. Guy W. Clinical global impressions. In: ECDEU assessment manual for psychopharmacology-revised (DHEW Publ No ADM 76-338). Rockville: U.S. Department of Health, Education, and Welfare; 1976. p. 217–22.

18. Conners CK, Erhardt D, Sparrow EP. Conner's adult ADHD rating scales (CAARS) technical manual. North Tonawanda: Multi-Health Systems Inc.; 1999.

19. Adler LA, Kessler RC, Spencer T. Adult ADHD Self-Report Scale-v1.1 (ASRS-v1.1) Symptom Checklist. New York, NY: World Health Organization; 2003. Available at: http://www.med.nyu.edu/Psych/training/adhd.html. Accessed 22 July 2010.

20. Medori R, Ramos-Quiroga JA, Casas M, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2008;15(63):981–9.

21. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry. 2003;53:112–20.

22. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Earlbaum Associates; 1988.

23. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586–604.

24. Ginsberg Y, Lindefors N. Methylphenidate treatment of adult male prison inmates with attention-deficit hyperactivity disorder: randomised double-blind placebo-controlled trial with open-label extension. Br J Psychiatry. 2012;200:68–73.

25. Wigal SB, Childress AC, Belden HW, Berry SA. NWP06, an extended-release oral suspension of methylphenidate, improved attention-deficit/hyperactivity disorder symptoms compared with placebo in a laboratory classroom study. J Child Adolesc Psychopharmacol. 2013;23:3–10.

26. Duong S, Chung K, Wigal SB. Metabolic, toxicological, and safety considerations for drugs used to treat ADHD. Expert Opin Drug Metab Toxicol. 2012;8:543–52.

27. Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry. 2007;190:402–9.

28. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. BMC Pediatr. 2012;12:78.

29. Asherson P. Clinical assessment and treatment of attention deficit hyperactivity disorder in adults. Expert Rev Neurother. 2005;5:525–39.

30. Asherson P, Chen W, Craddock B, Taylor E. Adult attention-deficit hyperactivity disorder: recognition and treatment in general adult psychiatry. Br J Psychiatry. 2007;190:4–5.

31. Castells X, Ramos-Quiroga JA, Rigau D, et al. Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. CNS Drugs. 2011;25:157–69.

32. Konstenius M, Jayaram-Lindström N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for ADHD and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2013. doi:10.1111/add.12369.

33. Koesters M, Becker T, Kilian R, Fegert JM, Weinmann S. Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. J Psychopharmacol. 2009;23:733–44.

34. Adler LA, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. J Atten Disord. 2009;12:449–59.

35. Hammerness P, Surman C, Miller K. Update on adult attention-deficit/hyperactivity disorder. Curr Neurol Neurosci Rep. 2008;8:484–9.

36. Rosler M, Casas M, Konofal E, Buitelaar J. Attention deficit hyperactivity disorder in adults. World J Biol Psychiatry. 2010;11:684–98.

37. Surman CB, Monuteaux MC, Petty CR, et al. Representativeness of participants in a clinical trial for attention-deficit/hyperactivity disorder? Comparison with adults from a large observational study. J Clin Psychiatry. 2010;71:1612–6.

38. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fourth edition. Text Revision: DSM-IV-TR Arlington. 2000. Available from http://dsm.psychiatryonline.org/book.aspx?bookid=22. Accessed 6 November 2012.