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

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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), ClinicalTrials.gov #NCT01259492.

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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 (dexamethylphenidate 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](image)

Methods outline, 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/m² or >35 kg/m².

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.

| 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|

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

△ Adis
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 \( (M_1 - M_2)/\text{SD} \), where \( M_1 \) and \( M_2 \) 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 \( \geq 30\% \) 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
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

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/m²)  | 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
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 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.

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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
The 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
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 
waranted.

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.
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) |
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 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)           |
| Any preferred term |
| Any preferred term | 378 (65.2)          | 78 (13.4)              | 62 (10.7)              | 50 (8.6)               | 43 (7.4)          |
| Depression     | 3 (0.5)               | 2 (1.1)                | 2 (1.1)                | 2 (1.1)                | 1 (0.6)           |
| Insomnia       | 54 (9.3)              | 11 (6.1)               | 11 (6.1)               | 11 (6.1)               | 11 (6.1)          |
| SAEs           | 1 (0.2)               | 1 (0.2)                | 1 (0.2)                | 1 (0.2)                | 1 (0.2)           |
| 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)              |
| 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
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

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 |
|------------|-------------|-------------|-------------|---------|
| 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
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.

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Michael Huss was responsible for the study design and provided medical advice, as well as contributing to literature searches, data collection, data interpretation, and editing the manuscript. Ylva Ginsberg was responsible for
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.

Conflict of interest. Michael Huss has served as an advisory board member for Eli Lilly, Engelhardt Arzneimittel, Janssen-Cilag, Medice, Novartis, Shire, and Steiner Arzneimittel, and as a consultant for Engelhardt Arzneimittel, Medice, and Steiner Arzneimittel. He received honoraria from Eli Lilly, Engelhardt Arzneimittel, Janssen-Cilag, Medice, Novartis, and Shire. He has received unrestricted grants for investigator-initiated trials from Eli Lilly, Engelhardt Arzneimittel, and Steiner Arzneimittel. Ylva Ginsberg has served as a consultant and speaker for Janssen-Cilag and Novartis and as a speaker for Lundbeck. She has also been a principal investigator of two international multicenter trials initiated by Janssen-Cilag, and she was the coordinating investigator of a MPH trial conducted in adult prison inmates with ADHD, funded by the Swedish Ministry of Health and Social Affairs. Torbjorn Tvedten has received speaker fees from Novartis and Lundbeck. Torben Arngrim has been involved in clinical trials conducted by Janssen-Cilag and Novartis. He has received speaker fees from Janssen-Cilag, Novartis, Eli Lilly, and HB Pharma, and has served as an advisory board member for Novartis and Shire. Alexandra Philipsen has received speaker fees and/or travel grants from Eli Lilly, Janssen-Cilag, Medice, Novartis, and Shire, and has been involved in clinical trials conducted by Eli Lilly, Janssen-Cilag, Medice, and Novartis. She has served as an advisory board member for Eli Lilly, Janssen-Cilag, Medice, Novartis, and Shire. She is the co-ordinating investigator of a multicenter trial on the treatment of adult ADHD (Current Controlled Trials ISRCTN54096201, funded by the Federal Ministry of Education and Research 01GV0606). Katherine Carter is an employee of Novartis Pharmaceutical Corporation. Chien-Wei Chen is an employee of Novartis Pharmaceutical Corporation. Vinod Kumar is an employee of Novartis Pharmaceutical Corporation.

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.

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